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Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Glucocorticoid-induced Osteoporosis

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A B S T R A C T

Background: Patients receiving long-term glucocorticoid therapy are at risk of developing GIOP. However, until today, there is still no guideline that specifically explains how to diagnose and manage GIOP patients in Indonesia. **Methods:** 10 selected rheumatologists from the Indonesian Rheumatologist Association (IRA) made recommendations based on key questions formed by a steering committee from IRA. These recommendation materials were taken from several online databases such as Pubmed, Science Direct, and Cochrane. Level of evidence and grades of recommendation were then assigned, and every member of the panelist team will assign a score for the level of agreement. **Results:** A total of 17 recommendations regarding screening, prevention, diagnosis, therapy, and monitoring for GIOP were made. **Conclusion:** These recommendations can be used for adult patients receiving long-term glucocorticoids with or at risk of developing GIOP. The prevention measure, diagnostic, therapy, and monitoring algorithm in this recommendation are all created with the consideration of Indonesia's clinical setting, facility, and drug availability.

1. Introduction

Glucocorticoids are among the most widely used drugs as they have powerful anti-inflammation, immunosuppressive, and anti-proliferative (for tumors) properties. It is estimated that glucocorticoids are used for the long term in 0.5-1% of the general population.[1] Glucocorticoids are often widely prescribed for various medical conditions, such as autoimmune diseases, allergic reactions, asthma exacerbation, chronic obstructive pulmonary disease, or even in malignancies. Rheumatology is one of the medical specialties that often prescribe glucocorticoids to control disease activity along with other therapies.[2]

Glucocorticoid dose and duration depend on the diagnosis, therapy indication, and goals of the therapy itself.[3] Data from cohort studies shows that 64.1% of rheumatoid arthritis patients receive prednisone with an average daily dose of 3.1 mg for 7 years. An observational study in Indonesia involving 685 autoimmune patients shows that 38% of these

patients use less than 7.5 mg of glucocorticoids daily, while the rest of them use more than 7.5 mg of glucocorticoids daily.[2]

Although glucocorticoids have an excellent therapeutic effect in inducing remission in inflammatory diseases, they may also cause harmful side effects, ranging from mild to severe side effects. A survey conducted in the U.S. revealed that at least 90% of patients would experience at least one side effect after consuming glucocorticoids for more than 60 days.[4] These side effects happened in patients receiving glucocorticoids of various doses and routes, even in patients that received low-dose glucocorticoids (≤ 7.5 mg/day).[4] Among all of the side effects that may arise, osteoporosis and fracture are the most harmful side effects.[4] It is estimated that 30-40% of patients receiving long-term glucocorticoid therapy will one-day experience a fracture.[5,6] This fracture can appear in any bone and any part of the bone, though the vertebral body is the most common site of fracture.[7]

Osteoporosis that is secondarily caused by glucocorticoid usage is then called glucocorticoid-induced osteoporosis (GIOP).[5,8] GIOP may cause a significant decline in patients' quality of life and increase morbidity in patients with chronic glucocorticoid usage. Research data shows that the prevalence of GIOP is 22-46.8% in rheumatoid arthritis patients, 28-68% in Systemic Lupus Erythematosus (SLE) patients, and 14.9-46.8% in polymyalgia rheumatica patients.[9–13]

The number of GIOP patients in Indonesia is currently unknown. Nevertheless, considering the sheer number of glucocorticoid usage and the fact that glucocorticoid usage without a medical doctor's prescription is a common phenomenon in Indonesia, it can be estimated that Indonesia's GIOP prevalence is quite high. In addition to that, GIOP does not always exhibit any symptoms until a fracture happens. The lack of diagnostic and therapeutic facilities also contributes to difficulties in the early diagnosis and therapy of GIOP in Indonesia. Therefore, it is necessary to provide a recommendation for diagnosing and managing GIOP, which is more applicable in Indonesia, considering the local conditions and limitations. This is the first published GIOP recommendation in Indonesia. The authors hope that this recommendation can guide Indonesian medical doctors and other healthcare providers in screening, preventing, diagnosing, managing, and also monitoring GIOP patients.

2. Methods

The recommendation team was assembled by The Indonesian Rheumatologist Association (IRA), consisting of 10 rheumatologist consultants and one secretary. The recommendation team was in charge of forming recommendation questions for early detection, diagnosis, therapy, and monitoring of GIOP. There was also a team of supervisors (steering committee), consisting of 5 core members from IRA. The steering committee gave advice regarding the recommendation questions that were discussed by the recommendation team. The panelist team consists of 47 rheumatologists from various branches of IRA and institutions in Indonesia, with at least 5 years of working experience as a rheumatologist. Each member of the panelist team gave an independent opinion regarding the level and strength of the recommendation that was issued by the recommendation team.

A total of seventeen key questions were formed to determine the recommendations for diagnosing and managing GIOP in Indonesia: 1) Who needs to be screened in the early detection of GIOP?, 2) What are the supporting examinations that are necessary for the early detection of GIOP?, 3) How do doctors make a repeated assessment in patients with high suspicion of GIOP?, 4) How do doctors rationally prescribe steroids in the prevention of GIOP?, 5) What is the role of calcium and vitamin D in the prevention of GIOP?, 6) What is the role of a healthy lifestyle in the prevention of GIOP?, 7) What is the role of education in the treatment of GIOP? 8) What is the role of a healthy lifestyle in the treatment of GIOP?, 9) What is the role of physical activity in the treatment of GIOP?, 10) What is the role of calcium and vitamin D in the

treatment of GIOP?, 11) What is the role of bisphosphonates in the treatment of GIOP?, 12) What is the role of denosumab and teriparatide in the treatment of GIOP?, 13) When can pharmacological treatment be initiated in GIOP patients?, 14) When should pharmacological treatment be given to GIOP patients?, 15) How do doctors evaluate treatment results in GIOP patients?, 16) How do doctors monitor side effects that arise from bisphosphonate treatment?, 17) How do doctors determine the failure of therapy in GIOP?.

Literature searching was done online using Pubmed, Science Direct, and Cochrane databases. The literature was limited to published English meta-analysis, systematic reviews, clinical trials, randomized controlled trials (RCT), and observational studies. The literature was also limited to studies involving the human population the age of 19 years or older and published from January 2011 to September 2021. The literature-searching process can be seen in Figure 1.

Recommendations were then issued based on the 17 key questions above. The recommendation team then assigned the level of evidence (LoE) and grades of recommendation (GoR) based on the criteria listed in Table 1.[14] The recommendations were then reviewed by a steering committee with experience in managing GIOP. In the final step, the panelist team members were asked to give a score of 0-100 for each recommendation to determine the level of agreement (LoA). A score of 0 means complete disagreement, and 100 means complete agreement. The panelist member would be asked for comments should a score below 70 be issued. Each recommendation with a score below 70 was then rediscussed by the recommendation team to be revised and then reassessed for determining the LoA by the panelist team.

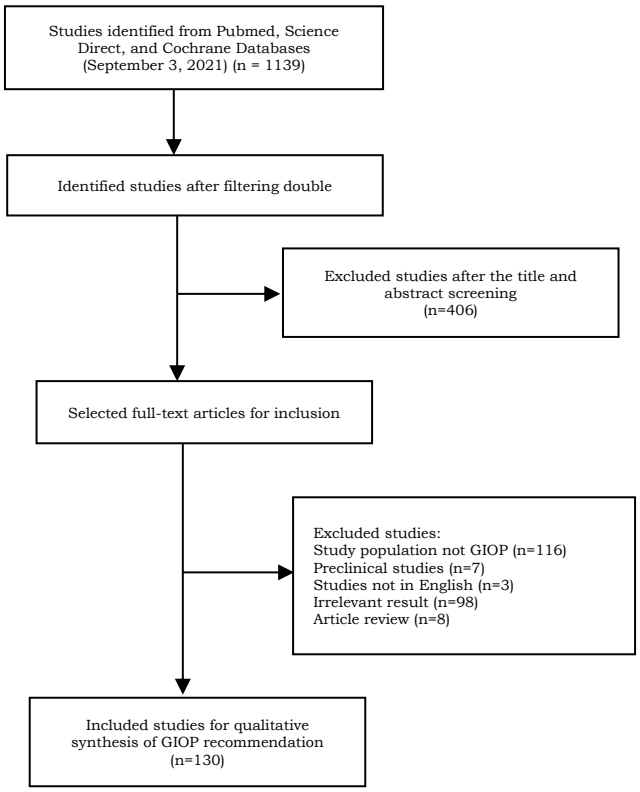

Figure 1. The literature searching and article selection process in the formation of GIOP recommendations.

Table 1. Level of evidence and grades of recommendations.

Level of evidence (LoE)		Grades of recommendation (GoR)	
I	High-quality meta-analysis or systematic review of RCTs or individual RCTs with low risk of bias	A	Strong recommendation: referring to level I studies
II	A high-quality systematic review of observational studies (case-control or cohort) or individual observational studies	B	Moderate recommendation: referring to level II studies or extrapolation of level I studies
III	Non-analytic studies (case report or case series)	C	Weak recommendation: referring to level III studies or extrapolation of level II studies
IV	Non-analytic studies (case report or case series)	D	Consensus recommendation: expert opinion or based on limited evidence

3. Results

Based on the discussion, 17 recommendations were agreed by the recommendation team, steering committee, and panelist team. A summary of these recommendations can be seen in Table 2.

Table 2. Summary of recommendations for diagnosis and management of GIOP.

No.	Recommendation	LoE	GoR	LoA
1.	Patients who receive glucocorticoid therapy equivalent to ≥5 mg/day of prednisone for ≥3 months should be screened for GIOP.	I	A	94.6 ± 9.6
2.	Early screening of GIOP is conducted by using BMD (I/A), conventional X-ray radiology (II/C), fracture risk scoring (II/C), bone markers measurement (II/C), clinical evaluation (IV/B), and measurement of calcium and vitamin D concentration (IV/C).	I-IV	A-C	93.7 ± 9.3
3.	Patients who receive glucocorticoids therapy equivalent to ≥5 mg/day of prednisone for ≥3 months, but have not been diagnosed with GIOP, should be reassessed every 6-12 months using clinical evaluation and/or BMD, and/or conventional X-ray radiology and/or fracture risk scoring, and/or bone marker measurement, and/or measurement of calcium and vitamin D concentration.	IV	B	93.5 ± 7.7
4.	Glucocorticoids are recommended to be used with the lowest daily or cumulative dose in the shortest possible duration to prevent GIOP.	II	B	97.0 ± 7.0
5.	Calcium and Vitamin D consumption through daily diet or supplementation is recommended to prevent GIOP.	I	A	96.9 ± 5.8
6.	Lifestyle modification, including a balanced diet, maintaining an ideal body weight, smoking cessation, alcohol avoidance, and routine physical activity, are recommended to prevent GIOP.	IV	C	96.2 ± 6.4
7.	Patients who receive glucocorticoid therapy should be educated regarding risk factors, disease progression, prevention, and osteoporosis management caused by GIOP.	II	A	97.6 ± 5.1
8.	Lifestyle modification, including a balanced diet, maintaining ideal body weight, smoking cessation, alcohol avoidance, and routine physical activity, is recommended in the treatment of GIOP.	IV	B	96.2 ± 6.5
9.	Routine physical activity adjusted to the patient's condition is recommended in GIOP therapy.	III	B	96.2 ± 6.9
10.	Calcium and Vitamin D consumption through daily diet or supplementation are recommended in the therapy of GIOP.	I	A	97.4 ± 5.6
11.	Pharmacological therapy can be initiated in adult patients who receive glucocorticoid therapy equivalent to ≥5 mg/day of prednisone for ≥3 months with BMD-T-score of ≤-2.0 or with history of osteoporosis fracture or with a moderate to high risk of fracture.	II	A	94.8 ± 7.7

12.	Bisphosphonates (alendronate, risedronate, zoledronate) are recommended as first-line therapy for GIOP patients (I/A). If these drugs are not available, ibandronate is recommended as an alternative therapy to bisphosphonates for GIOP patients (II/B).	I-II	A-B	92.7 ± 9.5
13.	Denosumab or teriparatide are recommended for GIOP patients who give inadequate response towards bisphosphonates or are contraindicated to bisphosphonates.	II	B	95.4 ± 7.3
14.	GIOP pharmacological therapy should be continued for as long as glucocorticoids are still given to the patient. If glucocorticoids are stopped, discontinuation of osteoporosis therapy (drug holiday) refers to postmenopausal osteoporosis.	IV	C	92.3 ± 9.8
15.	Monitoring of GIOP treatment efficacy is recommended using BMD (II/B), conventional X-ray radiology (II/B), fracture scoring (II/B), bone turnover markers (BTM) measurement (II/B), serum calcium and vitamin D concentration measurement (II/B), trabecular bone score (TBS) (III/C), clinical judgment (IV/D), and body height measurement (IV/D) every 6-12 months.	II-III	B-C	93.8 ± 8.0
16.	Assessment of gastrointestinal disorder, musculoskeletal pain, blood calcium concentration, osteonecrosis of the jaw (ONJ), and atypical femoral fracture (AFF) are recommended during side effects and safety monitoring of bisphosphonates therapy.	II	B	94.9 ± 6.6
17.	Failure in GIOP therapy is defined as: - fracture in patients receiving ≥18 months of bisphosphonates therapy; or - osteoporosis fracture occurring twice after bisphosphonates administration; or - significant decrease in BMD (≥10% per year) after one year of therapy.	IV	C	94.6 ± 7.9

4. Discussion

Recommendation 1: Patients who receive glucocorticoid therapy equivalent to ≥5 mg/day of prednisone for ≥3 months should be screened for GIOP.

Multiple pieces of evidence stated that the usage of glucocorticoid therapy equivalent to ≥5 mg/day of prednisone for ≥3 months is related to the increased risk of suffering from a fracture, decrease of T-score in BMD of femur and vertebrae, and decrease of TBS Z-score. [9,15–20]

Recommendation 2: Early screening of GIOP is conducted by using BMD (I/A), conventional X-ray radiology (II/C), fracture risk scoring (II/C), bone marker measurement (II/C), clinical evaluation (IV/B), and measurement of calcium and vitamin D concentration (IV/C).

BMD (interpreted using T-score) is the main supporting examination that can be used to assess bone density and predict new fractures in patients receiving glucocorticoids.[9,15,21–24] Initiation of therapy is recommended in patients with a T-score of ≤-1.5 or ≤-2.0.[21] Central dual-energy X-ray absorptiometry (DXA) is the most commonly used BMD, as vertebrae and hip bones are the most commonly affected bones in GIOP.[25]

However, considering the difficulty in accessing BMD in Indonesia, conventional X-ray of the vertebrae (thorax and lumbar region, in AP and lateral projection) can also be used as an early detection tool of GIOP.[25,26] In addition to that, vertebral fractures can also happen in patients with normal BMD scores.[21] Fracture risk scoring using the fracture risk assessment tool (FRAX) developed by World Health Organization (WHO) is also a good choice for early screening of GIOP. FRAX can predict 10-year risk of osteoporosis fracture without using BMD or conventional X-ray.[27,28] It is to be noted that the FRAX score must be multiplied with a multiplying factor based on the dose of glucocorticoids used. FRAX score multiplying factor can be seen in Table 3, and its interpretation can be seen in Table 4.

Aside from BMD, bone turnover markers (BTM), such as serum N-telopeptide (NTx), serum C-telopeptide (CTx), and urine NTx, are also important to identify patients with a high risk of having a fracture, as they can assess the rate of bone remodeling

process.[21,29]

Clinical evaluation is also very important in the early screening of GIOP, including an anamnesis of a current complaint, past medical history, family history, and careful physical examination.

Studies show that low serum vitamin D concentration (<30 ng/ml) is related to the incidence of hip and vertebral fractures.[30] Improving serum calcium concentration was also shown to be able to prevent vertebral fracture in postmenopausal women.[31] Therefore, measuring serum vitamin D and calcium concentration can be recommended in the early detection of GIOP.

Table 3. The multiplying factor of FRAX scores adjusted to glucocorticoid dose.

Glucocorticoids dose	Multiplying factor
Risk of hip fracture	
Prednisone <2.5 mg/day	0.65
Prednisone ≥7,5 mg/day	1.20
Risk of major osteoporosis fracture	
Prednisone <2.5 mg/day	0.80
Prednisone ≥7,5 mg/day	1.15

Table 4. FRAX score interpretation of fracture risk.

Interpretation	10-year risk of hip fracture	10-year risk of major osteoporosis fracture
High risk of fracture	≥3%	≥20%
Moderate risk of fracture	>1-3%	>10-19%
Low risk of fracture	≤1%	≤10%

Recommendation 3: Patients who receive glucocorticoids therapy equivalent to ≥5 mg/day of prednisone for ≥3 months, but have not been diagnosed with GIOP, should be reassessed every 6-12 months using clinical evaluation and/or BMD, and/or conventional X-ray radiology and/or fracture risk scoring, and/or bone marker measurement~~,~~ and/or measurement of calcium and vitamin D concentration.

Patients receiving glucocorticoids but have not been diagnosed with GIOP in the early screening of GIOP, do not require any specific therapy for osteoporosis (other than calcium and vitamin D supplementation). Reassessment should be done 6-12 months after the previous examination.[32]

Recommendation 4: Glucocorticoids are recommended to be used with the lowest daily or cumulative dose in the shortest possible duration to prevent GIOP.

Glucocorticoid consumption is associated with an increased risk of vertebral and hip ~~bone~~ fracture.[17,33] The risk is also affected by glucocorticoids cumulative and daily dose and therapy duration.[10,17,19,25,33–37] Several studies show that non-oral glucocorticoids (intravenous pulse dose, inhaled, and topical glucocorticoids) do not significantly reduce bone mineral density (BMD).[8,35,38–42] Therefore, it is recommended that glucocorticoids usage, especially oral glucocorticoids), should be adjusted to the most effective and lowest possible dose in the shortest

possible duration in order to prevent the occurrence of new fracture caused by GIOP.[43–45]

Recommendation 5: Calcium and Vitamin D consumption through daily diet or supplementation are recommended to prevent GIOP.

Several studies show that consumption of vitamin D and calcium, whether through daily diet or supplementation, is associated with higher bone mineral density (BMD).[46–48] The recommended dose of calcium is 1000-1200 mg/day, and the recommended dose of vitamin D is 600-800 U/day.[32]

Recommendation 6: Lifestyle modification, including a balanced diet, maintaining ideal body weight, smoking cessation, alcohol avoidance, and routine physical activity, are recommended to prevent GIOP.

Evidence shows no significant effect of lifestyle modification on the risk of osteoporosis. However, several guidelines and recommendations from other countries still recommend a balanced diet, maintaining ideal body weight, smoking cessation, alcohol avoidance, and routine physical activity to prevent GIOP.[21,32,49,50]

Recommendation 7: Patients who receive glucocorticoid therapy should be educated regarding risk factors, disease progression, prevention, and osteoporosis management caused by GIOP.

Education should be given to every patient who receives glucocorticoid therapy. Research shows that education significantly increases awareness towards GIOP, physical exercise duration, therapy compliance, initiation of vitamin D and calcium supplementation, therapy initiation of GIOP, and BMD examination in GIOP patients.[15,51] Direct education is more recommended than education through the internet or video.[52]

Recommendation 8: Lifestyle modification, including a balanced diet, maintaining ideal body weight, smoking cessation, alcohol avoidance, and routine physical activity, are recommended in the treatment of GIOP.

Limited studies were found regarding the effect of lifestyle modification on the treatment of GIOP. However, a balanced diet, maintaining ideal body weight, smoking cessation, and alcohol avoidance were shown to have a positive effect on the osteoporosis treatment of postmenopausal women.[53–62] Therefore, we still recommend lifestyle modification in the treatment of GIOP.

Recommendation 9: Routine physical activity adjusted to the patient's condition is recommended in GIOP therapy.

Multiple evidence shows that routine physical activity combined with pharmacological therapy may restore or increase a patient's BMD, compared to only receiving pharmacological therapy.[63–66] Nevertheless, choosing the type and duration of physical activity should be based on the patient's condition, physical capacity, and comorbid.

Recommendation 10: Calcium and Vitamin D consumption through daily diet or supplementation are recommended in the therapy of GIOP.

A combination of calcium and vitamin D are shown to be significantly effective in increasing BMD in GIOP patients.[47] But it is to be noted that supplementation of calcium alone or vitamin D alone does not yield effective results.[47,67] Studies also show that vitamin D analog, especially eldecalcitol, is more effective in maintaining the BMD of GIOP patients.[48,68–70] The recommended supplementation dose of calcium is 1000-1200 mg/day, and the recommended supplementation dose of vitamin D is 600-800 U/day.[32]

Recommendation 11: Pharmacological therapy can be initiated in adult patients who receive glucocorticoids therapy equivalent to ≥5 mg/day of prednisone for ≥3 months with a BMD-T-score of ≤-2.0 or with a history of osteoporosis fracture or with moderate to high risk of fracture.

Several parameters can be used to determine the initiation of pharmacological therapy in GIOP patients, which include BMD examination, history of osteoporosis fracture, and fracture risk assessment.[71] A BMD T-score of ≤-2.0 is recommended as a baseline indicator in initiating bisphosphonates or other anti-osteoporotic therapy in GIOP patients.[24,72,73] History of fracture can also be used as an indicator in initiating pharmacological therapy in GIOP because the occurrence of fracture is known to be related to a higher risk of subsequent fracture and mortality in osteoporosis patients.[74,75]

In the case that BMD is not available, we recommend assessing fracture risk using FRAX score that is already glucocorticoid-adjusted with the multiplying factor (Table 3).[76,77] However, FRAX score can only be used in ≥40-year-old patients. Therefore, we recommend using fracture risk classification, as explained in Table 5. Based on this classification, pharmacological therapy or anti-osteoporosis therapy can be initiated in patients with a moderate to high risk of fracture. Patients with a low risk of fracture are only recommended to receive calcium and vitamin D supplementation.

Table 5. Fracture risk classification in patients receiving glucocorticoids.

	≥40-year-old patients	**<40-year-old patients**
High risk of fracture	- History of fracture; or - FRAX (glucocorticoid-adjusted) 10-year-risk of major osteoporosis fracture ≥20%; or - FRAX (glucocorticoid-adjusted) 10-year-risk of hip fracture ≥3%	- History of fracture
Moderate risk of fracture	- FRAX (glucocorticoid-adjusted) 10-year-risk of major osteoporosis fracture 10-19%; or - FRAX (glucocorticoid-adjusted) 10-year-risk of hip fracture >1% and <3%	- Z-score from hip or vertebral BMD <-3; or - Rapid decrease of bone density (≥10% of hip or vertebral BMD in 1 year); and - Consuming glucocorticoids equivalent to ≥7.5 mg/day of prednisone for ≥6 months
Low risk of fracture	- FRAX (glucocorticoid-adjusted) 10-year-risk of major osteoporosis fracture <10%; or - FRAX (glucocorticoid-adjusted) 10-year-risk of hip fracture ≤1%	- No risk factor mentioned above found

Recommendation 12: Bisphosphonates (alendronate, risedronate, zoledronate) are recommended as first-line therapy for GIOP patients (I/A). If these drugs are not available, ibandronate is recommended as an alternative therapy to bisphosphonates for GIOP patients (II/B).

Bisphosphonates are the first-line therapy for osteoporosis, which are beneficial for GIOP patients by significantly increasing BMD, repairing bone markers, and preventing new fractures.[78–80] Most commonly used bisphosphonates include alendronate, risedronate, and zoledronate. Research shows that consumption of alendronate with a 10 mg/day dose for 6-24 months significantly increases vertebral, lumbar, hip, femoral neck, and trochanter BMD.[81,82] But there was no significant decrease in a vertebral fractures in GIOP patients using alendronate.[81,82] Combination of alendronate and alfacalcidol (1 gram/day) for 12 months was also shown to be able to significantly reduce the incidence of bone fracture.[68]

Trials involving risedronate also shows the promising result. Administration of 75 mg/month of risedronate for 6 months was shown to significantly increase lumbar vertebrae BMD of GIOP patients, although there were no significant changes in the femoral neck and hip BMD.[83] It was also found that there was decreased vertebral fracture incidence after one year of therapy using 5 mg/day of risedronate.[83] Intravenous zoledronate (5 mg single dose) was shown to be superior to oral risedronate in increasing lumbar BMD and decreasing bone markers in GIOP patients.[84–86] However, patients receiving intravenous zoledronate have a higher incidence of influenza and hyperpyrexia.[84] Therefore, intravenous zoledronate is only recommended in GIOP patients with gastrointestinal disturbances causing an inability to consume oral bisphosphonates.

There was still limited evidence regarding ibandronate usage in GIOP. Several studies show that 150 mg of oral ibandronate every month for 48 weeks can increase lumbar, femoral neck and hip BMD compared with a placebo.[87] But it is not known whether there ibandronate can prevent fracture incidence in GIOP patients. Therefore, ibandronate is only recommended as alternative therapy when alendronate, risedronate, or zoledronate is unavailable.

Bisphosphonates are contraindicated in several conditions: a) History of bisphosphonates hypersensitivity, b) Hypocalcemia, c) Chronic kidney disease with eGFR <30 or 35 ml/minute, d) Patients with esophageal disease, such as achalasia, esophageal stricture, esophageal varices, Barrett's esophagus, inability to stand up for 30 minutes, and history of bariatric surgery (especially in patients receiving oral bisphosphonates), e) History of atypical femoral fracture caused by bisphosphonates, f) History of osteonecrosis of the jaw caused by bisphosphonates.

Recommendation 13: Denosumab or teriparatide are recommended for GIOP patients who give inadequate response towards bisphosphonates or are contraindicated to bisphosphonates.

Denosumab is a monoclonal antibody that prevents linking between RANK and RANKL, thus halting osteoclast maturation and inducing its apoptosis. The newest evidence shows that denosumab can significantly increase BMD and prevent fracture in GIOP patients.[88,89] Administration of 60 mg of subcutaneous denosumab every 6 months was shown to be more effective in increasing lumbar vertebrae BMD after 12 months compared to 5 mg of oral risedronate daily, with similar side effects.[24,90] Compared with alendronate, denosumab was also shown to be more effective in suppressing biochemical bone markers and increasing lumbar vertebrae BMD after 12 months of therapy in GIOP patients.[91] Patients who switched from bisphosphonates therapy to denosumab were also shown to have a significant increase in vertebral BMD and suppression in bone marker compared to those who continue using bisphosphonates.[92]

Another novel therapy of GIOP is teriparatide, which is a parathyroid hormone (PTH) analogue. A

clinical trial using 56.5 ug/week of teriparatide for 72 weeks showed a 5.09% of the increase in lumbar vertebrae BMD.[93] Teriparatide was also shown to be able to suppress bone turnover markers in GIOP patients.[94] Other studies also revealed that subjects receiving 20ug/day of teriparatide had significantly higher trabecular BMD compared to those receiving 35 mg/week of risedronate after 18 months of therapy.[95] Study comparing teriparatide and alendronate also shows that patients receiving teriparatide had a significant increase in TBS after 18 and 36 months of therapy, whereas alendronate showed no significant changes in TBS after 18 and 36 months of therapy.[96]

Both denosumab and teriparatide show promising efficacy. However, both drugs are currently not yet available in Indonesia. Therefore, we recommend denosumab and teriparatide as GIOP therapy only if bisphosphonates therapy does not give an adequate result or there is a contraindication to oral or intravenous bisphosphonates therapy.

Recommendation 14: GIOP pharmacological therapy should be continued for as long as glucocorticoids are still given to the patient. If glucocorticoids are stopped, discontinuation of osteoporosis therapy (drug holiday) refers to postmenopausal osteoporosis.

There was still limited evidence regarding long-term bisphosphonates therapy. Guideline from the American College of Rheumatology (ACR) in 2017 still recommend continuation of anti-osteoporosis therapy in GIOP patients who still consume glucocorticoids and have moderate to high risk of fracture based on fracture risk assessment.[32] Discontinuation of anti-osteoporosis therapy can be considered in patients who have stopped consuming glucocorticoids with low fracture risk based on FRAX scoring.[32] Studies showed that discontinuing glucocorticoids can increase BMD and lower the risk of fracture.[19]

There was still no evidence regarding drug holiday in bisphosphonates therapy. Therefore, drug holiday in GIOP patients is only recommended in patients who have stopped consuming glucocorticoids, and the method of drug holiday refers to the management of postmenopausal osteoporosis guidelines.

Recommendation 15: Monitoring of GIOP treatment efficacy is recommended using BMD (II/B), conventional X-ray radiology (II/B), fracture scoring (II/B), bone turnover markers (BTM) measurement (II/B), serum calcium and vitamin D concentration measurement (II/B), trabecular bone score (TBS) (III/C), clinical judgment (IV/D), and body height measurement (IV/D) every 6-12 months.

GIOP therapy monitoring is required to assess therapy effectiveness, find new bone fractures, and detect whether there is a failure in GIOP therapy. Early monitoring includes drug compliance evaluation, dose evaluation, and evaluation of adequacy in calcium and vitamin D consumption.[97]

BMD is recommended to monitor therapy effectiveness in GIOP patients.[50] Increase in lumbar vertebrae BMD can be observed 6 months after therapy, but an increase of other vertebrae, femoral neck, and hip BMD can only be observed after 12 months of therapy.[24,68,79,83–85,88,90–92,98–105] Serial BMD monitoring is needed not only to detect a failure in therapy but also to assess bone response towards therapy.[97] If a significant decrease in BMD is found even though the patient already received anti-osteoporosis therapy, several factors should be explored, such as drug compliance, risk of failure of therapy, or other secondary osteoporosis causes that were previously unknown.[97] BMD score after 5 years of alendronate therapy or 3 years of zoledronate therapy can predict bone fracture risk in the future.[106]

Conventional X-ray radiology can also be used to monitor fractures in GIOP patients. Bisphosphonates, teriparatide, and denosumab were shown to decrease the incidence of fracture detected by conventional X-ray radiology after 12 months of therapy.[68,79,107] Fracture assessment through conventional X-ray radiology should be done very carefully since costal and vertebral fractures often happen asymptomatically.[90,97,105,106] Radiography should be

done if there is a significant body height decrease (>2 cm), low back pain, or other symptoms that give suspicion of bone fracture. Based on Genant criteria, the vertebral fracture is defined as a decrease in vertebral bone height by 20% or ≥4 mm or both.[79,106]

Another method to monitor GIOP therapy is by measuring BTM, which can differentiate patients with high and low bone turnover activity, which in turn helps doctors to choose the correct anti-osteoporosis regimen.[24,83–86,88–94,98–101] BTM can also show earlier response to GIOP therapy, displaying significant changes in just several weeks after therapy.[108,109] Bone formation markers include osteocalcin, bone alkaline phosphatase (BAP), and type 1 collagen propeptides (P1NP and P1CP), whereas bone resorption markers include serum type 1 collagen telopeptides (NTx, CTx), tartrate-resistant acid phosphatase (TRACP), urine pyridinoline (PYR), and urine deoxy-pyridinoline (DPYR).[29,106] CTx and P1NP are the most commonly used markers in clinical studies, as recommended by International Osteoporosis Foundation (IOF). Several studies showed a significant decrease in CTx as a bone resorption marker and P1NP as a bone formation marker in GIOP patients receiving anti-resorptive therapy such as bisphosphonates and denosumab after 3, 6, and 12 months of therapy.[84,86,90–94,99,100,105] While in anabolic therapy using teriparatide, an increase in P1NP and CTx can be seen significantly after 3 and 6 months of therapy. Studies also showed that response in BTM after therapy could predict changes in BMD.[93,94,100,101]

We also recommend measuring vitamin D and calcium level concentration every 6 months to monitor therapy effectiveness.[91,110] Low serum levels of vitamin D and calcium are shown to be related to the incidence of fracture.[30]

TBS is another examination that can be used to monitor GIOP therapy. TBS can give more detailed information about bone microarchitecture compared to BMD. High TBS reflects strong bone microarchitecture that is resistant to fracture, while low TBS reflects weak bone that is prone to fracture. TBS is superior to BMD in assessing fracture risk of vertebral bone examination.[96] TBS increase can be significantly detected after 18, 24, and 36 months of teriparatide administration.[96] However, there were only limited studies that analyze TBS effectiveness as a fracture risk assessment. Therefore, we recommend TBS as a monitoring method only when BMD cannot be used to assess anti-osteoporosis effectiveness.

Clinical evaluation should be used to monitor therapy effectiveness, which includes evaluation of drug compliance, drug dose, adequacy of vitamin D and calcium supplementation, new side effects, and finding new fractures. Patients should also be asked regarding fall history, a risk factor for falling, and other symptoms that lead to suspicion of bone fracture. In elderly patients, compliance to fall prevention measures should also be evaluated.[49] We also recommend body height measurement once a year, as a vertebral fracture can cause body height to decrease.[49,106] Significant body height decrease (>2 cm) is a non-specific sign of vertebral fracture.[49,106]

Recommendation 16: Assessment of gastrointestinal disorder, musculoskeletal pain, blood calcium concentration, osteonecrosis of the jaw (ONJ), and atypical femoral fracture (AFF) are recommended during side effects and safety monitoring of bisphosphonates therapy.

Side effects and safety monitoring are very important in patients receiving bisphosphonates. Long-term bisphosphonates therapy, which suppresses bone remodeling, may have a larger inhibitory effect on bone formation than its resorption effect. The most common side effects of bisphosphonates therapy include gastroesophageal irritation and musculoskeletal pain.[111] Other more serious complications are ONJ and AFF.

Some examples of gastrointestinal symptoms that may occur in patients receiving gastrointestinal are nausea, vomiting, epigastric pain, bloating, and esophageal reflux.[111–126] These symptoms can be caused by erosive esophagitis while the patient is consuming oral bisphosphonates. Therefore, patients are advised to consume bisphosphonates in an empty

stomach and patients are required to maintain an upright position for 30-60 minutes after ingesting oral bisphosphonates. Proton pump inhibitors may be prescribed to help relieve some gastrointestinal symptoms. Gastrointestinal symptoms are the main side effects that cause the patient to stop consuming drugs and decrease drug compliance.[112,113,115,116,118,124]

Musculoskeletal pain, such as myalgia and arthralgia are one example of acute phase reactions that may happen after the first day of bisphosphonates therapy.[127] Several studies showed that musculoskeletal pain is more likely to be found in patients receiving intravenous rather than oral bisphosphonates. However, these symptoms are often mild and usually resolve within a week.[104,128,129]

Temporary hypocalcemia and secondary hyperparathyroidism are other common side effects that often happen after the administration of intravenous bisphosphonates. Therefore, every patient who intends to start bisphosphonates therapy should receive adequate calcium and vitamin D intake.[130]

ONJ may happen in patients receiving long-term bisphosphonates therapy, with the incidence between 1 in 10,000 to 1 in 100,000 every year.[104,118,119,131–135] Bad oral hygiene, invasive teeth procedures, dentures usage, and high dose intravenous bisphosphonates are risk factors for ONJ.[131] Some ONJ symptoms include pain, mucosal edema, teeth displacement, erythema, ulceration, paresthesia, and anesthesia of the affected trigeminal nerve.[132] Therefore, patients are recommended to maintain good oral hygiene and do teeth and mouth examinations every 6 months.

Bisphosphonates are effective in treating GIOP in the lumbar vertebrae and femur. But some studies reported that there was an association between bisphosphonates and the increased risk of AFF.[104,119,136–141] Some comorbidities such as rheumatoid arthritis, systemic lupus erythematosus, and asthma, were found in around 25% of AFF cases.[104,119,138–140] Patients receiving long term glucocorticoids were reported to have 3 times higher risk and receiving long-term bisphosphonates has 5.2 times higher risk of suffering from AFF.[136] Conventional radiography of the femur should be considered in patients receiving bisphosphonates therapy and reporting pain in the femoral region.

Recommendation 17: Failure in GIOP therapy is defined as: a) fracture in patients receiving ≥18 months of bisphosphonates therapy, b) osteoporosis fracture occurring twice after bisphosphonates administration, c) significant decrease in BMD (≥10% per year) after one year of therapy.

Patients who fail in oral bisphosphonates therapy caused of drug compliance or absorption disturbances can be recommended to use intravenous bisphosphonates instead.[32,49] Other anti-osteoporosis therapies, such as denosumab or teriparatide, are recommended in failure of GIOP therapy. [32,49]

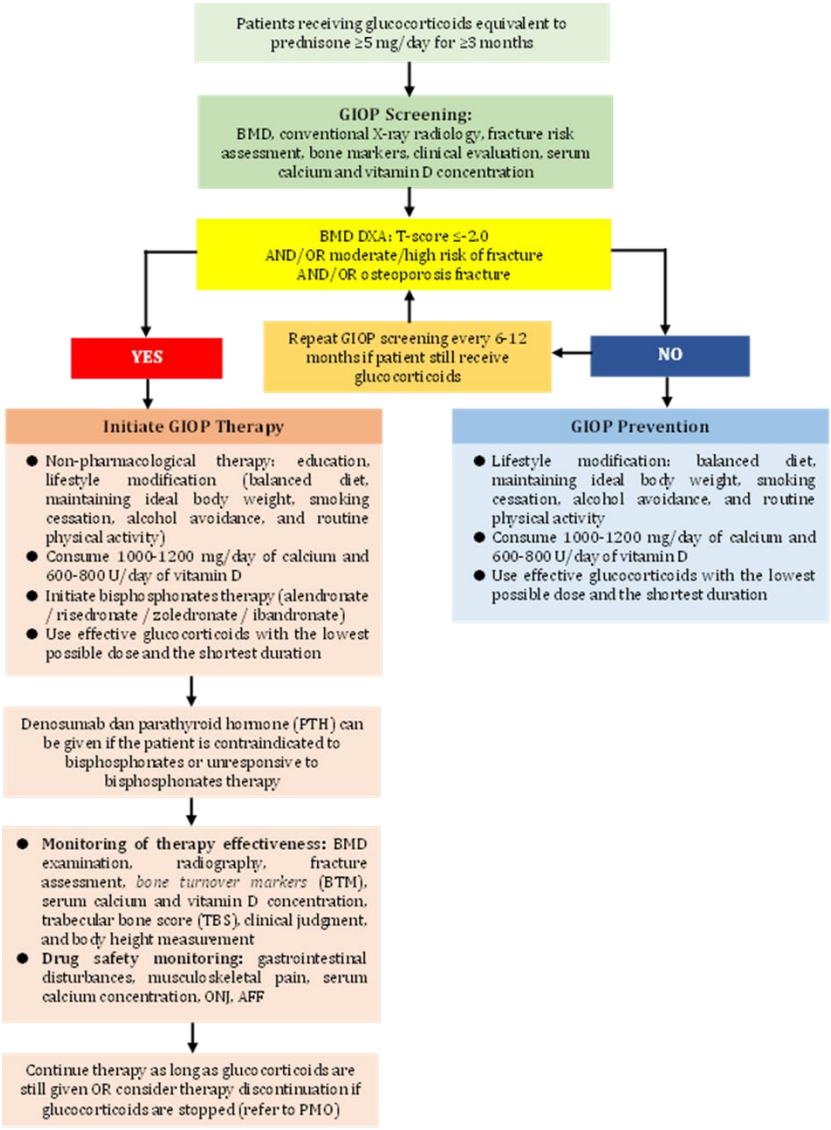

Figure 2. GIOP management algorithm.

5. Conclusion

These recommendations are created to give information regarding the diagnosis and management of GIOP in Indonesia. They can be implemented in adult patients receiving long-term glucocorticoids, both those who are at early risk of developing GIOP or those who are already diagnosed with GIOP. The prevention measure, diagnostic, therapy, and monitoring algorithm in this recommendation are all created with the consideration of Indonesia's clinical setting, facility, and drug availability. Summary of GIOP management from screening to monitoring algorithm can be seen in Figure 2. The authors hope that as the first recommendation of GIOP in Indonesia, this recommendation can serve as a guideline for every doctor in Indonesia in managing GIOP patients.

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