Aging Clinical and Experimental Research (2022) 34:2591–2602
https://doi.org/10.1007/s40520-022-02261-2

CONSENSUS DOCUMENT

Evidence based Latin American Guidelines of clinical practice on prevention, diagnosis, management and treatment of glucocorticoid induced osteoporosis. A 2022 update

This manuscript has been produced under the auspices of the Committee of National Societies (CNS) and the Committee of Scientific Advisors (CSA) of the International Osteoporosis Foundation (IOF)

Osvaldo Daniel Messina[1,2] · Maritza Vidal[3] · Jorge A Morales Torres[4] · Luis Fernando Vidal[3,5] · Constanza Arguissain[1] · Rosa María Pereira[6,7] · Patricia Clark[2,8] · Sonia Cerdas Perez[9,10] · Claudia Campusano[2,11] · Marise Lazaretti-Castro[12] · Cristiano Zerbini[13] · Juan J. Scali[14,15] · Lucia Mendez Sanchez[8] · Maria L. Peralta-Pedrero[16] · Andrea Cavallo[1] · Francisco J. Valdivia Ibarra[17] · Talina Hernandez Pérez[17]

Received: 17 August 2022 / Accepted: 16 September 2022 / Published online: 9 November 2022

Abstract
Guidelines and recommendations developed and endorsed by the International Osteoporosis Foundation (IOF) are intended to provide guidance for particular pattern of practice for physicians who usually prescribe glucocorticoid (GC) therapy, and not to dictate the care of a particular patient. Adherence to the recommendations within this guideline is voluntary and the ultimate determination regarding their application should be made by the physician in light of each patient's circumstances. Guidelines and recommendations are intended to promote a desirable outcome but cannot guarantee any specific outcome. This guideline and its recommendations are not intended to dictate payment, reimbursement or insurance decisions. Guidelines and recommendations are subjected to periodic revisions as a consequence of the evolution of medicine, technology and clinical practice. A panel of Latin American (LATAM) experts specialized in osteoporosis with recognized clinical experience in managing patients with glucocorticoid-induced osteoporosis (GIO) met to produce evidence-based LATAM recommendations for the diagnosis and management of GIO. These guidelines are particularly intended to general practitioners and primary care physicians who prescribe GC treatments in LATAM to guide their daily clinical practice in terms of evaluation, prevention and treatment of GIO. These recommendations were based on systematic literature review using MEDLINE, EMBASE, SCOPUS and COCHRANE Library database during the period from 2012 to 2021. Randomized clinical trials (RCT), systematic reviews of RCT, controlled observational studies, guidelines and consensus were considered. Based on the review and expert opinion the panel members voted recommendations during two successive rounds of voting by panel members. Agreements for each statement were considered if a concordance of at least 70% was achieved following Delphi methodology. Grading of recommendations was made according to the Oxford Centre for the Evidence-based Medicine (EBM) criteria. Among five GIO guidelines and consensus initially identified, two of them (American College of Rheumatology 2017 and the Brazilian Guidelines 2021) were selected for comparison considering the latter as the most current guides in the LATAM region. Based on this methodology fifty statements were issued. All of them but four (1.20, 1.21, 1.23 and 4.2) attained agreement.

Keywords Osteoporosis · Glucocorticoids · Guideline · Prednisone · Adverse effects · Bone density

Rosa Maria Pereira: Deceased.

Extended author information available on the last page of the article

Introduction

Glucocorticoid (GC) therapy is widely used in daily clinical practice to treat several diseases such as chronic arthritides, connective tissue disorders, chronic pulmonary and inflammatory bowel diseases, among many others. It is estimated that 1–2% of the population is receiving long-term GC therapy. Most frequent prescribers are internal medicine specialists, rheumatologists, immunologists, general practitioners, gastroenterologists, pulmonologists and dermatologists [1].

Daily oral doses as low as 2.5 mg of prednisone for more than 3 months can impair bone integrity even at higher bone mineral density values when compared to patients with postmenopausal osteoporosis. Population at risk, identified based on the dose and duration of GC therapy should be stratified according to FRAX® (Fracture Risk Assessment Tool) values, major osteoporotic fracture, prior fractures and bone mineral density (BMD) values [2–6]. In glucocorticoid-induced osteoporosis (GIO) the risk of fracture occurs with higher BMD values than those that occur in postmenopausal osteoporosis. The risk of fractures increases with advancing age and previous fragility fractures [5].

Three countries in LATAM have published guidelines for the prevention and treatment of GIO, two of them, several years ago (Mexico and Argentina) and Brazil, with a recent update in 2021 in Brazil [7–9], however, the majority of the Latin American countries does not have any specific guidelines for GIO. GC are widely used in daily clinical practice in our region as we share similarities in our health care systems, diagnostic resources, therapeutic armamentarium availability and access to health care that may be different than in other regions of the world. This led us to gather a panel of clinical experts in the field representing several countries of the region (Argentina, Brazil, Chile, Costa Rica, Mexico and Peru). The working group included different clinical specialties (rheumatology, endocrinology, dermatology, family medicine, internal medicine and epidemiology). This group was designed to evaluate, update and modify when needed the current recommendations about diagnosis, prevention and treatment of GIO that are widely disseminated and accepted internationally.

Aims and scope

The aim of this guideline is to provide meaningful evidence-based recommendations directed to physicians who usually prescribe oral or inhaled GC, to guide their daily clinical practice in terms of evaluation, prevention and treatment of GIO. The application of these guidelines will lead to an evident benefit to patients who require chronic treatment with supraphysiological doses of GC. It is important to highlight that performing of these guidelines are warranted due to several differences in diagnostic and therapeutic tools between LATAM countries and other countries with more financial resources and less barriers to access to them. Therefore, adaptation and clinical judgment in specific cases is extremely important, for example, FRAX tool, biochemical markers of bone turnover and trabecular bone score (TBS) are not widely available in some LATAM countries. Particular cases such as patients with renal or hepatic insufficiency were not included. In any case, the purpose is to guide decision-making during daily practice, but the final clinical decision will be at the physician's best knowledge, experience and criteria in each determined clinical setting. These guidelines will be updated every 3–5 years following the evolving new medical knowledge.

Methods

An expert committee in osteoporosis with broad representation and experience from LATAM countries were gathered to review and evaluate the most recent guidelines and relevant literature published to develop a list of recommendations based on the best evidence, and carry out a Delphi Consensus with a larger group of experts panel from different specialties [10, 11].

There were two zoom meetings to update assessments related to prevention, diagnosis and treatment of GIO in males and females. Two bibliographic searches from the medical literature were carried out, the first one to find all relevant guidelines and specific consensus for prevention and treatment of GIO between 2012 and 2021. The second search was conducted after the selection of the guidelines to find relevant systematic reviews or primary studies to cover prevention and treatment.

Electronic databases searched were MEDLINE, EMBASE, SCOPUS and COCHRANE. The following key words were used: osteoporosis, glucocorticoids, guideline, prednisone, adverse effects, bone density, fractures, spinal fractures, vertebral fractures, osteoporosis prevention, osteoporosis treatment, calcium, vitamin D, vitamin D deficiency, calcitriol, lifestyle, alcohol consumption, smoking, exercise, training, DXA, TBS, radiography, alendronate, bisphosphonates, risedronate, ibandronate, zoledronic acid, teriparatide, denosumab, romosozumab, men, premenopausal women, pregnancy, lactation, breastfeeding, children, adolescence. Randomized clinical trials (RTC), systematic reviews of RTC's and guidelines were primarily the designs considered to review.

Based on the first search, six recent published guidelines were found (Pereira RM 2021, Buckley L 2017, Compston J 2018, Laurent MR 2022, Park SY 2018 and Weare-Regales N 2021) [6, 7, 12–15]. After reviewing all of them, two were

Table 1 Comparison of ACR 2017 and Brazilian 2020 guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis

	ACR Guide 2017	Brazilian Guide 2020
Who should start prevention/treatment of GIOP?	All adults taking prednisone ≥2.5 mg/day for ≥3 months	All adults taking prednisone ≥5 mg/day for ≥3 months
Lifestyle changes for prevention/treatment of GIOP?	Smoking cessation; adequate diet; limit alcohol intake; weight bearing exercise	Smoking cessation; limit alcohol intake; avoid low body weight and sedentarism
Calcium/Vitamin D intake optimized to:	1000 to 1200mg/600 to 800IU per day. Reach serum 25OHD of 20 ng/mL	1000mg/500IU per day
Perform risk evaluation	Within 6 months of starting GC	Within 3 months of starting GC
BMD test to whom?	Adults <40 years with a history of fragility fracture or severe risk factors All adults >40 years	All the patients
Fracture risk stratification		
FRAX to evaluate fracture risk (Adults ≥ 40 years)	FRAX with GC dose adjustment	Brazilian FRAX model
High fracture risk	Prior fragility fracture T-Score ≤-2.5 10-year risk of MOF ≥20% or HF ≥3%	Not available
Moderate fracture risk	10-year risk of MOF 10-19% or HF >1% and <3%	Not available
Low fracture risk	10-year risk of MOF <10% or HF ≤1%	Not available
Adults <40 years		
High fracture risk	Prior fragility fracture	Not available
Moderate fracture risk	Hip or spine Z-Score <-3, or rapid bone loss (≥ 10% in 1 year) and continuing GC ≥7.5mg/day ≥6 months	Not available
Low fracture risk	None of the above risk factors	Not available
BMD threshold to prevent or treat men on GC	Not available	Prevention: T-score ≤-1 Treatment: T-score ≤-1.9
Vertebral fracture detection	Clinical assessment	X-Ray or DXA vertebral fracture assessment
Recommendations for special populations		
Children	Included	Included
Women of childbearing potential	Included	Included
People with organ transplant	Included	Not included
Patients on inhaled GC	Not included	Included
Patients on IV pulse GC	Not included	Included
Preferred initial pharmacological intervention for patients with moderate/high fracture risk	Oral bisphosphonates	Not stated
IV-Bisphosphonates; teriparatide; denosumab	Recommended for prevention and treatment	Recommended for prevention and treatment
Duration of pharmacological intervention	Discussed	Discussed
Definition of treatment failure	Discussed	Not discussed

GC Glucocorticoid, *BMD* Bone mineral density, *25OHD* 25-hydroxyvitamin *D, MOF* Major osteoporotic fracture, *HF* Hip fracture. Table adapted from references [6, 9]

selected as the most appropriated to use for this study: the ACR 2017 and the Brazilian Guidelines 2021, since these guidelines were considered the most complete and updated [6, 9]. Comparative aspects of ACR and the Brazilian guidelines are depicted in Table 1, to highlight the similarities and differences between these two guidelines (See Table 1).

A list of fifty recommendations was chosen and developed for consensus within the group of experts. From these, 26 were selected and updated from the Brazilian guidelines, 14 from the ACR guidelines and 10 were de novo statements. The novo recommendations were formulated from the updated literature up to 2022. Questions, level of evidence and recommendations were identified preserving the level of evidence and strength of recommendation published in the original guidelines; grading of the recommendations based on the strength of scientific evidence of the studies was made according to the criteria of the Oxford Centre for the Evidence-based Medicine (EBM) [10]. These recommendations (statements) were submitted to the expert panel members for two successive voting rounds according to Delphi methodology (looking for at least a 70% of agreement for each statement). Evidence-based recommendations were submitted to the panel expert for a consensus according to Delphi methodology [11]. Every recommendation and statement were scored by each member according to Likert Scale from 1 (absolutely in agreement) to 5 (absolutely in disagreement) [16]. The recommendations were sent by electronic mail to the group of experts. Recommendations were classified into four categories: preventive measures, follow-up and subsequent evaluation risk, diagnostic procedures and treatment.

Results

Recommendations

1.0 Preventive measures

Preventive measures and basal work-up in patients who will start GC therapy or continuing GC therapy should include initial evaluation of risk factors. Clinical actions should be taken in patients who will receive treatment with GC for more than 3 months. Inhaled and topical GC, although not innocuous at high doses, showed a less deleterious effects on bone than oral GC and should be preferred, when possible, over oral GC [6, 9, 17–19].

1.1 Taking 2.5 mg/day of prednisone or equivalent for at least 3 months, orally, is the minimum GC dose that indicates an increased risk of fracture, for which preventative measurements should be prescribed [**Grade A**] [1–5].

1.2 Clinical risk factors are useful to predict the risk of fracture in patients taking GC, including low body mass index (< 19 kg/m^2), history of previous fractures, familial history of hip fractures, alcohol abuse or tobacco consumption, rheumatoid arthritis and other conditions that affect bone health [**Grade B**] [6, 9].

1.3 Daily dose of GC correlate with relative risk of fractures (from a RR of 1.55 to 5.18 with doses of 2.5 to higher than 7.5 mg of prednisone) [**Grade A**] [2].

1.4 Patients receiving inhaled GC (IHGC) need to be evaluated to detect low BMD as do patients receiving oral GC, although IHGC have a less deleterious effect on bone. Oral GC should be replaced by IHGC when possible [**Grade B**] [18, 20].

1.5 Individuals taking larger doses of GC (> 7.5 mg/day prednisone or equivalent) that exceed the intervention threshold based on GC dose-adjusted FRAX® tool, should be considered for bone protective therapy [**Grade B**] [1–6, 21–25].

1.6 Patients facing the need to receive long-term GC should be evaluated with BMD testing at lumbar spine, proximal femur and non-dominant radius [**Grade A**] [6, 9, 12–17, 22, 26, 27, 29, 30].

1.7 Trabecular bone score (TBS) is potentially useful in the evaluation of bone status and risk fracture in patients receiving GC, although access is limited and the technique is not considered mandatory [**Grade D**] [31, 32].

1.8 Biochemical markers of bone turnover are useful but not essential to determine initial risk in patients receiving GC [**Grade D**] [33–35].

1.9 Initial evaluation in patients who start long-term treatment with GC should include assessment of GC dose, duration and patterns of use, as well as a history of fractures, falls, frailty and other risk factors for fractures. General laboratory tests should include evaluation of existing comorbidities, as suggested by the history and physical exam [**Grade A**] [6, 8, 9, 12, 13, 15, 17, 22, 27, 28, 34, 36].

1.10 Calcium and vitamin D supplementation should be considered because of the reduction in intestinal calcium absorption due to GC therapy [37]. Calcium supplements are required in those individuals whose intake is below 1000 mg of dietary calcium per day. Calcium carbonate or citrate should be supplemented in those patients who do not fulfill this dietary intake [**Grade A**] [6, 8, 9, 12–15, 17, 22, 27, 28, 38–41].

1.11 Non-active (cholecalciferol and ergocalciferol) and active (alfacalcidol and calcitriol) forms of vitamin D administered concomitantly, are useful to prevent bone mass loss in chronic users of GC [**Grade A**] [6, 9, 22, 28, 38, 40, 42–44].

1.12 The recommended dose of vitamin D in patients with GIO is 1000 to 2000 IU/day, with the goal of reaching a serum level of 25-hydroxyvitamin D (25OHD) of 30 ng/mL [**Grade B**] [6, 9, 28, 38, 40].

1.13 Regular weight-bearing exercise is recommended for the management of every patient at risk of GIO as it

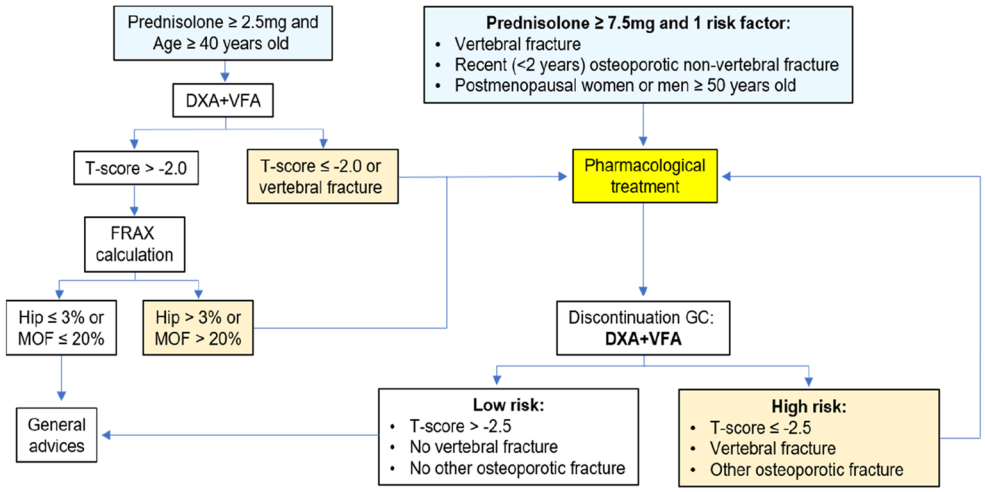

Fig. 1 Algorithm of diagnosis and management of glucocorticoid-induced osteoporosis. For women age 70 years and above, the intervention threshold set by NOGG is a MOF 10-year probability of 20% (or hip fracture probability of 4.8%) Assessment thresholds between which a BMD test would be undertaken to refine the probability assessment lie between 11 and 24%. Figure adapted from original article of Messina et al. [22]

brings improvements in BMD and a decrease in the risk of falling (data are extrapolated from the primary osteoporosis recommendations) [**Grade B**] [45–52].

1.14 Lifestyle recommendations such as avoiding smoking, alcohol excess consumption, sedentary lifestyle and low body weight (BMI < 19 kg/m^2) should be indicated to every patient at risk of GIO (as per primary osteoporosis recommendations) [**Grade B**] [53].

1.15 The association of calcium and vitamin D is preferred to either of them alone in patients with GIO [**Grade A**] [6, 8, 9, 12–17, 22, 27, 28, 36, 38–40].

1.16 FRAX with GC adjustment assessment should be used to determine fracture risk and define the need of pharmacological therapy to prevent GIO in patients 40 years and older [**Grade A**]. (See Fig. 1) There are no tools available to evaluate absolute risk in children and patients younger than 40 years old. In these populations, the main risk factors are history of previous fractures and BMD values [**Grade B**] [6, 9, 21–23, 28]. The FRAX tool has been calibrated in seven LATAM countries (Mexico, Argentina, Chile, Ecuador, Brazil, Colombia and Venezuela). However, it is highly advisable to apply local FRAX values for those

Table 2 Risk stratification of fractures in adults receiving GC therapy from ACR guidelines

Fracture risk	High	Moderate	Low
Adults <40 years	History of osteoporotic fracture(s)	Hip or spine Z score <-3 or Rapid bone loss of ≥10% (at the hip or spine) over 1 year and Continuing GC treatment of ≥7.5 mg/day for ≥6 months	None of the above risk factors other than GC treatment
Adults ≥40 years	History of osteoporotic fracture(s) Hip or spine T-score ≤ -2.5 in men age ≥50 years and postmenopausal women FRAX® (GC adjusted) 10-year risk of major osteoporotic fracture ≥20% FRAX® (GC adjusted) 10-year risk of hip fracture ≥3%	FRAX® (GC adjusted) 10-year risk of major osteoporotic fracture 10 - 19% FRAX® (GC adjusted) 10-year risk of hip fracture >1% and < 3%	FRAX® (GC adjusted) 10-year risk of major osteoporotic fracture <10% FRAX® (GC adjusted) 10-year risk of hip fracture ≤1%

Table adapted from Buckley L et al. [6]

countries of the LATAM region where this useful tool was validated locally [23, 24, 54].

1.17 An increased risk for fractures in patients younger than 40 years old should be determined according to *Z* score < -3, or rapid bone loss (> 10% in spine or hip in one year) and continuing treatment with GC for more than 6 months [**Grade B**] [6, 9, 12, 26, 55, 56] (See Table 2).

1.18 DXA measurement is recommended in children and teenagers who will start treatment with GC at a dose > 0.16 mg/kg/day or those who have received four or more systemic GC courses [**Grade A**] [6, 9, 12, 22, 55].

1.19 FRAX values should be increased in a relative value of 15% for major OP fractures and 20% for hip fractures in relation to GC dose [**Grade B**] [21].

1.20 Patients who will use GC for over 3 months at a dose of 2.5 mg or higher should be studied with BMD testing (lumbar spine, femoral neck and if possible, forearm) when starting GC therapy [**Grade A**] [6, 9, 15, 22]. BMD testing should be performed at least yearly in patients receiving long-term GC [**Grade C**] [2, 6, 9, 22, 28].

1.21 Spinal radiograph (thoracic lateral view and lumbar spine) or vertebral fracture assessment (VFA) should be performed at the start of GC therapy (if daily dose is expected to be 2.5 mg/day or higher for at least 3 months) and every 6 months during the first year and annually later [**Grade A**] [4, 6, 9, 22].

1.22 In men, a spine or femoral neck *T* score < − 1.0 should be an indicator for prevention and a *T* score < − 1.9 for starting treatment [**Grade C**] [2, 57].

1.23 Biochemical markers of bone turnover may be useful but are not essential to manage patients with GIO [**Grade D**] [33–35].

1.24 Bone densitometry should be performed in children and adolescents who will initiate GC therapy (prevention at prednisone doses > 0.16 mg/kg/day and in those who have undergone four or more courses of systemic GC). BMD testing should be performed at the beginning of GC use and as a control to assess lumbar spine and whole body (excluding the head). The term "low bone mass" should be used instead of "osteopenia" or "osteoporosis", and the *Z* score rather than the *T* score should be used. Monitoring and follow-up should be based on the bone mineral content rather than on bone mineral density because BMD is affected by bone area [**Grade B**] [4, 6, 9, 12, 22, 55].

1.25 Alendronate at a dose of 70 mg weekly may be used to prevent and treat GIO because it increases bone mass [**Grade A**] [6, 9, 12, 27, 43, 58, 59].

1.26 Risedronate may be used for prevention and treatment of GIO because it increases bone mass and reduces vertebral fractures in up to 70% of patients [**Grade A**] [60].

1.27 Alendronate, at a dose of 5–10 mg/day can be used to prevent and treat GIO in men, with evidence of a reduction of bone loss but no reduction on vertebral fractures. Risedronate at a dose of 5 mg/day reduces bone loss and vertebral fractures in as much as 82.4%. Bisphosphonates have some benefits in reducing non-vertebral fractures [**Grade A**] [6, 9, 60].

1.28 Zoledronic acid at a dose of 5 mg/year may be used to prevent and treat GIO, with evidence of an increase in BMD at lumbar spine and proximal femur although this increase did not reduce significantly the occurrence of new fractures [**Grade B**] [6, 9, 61].

1.29 Teriparatide at a dose of 20mcg/day administered subcutaneously may be considered both for prevention and treatment of GIO in women and men. Hirooka et al. published a 48 months sequential study including 47 patients compared teriparatide during 2 years followed by 2 years of denosumab vs denosumab from the beginning of the study in GIO showing higher BMD increments in the teriparatide–denosumab group [**Grade B**] [62–64].

1.30 Teriparatide should be indicated as a first therapeutic agent in GIO when there is a history of previous fracture and a *T* score < − 3.0. Teriparatide reduce the risk of vertebral fractures but does not have the same effect in non-vertebral fractures. In patients at a very high fracture risk, it is recommended an anabolic agent first and then maintenance with an antiresorptive agent [**Grade A**] [6, 9, 22, 61, 66, 67].

1.31 Denosumab administered subcutaneously 60 mg every 6 months may be considered for both prevention and treatment of GIO in adult patients and showed to be superior to risedronate [**Grade A**] [62, 63].

1.32 In premenopausal women treated with GC, the need for treatment should be decided considering not only BMD, but also the occurrence of previous fractures, dose of GC, estimated time on GC therapy and childbearing potential [**Grade A**] [68, 69]. Bisphosphonates must be used with caution in premenopausal women with a possibility of pregnancy [69–72]. In postmenopausal women, evidence from large population clinical studies, although not focused on GIO, show a decrease in non-vertebral fractures. Other publications demonstrated that teriparatide, zoledronic acid and denosumab increase hip BMD more than other agents [**Grade B**] [65, 66, 73].

Table 3 Fracture risk reassessment in patients receiving GC [6, 9, 15, 65]

Consider FRAX® and BMD testing every 2 years in patients with these conditions
• Very high dose of GC
•History of osteoporotic fracture
•Z score < − 3.0 in < 40 years or T score < − 2.5 in > 40 years or older
• > 10% bone loss in hip or spine
•In patients already receiving treatment for osteoporosis (OP)
- Osteoporotic fracture at least 18 months after the beginning of OP treatment in > 40 years
- Patients with poor adherence to treatment or poor gastrointestinal absorption
- Other risk factors as malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use (at ≥ 3 units/day) or smoking
- After completing the OP treatment

2.0 Follow-up and subsequent evaluation of risk

2.1 Patients must be evaluated by DXA every 12–24 months at lumbar spine and femoral neck except in the case of very high doses of GC in organ transplantation recipients who may have very rapid bone loss. In this case an evaluation after 6 months of GC treatment may be warranted [**Grade B**] [6, 9, 22, 28] (See Table 3).

2.2 Biochemical markers of bone turnover, although useful, are not essential for follow-up [**Grade C**] [26, 27, 35].

3.0 Diagnostic procedures

3.1 All the patients who start GC therapy for more than 3 months (2.5 mg of prednisone or equivalent daily) should have a BMD test at lumbar spine and proximal femur [**Grade A**] [2, 6, 9, 22, 36]. Non-dominant radius BMD may be useful considering that BMD may decrease earlier than vertebral BMD and that increased vertebral bone marrow adiposity may bias BMD measurement in patients receiving GC [**Grade D**] [29, 30]. DXA may underestimate the risk of fracture in patients treated with glucocorticoids, this artifact may be counteracted by TBS technique [31, 32, 74].

3.2 All patients should be evaluated by FRAX according to the correction coefficient of GC doses at the beginning of GC therapy [**Grade A**] [5, 21].

3.3 Bone densitometry evaluation (lumbar spine, proximal femur) is warranted in patients who receive high

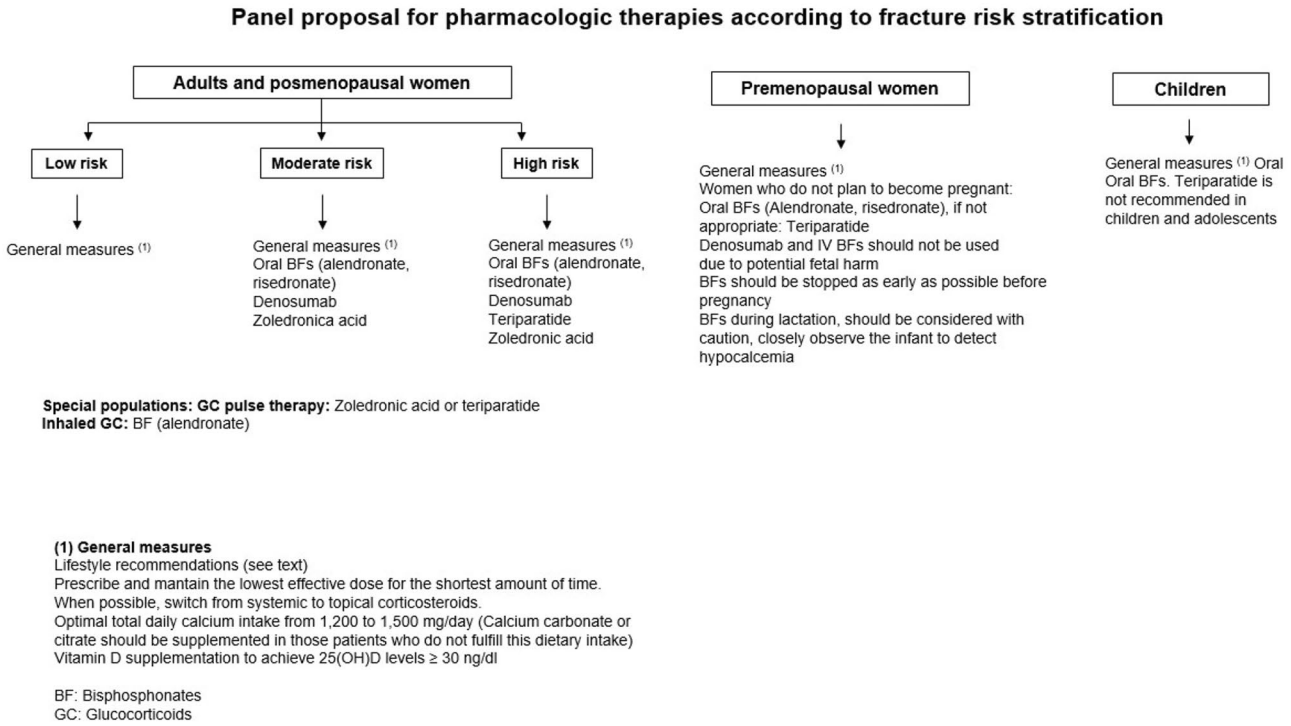

Fig. 2 The LATAM GIO panel proposal for pharmacological therapies according to fracture risk stratification

GC doses before and yearly after organ transplantation [**Grade A**] [6, 9, 12, 17, 22, 75–77].

3.4 TBS is a useful tool that increases the diagnostic accuracy but is neither essential nor indispensable to study patients on GC therapy. However, TBS may be useful to measure trabecular BMD in patients receiving GC to avoid the artifact that may introduce variations in bone marrow fat into vertebral bodies. Comparative studies between whole vertebral BMD and TBS showed TBS utility in these cases [**Grade B**] [29, 31, 32, 77].

4.0 Treatment

4.1 Bisphosphonates may be used continuously if GC treatment is maintained and the patient has a moderate to high risk of fracture according to FRAX tool [**Grade B**]. If GC are discontinued, the interruption of osteoporosis drug treatment may be recommended if fracture risk is low according to FRAX tool [**Grade B**] [6, 9, 12, 17, 21, 25, 73]. (See Fig. 2).

4.2 Considering the lack of evidence regarding the safety of bisphosphonates during pregnancy such drugs should be avoided or carefully used only in specific cases [**Grade C**] [69, 78–81].

4.3 Bisphosphonates should be stopped as early as possible before pregnancy and be used with special attention to contraception in girls [**Grade C**] [69, 80, 81].

4.4 Administration of bisphosphonates during lactation, should be considered with caution depending on the fracture risk being imperative to closely observe the infant to detect hypocalcemia [**Grade B**] [69, 81].

4.5 Treatment of GIO in children must include calcium and vitamin D [**Grade B**] [6, 9, 12, 38, 40, 41].

4.6 Teriparatide is not recommended in children and adolescents [**Grade D**] [56].

4.7 Patients treated with GC pulse therapy (methylprednisolone 250 mg orally or 250–1000 mg IV for 3 days) are at high risk of bone loss and fractures, especially with inflammatory diseases and other risk factors. Zoledronic acid or teriparatide may be indicated in these patients [**Grade B**] [6, 9, 36, 39, 61–63, 65–67].

4.8 Denosumab is approved for the treatment of GIO, and it has showed to increase bone mineral density and reduce bone turnover markers in patients with rheumatoid arthritis receiving GC. Discontinuation of denosumab results in a rebound effect and should be followed by any other antiresorptive agent [**Grade B**] [82–84].

4.9 Denosumab is useful in organ transplantation patients but should be used with caution after kidney transplantation due to increase in the incidence of infections [**Grade C**] [9, 85].

4.10 Clinical studies have shown that IHGC, mainly triamcinolone, could affect bone mass in a dose-dependent manner although to a lesser extent than oral GC. Reports on the effects of inhaled GC on fracture risk are limited. Bisphosphonates showed a positive effect and can be used for treatment in these patients [**Grade C**] [6, 9, 20, 86].

4.11 Calcium and vitamin D administration must be assured in these patients [**Grade C**] [6–9, 22, 38–41].

4.12 Romosozumab is a new bone forming agent that inhibits sclerostin and showed its efficacy to treat postmenopausal osteoporosis. To date there are no clinical trials about its efficacy on GIO [**Grade D**] [57].

After voting rounds all the statements, except 1.20, 1.21, 1.23 and 4.2, attained agreement.

Summary and final remarks

These GIOP guidelines are intended to be applied by physicians who practice in LATAM countries considering the limitations and restrictions in diagnostic and therapeutic tools in the region. Glucocorticoids are prescribed by general practitioners, internists, family physicians, rheumatologists, pneumonologists, allergy specialist among others. Patients receiving doses as low as 2.5 mg of prednisone or equivalent daily for more than 3 months should be considered for prevention and eventually for treatment.

FRAX is a very useful diagnostic tool in those countries that have FRAX validated in their population. Clinical risk factors evaluation is useful even in the case that FRAX tool have not been validated. Diagnostic measures and work-up should include minimally a complete clinical evaluation, thoracic and lumbar lateral view spine radiographs or vertebral fracture assessment to find vertebral fractures, and registering any previous appendicular fracture.

Complementary tests including calcium, phosphorus and 25-hydroxyvitamin D level, as well as biochemical markers of bone turnover are seldom available in LATAM countries and are not essential for the initial evaluation. Bone mineral density should include DXA evaluation of lumbar spine and proximal femur. Non-dominant radius DXA evaluation may be useful although not essential for the diagnosis.

Prevention measures should include adequate dietary calcium intake (1000 mg per day), maintaining levels of 25-hydroxyvitamin D above 30 ng/mL and aerobic weight-bearing exercises, avoiding of smoking and alcohol consumption.

Pharmacological treatment should include bone acting agents in the following cases:

- Patients with previous fractures
- Patients with moderate or high fracture risk according to FRAX tool

- Patients with low bone mineral density at lumbar spine and/or proximal femur (in patients older than 40 years of age T score < − 2.5 or, in patients younger than 40 years old Z score < − 3.0, rapid bone loss > 10% in 1 year or continuing GC > 7.5 mg/day for ≥ 6 months)
- Bone acting agents include antiresorptives such as oral bisphosphonates, alendronate and risedronate, IV zoledronic acid and denosumab
- Denosumab showed superiority when compared to risedronate
- Bone forming agent include teriparatide daily for 24 months
- In patients with previous fracture and very low BMD (*T* score < − 3.0) teriparatide, zoledronic acid and denosumab are preferred
- Patients should be evaluated annually and in the case of very high doses of GC (organ transplantation) a DXA measurement at 6 months after the basal evaluation is recommended
- These guidelines were planned to emphasize the importance of early risk assessment and interventions to prevent bone damage in patients receiving glucocorticoids

Acknowledgements This manuscript has been endorsed by the Committee of National Societies (CNS) and by the Committee of Scientific Advisors (CSA) of the International Osteoporosis Foundation (IOF)

Funding The authors have no financial or proprietary interests in any material discussed in this article.

Declarations

Conflict of interest OD Messina received honoraria from Amgen, E Lilly and Pfizer. S Cerdas Perez received honoraria from Amgen, Novo Nordisk, MSD, AstraZeneca and Faes Farma. The other authors declare no conflict of interests.

References

1. Walsh LJ, Wong CA, Pringle M et al (1996) Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 313:344–346
2. Van Staa TP, Leufkens HG, Abenhaim L et al (2000) Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15:993–1000
3. Van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13:777–787
4. Van Staa TP, Laan RF, Barton IP et al (2003) Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 48:3224–3229
5. Kaji H, Yamauchi M, Chihara K et al (2006) The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid-induced osteoporosis. Endocr J 53:27–34
6. Buckley L, Guyatt G, Fink HA et al (2017) American college of rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 69:1095–1110
7. Gobierno Federal del Estado de México (2012) Norma oficial mexicana NOM-035-SSA2–2012 para la prevención y control de enfermedades en la perimenopausia y postmenopausia de la mujer. Criterios para brindar atención médica. Secretaria de Salud-Gobierno Federal del Estado de México. SEGOB. Diario oficial de la federación. https://dof.gob.mx/nota_detalle.php?codigo=5284235&fecha=07/01/2013#gsc.tab=0
8. Messina OD, Somma LF, Tamporenea MI et al (2016) Guías para el diagnóstico, la prevención y el tratamiento de la osteoporosis inducida por glucocorticoides en el adulto. Actual Osteol 12:107–25
9. Pereira RM, Perez MO, Paula AP et al (2021) Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: an update of Brazilian society of rheumatology (2020). Arch Osteoporosis 16:1–16
10. OCEBM Levels of Evidence Working Group*. "The Oxford Levels of Evidence 2" Oxford Centre for Evidence-Based Medicine. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence * OCEBM Levels of evidence working group = Jeremy Howick, Jain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson
11. Boulkedid R, Abdoul H, Loustau M et al (2011) Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS ONE 6:e20476
12. Compston J, Cooper A, Cooper C et al (2017) National Osteoporosis Guideline Group (NOGG) UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 12:43
13. Laurent MR, Goemaere S, Verroken C et al (2022) Prevention and treatment of glucocorticoid-induced osteoporosis in adults: consensus recommendations from the belgian bone club. Front Endocrinol 13:908727
14. Park SY, Gong HS, Kim KM et al (2018) Korean guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. J Bone Metab 25:195–211
15. Weare-Regales N, Hudey SN, Lockey RF (2021) Practical guidance for prevention and management of glucocorticoid-induced osteoporosis for the allergist/immunologist. J Allergy Clin Immunol Pract 9:1841–1850
16. Preedy VR, Watson RR (2010) 5-Point Likert Scale. In: Ronald R (ed) Handbook of disease burdens and quality of life measures. Springer, New York
17. Duru N, van der Goes MC, Jacobs JW et al (2013) EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 72:1905–1913
18. Chalitsios C, Shaw D, McKeever TM (2021) Risk of osteoporosis and fragility fractures in asthma due to oral and inhaled corticosteroids: two population—based nested case-control studies. Thorax BMJ 76:21–28
19. Egeberg A, Schwartz P, Harslof T et al (2021) Association of potent and very potent topical corticosteroids and the risk of osteoporosis and major osteoporotic fractures. JAMA Dermatol 157:275–282
20. Gonzalez AV, Coulombe J, Ernst P et al (2018) Long-term use of inhaled corticosteroids in COPD and the risk of fracture. Chest 153:321–328
21. Kanis JA, Hans D, Cooper C et al (2011) Task force of the FRAX Initiative Interpretation and use of FRAX in clinical practice. Osteoporos Int 22:2395–2411
22. Messina OD, Vidal LF, Vidal M et al (2021) Management of glucocorticoid-induced osteoporosis. Aging Clin Exp Res 33:793–804

23. Morales Torres JA, Clark PE, Deleze-Hinojosa M et al (2010) Fracture risk assessment in Latin america: is FRAX an adaptable instrument for the region? Clin Rheumatol 29:1085–1091
24. Clark PE, Denova Gutierrez E, Zerbini C et al (2018) FRAX-based intervention and assessment thresholds in seven latin American countries. Osteoporos Int 29:707–715
25. Kanis JA, Harvey NC, Johansson H et al (2020) A decade of FRAX: how has it changed the management of osteoporosis? Aging Clin Exp Res 32:187–196
26. Shuhart CR, Yeap SS, Anderson PA, et al. (2019) Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA Cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. J Clin Densitom. 22 4 453 71
27. Lekamwasam S, Adachi JD, Agnusdei D et al (2012) A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 23:2257–2276
28. Adami G, Saag KG (2019) Glucocorticoid-induced osteoporosis: 2019 concise clinical review. Osteoporosis Int 30:1145–1156
29. Ferrau F, Giovinazzo S, Messina E et al (2020) High bone marrow fat in patients with Cushing's syndrome and vertebral fractures. Endocrine 67:172–179
30. Xiaojuan L, Schwartz AV (2020) MRI assessment of bone marrow composition in osteoporosis. Curr Osteoporos Rep 18:57–66
31. Florez H, Hernández-Rodríguez J, Muxi A et al (2020) Trabecular bone score improves fracture risk assessment in glucocorticoid-induced osteoporosis. Rheumatology 59:1574–1580
32. Silva BC, Leslie WD, Resch H (2014) Trabecular bone score: a non-invasive analytical method based upon the DXA image. J Bone Min Res 29:518–530
33. Yamauchi M (2009) Biochemical markers of bone turnover New aspect Biochemical bone markers of bone in patients treated with glucocorticoid. Clin Calcium 19:1092–1100
34. Burshell AL, Möricke R, Correa-Rotter R et al (2010) Correlations between biochemical markers of bone turnover and bone density responses in patients with glucocorticoid-induced osteoporosis treated with teriparatide or alendronate. Bone 46:935–939
35. Jacobsson M, van Raalte DH, Heijboer AC et al (2020) Short-term glucocorticoid treatment reduces circulating sclerostin concentrations in healthy young men: a randomized, placebo-controlled, double-blind study. JBMR plus 4:e10341
36. Briot K, Cortet B, Roux C et al (2014) Bone section of the French society for Rheumatology (SFR) and osteoporosis research information group (GRIO) Update of recommendations on the prevention and treatment of glucocorticoid- induced osteoporosis. J Bone Spine 81:493–501
37. Weaver CM, Alexander DD, Boushey CJ et al (2020) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the national osteoporosis foundation. Osteoporos Int 27:367–376
38. Homik J, Suarez-Almazor ME, Shea B et al (2000) Calcium and vitamin D for corticosteroid-induced osteoporosis cochrane database. Syst Rev 1998:CD000952
39. Rizzoli R, Biver E (2015) Glucocorticoid—induced osteoporosis: who to treat with what agent? Nat Rev Rheumatol 11:98–109
40. Rizzoli R (2021) Vitamin D supplementation: upper limit for safety revisited? Aging Clin Exp Res 33:19–24
41. Rizzoli R (2022) Dairy products and bone health. Aging Clin Exp Res 34:9–24
42. Sambrook P, Birmingham J, Kelly P et al (1993) A comparison of calcium, calcitriol, and calcitonin. N Engl J Med 328:1747–1752
43. Yeap SS, Fauzi AR, Kong NC et al (2008) A comparison of calcium, calcitriol, and alendronate in corticosteroid-treated premenopausal patients with systemic lupus erythematosus. J Rheumatol 35:2344–2347
44. Richy F, Ethgen O, Bruyere O et al (2004) Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int 15:301–310
45. Muir JM, Ye C, Bhandari M et al (2013) The effect of regular physical activity on bone mineral density in post-menopausal women aged 75 and over: a retrospective analysis from the Canadian multicentre osteoporosis study. BMC Musculoskelet Disord 23:253
46. El-Khoury F, Cassou B, Latouche A et al (2015) Effectiveness of two-year balance training programme on prevention of fall induced injuries in at risk women aged 75–85 living in community: Ossébo randomised controlled trial. BMJ 22:h3830
47. Madureira MM, Takayama L, Gallinaro AL et al (2007) Balance training program is highly effective in improving functional status and reducing the risk of falls in elderly women with osteoporosis: a randomized controlled trial. Osteoporos Int 18:419–425
48. de Jong Z, Munneke M, Lems WF et al (2004) Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum 50:1066–1076
49. Zhao R, Zhang M, Zhang Q (2017) The effectiveness of combined exercise interventions for preventing postmenopausal bone loss: a systematic review and meta-analysis. J Sports Phys Ther 47:241–251
50. Schmitt NM, Schmitt J, Dören M (2009) The role of physical activity in the prevention of osteoporosis in postmenopausal women-an update. Maturitas 63:34–38
51. Chow TH, Lee BY, Ang ABF et al (2017) The effect of Chinese martial arts Tai Chi Chuan on prevention of osteoporosis: a systematic review. J Orthop Translat 26:74–84
52. Pongchaiyakul C, Nguyen TV, Kosulwat V et al (2004) Effects of physical activity and dietary calcium intake on bone mineral density and osteoporosis risk in a rural Thai population. Osteoporos Int 15:807–813
53. Seo S, Chun S, Newell MA et al (2015) Association between alcohol consumption and Korean young women's bone health: a cross sectional study from the 2008 to 2011 korea national health and nutrition examination survey. BMJ Open 5:e007914
54. Lopez Gavilanez E, Gavilanes AW, Chedraui P et al (2018) New FRAX-based intervention and assessment thresholds for the Ecuadorian population. Arch Osteoporos 13:1–2
55. Bishop N, Arundel P, Clark E et al (2014) International society of clinical densitometry fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions. J Clin Densitom 17:275–280
56. Ward LM, Rauch F (2018) Anabolic therapy for the treatment of osteoporosis in childhood. Curr Osteoporos Rep 16:269–276
57. Cruse LM, Valeriano J, Vasey FB et al (2006) Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men. J Clin Rheumatol 12:221–225
58. Saag KG, Emkey R, Schnitzer TJ et al (1998) Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis Glucocorticoid-induced osteoporosis intervention study group. N Engl J Med 339:292–299
59. Stoch SA, Saag KG, Greenwald M et al (2009) Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol 36:1705–1714
60. Cohen S, Levy RM, Keller M et al (1999) Risedronate therapy prevents corticosteroid-induced bone loss: a 12-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 42:2309–2318
61. Reid DM, Devogelaer JP, Saag K et al (2009) Zoledronic acid and risedronate in the prevention and treatment of

glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 373:1253–1263
62. Glüer CC, Marin F, Ringe JD et al (2013) Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the Euro GIOPs trial. J Bone Miner Res 28:1355–1368
63. Saag KG, Shane E, Boonen S et al (2007) Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 357:2028–2039
64. Hirooka Y, Nozaki Y, Okuda S et al (2021) 4-year teriparatide followed by denosumab vs continuous denosumab in glucocorticoid-induced osteoporosis patients with prior bisphosphonate treatment. Front Endocrinol 27:753185
65. Curtis EM, Reginster JY, Al-Daghri N et al (2022) Management of patients at very high risk of osteoporosis fractures through sequential treatments. Aging Clin Exp Res 34:695–714
66. Lespessailles E, Chapurlat R (2020) High fracture risk patients with glucocorticoid-induced osteoporosis should get an anabolic treatment first. Osteoporos Int 31:1829–1834
67. Kanis JA, Harvey NC, McCloskey E et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporosis Int 31:1–12
68. Levy S, Fayez I, Taguchi N et al (2009) Pregnancy outcome following in utero exposure to bisphosphonates. Bone 44:428–430
69. Munns CF, Rauch F, Ward L et al (2004) Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. J Bone Miner Res 19:1742–1745
70. Patlas N, Golomb G, Yaffe P (1999) Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 60:68–73
71. Chan B, Zacharin M (2006) Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. J Clin Endocrinol Metab 91:2017–2020
72. Minsker DH, Manson JM, Peter CP (1993) Effects of the bisphosphonate, alendronate, on parturition in the rat. Toxicol Appl Pharmacol 121:217–223
73. Kanis JA, Johansson H, Harvey NC et al (2021) An assessment of intervention thresholds for very high fracture risk applied to the NOGG guidelines: a report for the National Osteoporosis Guideline Group (NOGG). Osteoporos Int 32:1951–1960
74. Sandru F, Carsote M, Dumitrascu MC et al (2020) Glucocorticoid and trabecular bone score. J Med Life 13:449–453
75. Brunova J, Kratochvilova S, Stepankova J (2018) Osteoporosis therapy with denosumab in organ transplant recipients. Front Endocrinol 9:162
76. Kageyama G, Okano T, Yamamoto Y et al (2016) Very high frequency of fragility fractures associated with high-dose glucocorticoids in postmenopausal women: a retrospective study. Bone Rep 17:3–8
77. McCloskey EV, Chotiyarnwong P, Harvey NC et al (2022) Population screening for fracture risk in postmenopausal women—a logical step in reducing the osteoporotic fracture burden? Osteoporos Int. https://doi.org/10.1007/s00198-022-06419-6
78. Green SB, Pappas AL (2014) Effects of maternal bisphosphonate use on fetal and neonatal outcomes. Am J Health Syst Pharm 71:2029–2036
79. Yarrington JT, Capen CC, Black HE et al (1976) Experimental parturient hypocalcemia in cows following prepartal chemical inhibition of bone resportion. Am J Pathol 83:569–588
80. French AE, Kaplan N, Lishner M et al (2003) Taking bisphosphonates during pregnancy. Can Fam Physician 49:1281–1282
81. Stathopoulos IP, Liakou CG, Katsalira A et al (2011) The use of bisphosphonates in women prior to or during pregnancy and lactation. Hormones (Athens) 10:280–291
82. Saag KG, Wagman RB, Geusens P et al (2018) Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. Lancet Diabetes Endocrinol 6:445–454
83. Saag KG, Pannacciulli N, Geusens P et al (2019) Denosumab versus risedronate in glucocorticoid-induced osteoporosis: final results of a 24-month randomized, double-blind. Double-Dummy Trial Arthritis Rheumatol 71:1174–1184
84. Al Adhoubi NK, Al Salmi I (2021) Safety of denosumab in patients with chronic kidney disease. Saudi J Kidney Dis Transpl 32:1235
85. Scanlon PD, Connett JE, Wise RA et al (2004) Loss of bone density with inhaled triamcinolone in lung health study II. Am J Respir Crit Care Med 170:1302–1309
86. Bianchi ML, Leonard MB, Bechtold S et al (2014) International society for clinical densitometry bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD pediatric official positions. J Clin Densitom 17:281–294

Authors and Affiliations

Osvaldo Daniel Messina[1,2] · Maritza Vidal[3] · Jorge A Morales Torres[4] · Luis Fernando Vidal[3,5] · Constanza Arguissain[1] · Rosa María Pereira[6,7] · Patricia Clark[2,8] · Sonia Cerdas Perez[9,10] · Claudia Campusano[2,11] · Marise Lazaretti-Castro[12] · Cristiano Zerbini[13] · Juan J. Scali[14,15] · Lucia Mendez Sanchez[8] · Maria L. Peralta-Pedrero[16] · Andrea Cavallo[1] · Francisco J. Valdivia Ibarra[17] · Talina Hernandez Pérez[17]

✉ Maritza Vidal
maritzavw@gmail.com

[1] Investigaciones Reumatológicas y Osteológicas (IRO). Collaborating Centre WHO, Buenos Aires, Argentina

[2] International Osteoporosis Foundation (IOF), Latin America Region
https://www.osteoporosis.foundation/

[3] Centro de Diagnóstico de Osteoporosis y Enfermedades Reumáticas (CEDOR), Lima, Peru

[4] Hospital Aranda de La Parra. Leon, Guanajuato, Mexico

[5] Chair of the Regional Advisory Council for Latin America – International Osteoporosis Foundation (IOF), Lima, Peru

[6] Hospital das Clinicas, School of Medicine, University of São Paulo (HCFMUSP), São Paulo, Brazil

[7] Regional Advisory Council Member-International Osteoporosis Foundation (IOF), Sao Paulo, Brazil

[8] Hospital Federico Gomez School of Medicine UNAM, Mexico City, Mexico

[9] Department of Endocrinology, Hospital CIMA, San José, Costa Rica

[10] Professor of Endocrinology, University of Costa Rica, San José, Costa Rica

[11] Universidad de Los Andes, Associate Professor, Santiago de Chile, Chile

[12] Escola Paulista de Medicina, São Paulo, Brazil

[13] Centro Paulista de Investigação Clinica, São Paulo, Brazil

[14] Hospital C Durand, Buenos Aires, Argentina

[15] Sociedad Iberoamericana de Osteología y Metabolismo Mineral (SIBOMM)-President, Mexico City, Mexico

[16] Professor of Medicine UNAM, Mexico City, Mexico

[17] IMSS, Mexico City, Mexico

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com