Korean Guideline for the Prevention and Treatment of Glucocorticoid-induced Osteoporosis

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Objective. To develop guidelines and recommendations to prevent and treat glucocorticoid-induced osteoporosis (GIOP) in Korea. Methods. The Korean Society for Bone and Mineral Research and the Korean College of Rheumatology developed this guideline based on Guidance for the Development of Clinical Practice Guidelines version 1.0 established by the National Evidence-Based Healthcare Collaborating Agency. This guideline was developed by adapting previously-published guidelines, and a systematic review and quality assessment were conducted. Results. This guideline applies to adults aged 19 years or older who are using or plan to use glucocorticoids (GCs), but does not include children and adolescents. An initial assessment of fracture risk should be performed within 6 months of initial GC use. Fracture risk should be estimated using FRAX (Fracture Risk Assessment Tool) with adjustments for GC dose, previous osteoporotic fracture history, and bone mineral density (BMD) results. All patients taking more than 2.5 mg/day prednisolone or equivalent for more than 3 months are recommended to take adequate calcium and vitamin D. Patients at moderate to high fracture risk should be treated with additional osteoporosis medication. All patients continuing GC therapy should receive an annual BMD measurement, vertebral X-ray, and fracture risk assessment using FRAX. When a treatment failure is suspected, switching to another drug should be considered. Conclusion. This guideline is intended to provide guidance for clinicians in prevention and treatment of GIOP. (J Rheum Dis 2018;25:263-295)

Key Words. Denosumab, Diphosphonates, Glucocorticoids, Osteoporosis, Teriparatide

INTRODUCTION

Glucocorticoids (GCs) are very effective drugs for the treatment of inflammatory diseases and have been widely used in various diseases [1-3]. However, long-term use of GCs has detrimental effects on bone microstructure, leading to a decrease in bone mass and an increase in the risk of fracture [3,4]. It is estimated that fractures occur in 30% – 50% of patients receiving long-term GC therapy, but many patients have no symptoms of fracture because of the analgesic effects of GCs [5-7]. There are no definitive data on the number of patients receiving GCs for three months or longer in Korea, but it is estimated to be much higher than the 1% reported in other countries.
Therefore, glucocorticoid-induced osteoporosis (GIOP) is recognized as the most common cause of secondary osteoporosis (OP) and, because there may be no specific symptoms, active management focused on prevention is needed.

The decrease of bone mass caused by GCs occurs in two stages. First, a rapid decrease in bone mass begins within the first 3 ~ 6 months of GC use, with a 6% ~ 12% loss of bone mass in the first year of GC use [10]. Second, long-term use of GCs can result in a 3% reduction in bone mass every year [11]. Glucocorticoids affect both cortical bone and trabecular bone, but fractures occur most commonly in the vertebral body, especially in areas rich in trabecular bone, such as the lumbar spine [3,4,12]. The risk of GC-induced fracture is already increased before a significant reduction in bone mass occurs [3]. Therefore, measurements of bone mineral density (BMD) are not sufficient to evaluate the degree of GC-induced bone loss, so it is very important to identify patients with a high risk of fracture to prevent fractures caused by GIOP [13-15]. The absolute risk of an individual fracture is determined by age, gender and other risk factors for OP. Currently, FRAX (Fracture Risk Assessment Tool, https://www.shef.ac.uk/FRAX/tool.jsp) is a well-known method for assessing the risk of fracture. In addition to the risk factors included in the FRAX, low bone strength at the beginning of GC treatment and the rate of bone loss during treatment are suggested as risk factors for GC-induced fractures, the latter being determined by the dose and duration of GC treatment [16]. In a study of individual absolute fracture probability, patients receiving prednisolone at a dose greater than 30 mg/day (cumulative dose > 5 g/year) showed significantly increased risk of vertebral and femoral fractures [17]. However, if GC treatment is terminated, BMD gradually increases and fracture risk decreases. Therefore, patients could benefit from continuous risk assessment with an emphasis on the appropriate duration of GC use [9,18,19].

As evidence of fracture risk in patients using GCs accumulates, drugs that effectively prevent fractures have been developed. However, many primary care physicians and specialists fail to recognize the severity of GIOP or determine which patients are at greatest risk for GIOP. Therefore, many patients still do not receive treatment to prevent fractures. To address this problem, guidelines for GIOP prevention and treatment have recently been developed by several countries. Notably, the guideline of the American College of Rheumatology (ACR) were revised in 2017 based on the latest evidence and applied to clinical practice [16]. In Korea, it is necessary to provide standardized clinical practical guideline (CPG) for the primary prevention and treatment of GIOP to all clinicians, to ensure that Korean patients who plan to use or use GCs receive the appropriate services for fracture prevention. The Korean Society for Bone and Mineral Research (KSBMR) and the Korean College of Rheumatology (KCR) have mutually developed guideline for the treatment of GIOP. Because of limited domestic data, this guideline was developed by adapting previously-published guidelines.

**MATERIALS AND METHODS**

This guideline was developed for adults over the age of 19 who plan to use or currently use GCs. Pediatric populations and people with a glomerular filtration rate of < 30 mL/minute were excluded. A development committee and a working committee were organized to develop guideline for the treatment of GIOP. These committees were composed of multi-disciplinary and multi-institutional organizations and included endocrinologists, rheumatologists, an orthopedist, and a methodologist (Supplementary Appendix 1). A systematic literature review was conducted, and guidelines were selected and adapted from the existing literature. The completed guideline should be revised within five years, and earlier revisions may be required if a new drug is approved for GIOP or if the evidence changes significantly.

**Framework for GIOP guideline development**

Methods were based on guidance for the development of CPGs version 1.0 by the National Evidence-based Healthcare Collaborating Agency (NECA) (Supplementary Appendix 2). The process of developing this guideline included three major stages [20]: planning, development, and finalization. Each stage was divided into individual steps, for a total of 12 steps. The planning stage consisted of selecting topics (Step 1), assembling the development committee (Step 2), reviewing previously published guidelines (Step 3), establishing the development plan (Step 4), and selecting key questions (Step 5). The development stage consisted of searching for, evaluating, and synthesizing evidence (Steps 6 ~ 8), making recommendations and determining the grades of recommendations (Step 9), and consensus building (Step 10). The finalization stage consisted of external reviews and
Selection of key questions

To select the key questions (KQs) to be addressed by the GIOP guideline, a working committee consisting of a total of nine members first reviewed six guidelines developed by the United States, France, Spain, Japan, Brazil, and the International OP Foundation-European Calcified Tissue Society (IOF-ECTS). From these six guidelines, the committee selected 14 topics. After reviewing these topics, the development committee considered domestic circumstances and clinical significance to select the most relevant KQs. A final list of seven KQs was chosen, which included the patient population (P), the intervention (I),

Table 1. Key questions

| KQ1 | Is non-pharmacological treatment beneficial for the preventing and treating GIOP in adults taking glucocorticoids? |
| KQ2 | Which pharmacological treatments are effective for preventing and treating GIOP in adults < 40 years of age? |
| KQ2-1 | Is calcium and vitamin D supplementation effective in the prevention and treatment of GIOP in adults < 40 years of age? |
| KQ2-2 | Is bisphosphonate effective in the prevention and treatment of GIOP in adults < 40 years of old? |
| KQ2-3 | Is teriparatide effective in the prevention and treatment of GIOP in adults < 40 years of old? |
| KQ2-4 | Is denosumab effective in the prevention and treatment of GIOP in adults < 40 years of old? |
| KQ3 | Which pharmacological treatments are effective for preventing and treating GIOP in adults ≥ 40 years of age? |
| KQ3-1 | Is calcium and vitamin D supplementation effective in the prevention and treatment of GIOP in adults ≥ 40 years of age? |
| KQ3-2 | Is bisphosphonate effective in the prevention and treatment of GIOP in adults ≥ 40 years of old? |
| KQ3-3 | Is teriparatide effective in the prevention and treatment of GIOP in adults ≥ 40 years of old? |
| KQ3-4 | Is denosumab effective in the prevention and treatment of GIOP in adults ≥ 40 years of old? |
| KQ3-5 | Are selective estrogen receptor modulators effective in the prevention and treatment of GIOP in postmenopausal women? |
| KQ4 | Is it safe to use OP medication in women planning to have a pregnancy? |
| KQ5 | How should response to treatment be monitored in patients with GIOP using physical measurements, imaging, and biochemical methods? |
| KQ6 | Should discontinuation of OP medication be considered if the fracture risk is reassessed to be low during GIOP treatment? |
| KQ7 | How should initial treatment failure be defined for GIOP? |

GIOP: glucocorticoid-induced osteoporosis, GC: glucocorticoid, OP: osteoporosis.
the comparator (C), and the outcome of the intervention (O) (PICO, Table 1).

**Literature search**

Two members of the working committee performed systematic literature searches, using the databases PubMed, OVID-EMBASE, KoreaMed, KMbase, National Guideline Clearinghouse, Guidelines International Network, and Korean Medical Guideline Information Center (KoMGI). The researchers identified a total of 309 potentially relevant articles published since 2010, excluding duplicates. By reviewing titles and abstracts, the researchers narrowed this list to the 27 most relevant articles. From these 27 articles, seven of previously-published guidelines were identified: 1) guidelines including PICO that are consistent with KQs; 2) evidence-based guidelines, which are defined by a clear link between the recommendation and the supporting evidence, including systematic literature searches; 3) guidelines for peer review; and 4) guidelines published in Korean or English (Figure 1, Supplementary Appendix 3 and 4).

**Final selection process for guidelines**

Seven guidelines were chosen based on the systematic literature review, selection criteria, and exclusion criteria (Table 2) [21-27]. A quality assessment was performed on these seven guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II). In this comprehensive assessment, the scope and objectives of the guidelines, strictness of development, participation of stakeholders, clarity of expression, applicability, and editorial independence were assessed [28]. The quality assessment of guidelines using AGREE II was conducted by three members of the working committee as per rec-

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**Table 2. The guidelines selected for 1st AGREE evaluation**

| No. | Title                                                                 | Country | Institute                                                                                                               | Year | Reference |
|-----|-----------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------|------|-----------|
| 1   | American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis | USA     | American College of Rheumatology                                                                                        | 2010 | 21        |
| 2   | A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis | International | Joint IOF-ECTS GIO Guidelines Working Group                                                                             | 2012 | 22        |
| 3   | 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary | Canada  | Scientific Advisory Council of Osteoporosis Canada                                                                        | 2010 | 23        |
| 4   | 2014 update of recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis | France  | Bone Section of the French Society for Rheumatology (SFR) and Osteoporosis Research and Information Group (GIO) Committee for Osteoporosis and Bone Metabolic Disorders of the Brazilian Society of Rheumatology; Brazilian Medical Association; Brazilian Association of Physical Medicine and Rehabilitation | 2014 | 24        |
| 5   | Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis | Brazil  |                                                                                                                         | 2012 | 25        |
| 6   | Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update | Japan   | Japanese Society for Bone and Mineral Research                                                                           | 2014 | 26        |
| 7   | Guidelines for the diagnosis, prevention and management of osteoporosis | Italy   | The Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)                                     | 2016 | 27        |

AGREE: Appraisal of Guidelines for Research and Evaluation, IOF-ECTS: International Osteoporosis Foundation-European Calcified Tissue Society, GIO: glucocorticoid-induced osteoporosis.
ommendations, and the items with given divergent scores by the three researchers were reviewed and agreed upon. The strictness of development was specifically considered in the process of selecting guidelines. Four guidelines published in the United States (2010), IOF-ECTS (2012), Canada (2010) and France (2014) were selected [21-24]. During the selection of guidelines, the National Osteoporosis Guideline Group (NOGG) and the ACR published new guidelines for GIOP treatment in 2017 [16,29]. Therefore, the 2010 ACR guideline was replaced by the 2017 ACR guideline (Table 3), and the quality assessment was reevaluated for the five guidelines. The 2017 ACR guidelines, which ranked highly in items of “comprehensive evaluation” and “strictness of development”, were chosen and adapted (Supplementary Appendix 5). The characteristics of final five guidelines were summarized in Supplementary Appendix 6.

Writing process for guidelines

The working committee reviewed the recommendations and evidence for the final five guidelines, and then summarized the primary recommendations for KQs (Supplementary Appendix 7). The acceptability and applicability of the recommendations of final five guidelines to the key question was assessed (Supplementary Appendix 8). After collecting the opinions of all committee members, the final recommendations were completed. If there was a lack of evidence or a need for clinical interpretation, the consensus process proceeded among the members of the working committee. The strength of evidence was divided into five levels (Table 4), and recommendation grade was assessed considering the level of evidence and clinical effects, patient satisfaction, quality of life, harmful reactions, and unnecessary use of resources (Table 5). The final recommendation grade was decided on the principle of agreement of more than 80%, along with the consent of the working committee.

Selection of eligible patients and fracture risk assessment

The development committee and working committee decided to apply the 2017 ACR guideline for the fracture risk classification and assessment, because relatively little evidence was available beyond these guidelines. Tables and figures were used with permission from the original author.

| Table 3. The additional guidelines for 2nd AGREE evaluation |
|----------------|----------------|----------------|-------------|-------------|
| No. | Title | Country | Institute | Year | Reference |
| 1 | 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis | USA | American College of Rheumatology | 2017 | 16 |
| 2 | UK clinical guideline for the prevention and treatment of osteoporosis | UK | National Osteoporosis Guideline Group (NOGG) | 2012 | 29 |

AGREE: Appraisal of Guidelines for Research and Evaluation.
Table 5. The grade of recommendations

| Grade | Expression | Type of recommendations |
|-------|------------|-------------------------|
| A     | Recommended | It is recommended that the intervention be conducted with sufficient evidence of the desired effect |
| B     | Conditionally recommended | The evidence for the desired effect of the intervention is between moderate and high grounds. It is recommended that intervention (inspection) be provided selectively, or to be conducted to a specific individual at the discretion of the expert |
| C     | Not recommended | There is sufficient evidence on the undesirable effects of the arbitration, and it is not recommended (not recommended) |
| I     | No recommendation | There is insufficient evidence that the intervention is effective or not, and further study of the effect is needed. The degree of confidence in the effectiveness of the intervention is so low that it is judged that the recommendation rating itself is not meaningful |

RESULTS

Fracture risk classification

It is important to classify patients according to fracture risk before deciding whether to use fracture-prevention treatments. To predict fracture risk, we decided to use FRAX, which is widely used in many guidelines for GIOP, including the 2017 ACR guidelines. In addition to FRAX, we also considered using history of previous fracture, BMD, and GC dose as predictors. Patients aged ≥50 years have been the focus of many studies of OP. However, FRAX applies only to patients ≥40 years old, so we divided our recommendations by adults ≥40 years for whom FRAX is applicable, and those under 40 years old who are not included in FRAX. Fracture risk was classified as high, moderate, and low (Table 6). For example, the high risk category included patients ≥40 years of age with previous osteoporotic fracture, BMD T-score ≤–2.5 in men who are ≥50 years of age or postmenopausal women, FRAX-calculated 10-year major osteoporotic fracture risk ≥20%, or FRAX-calculated 10-year hip fracture risk ≥3%. The risk of fracture is correlated with prednisolone dose. For patients taking prednisolone at a dose >7.5 mg/day, FRAX calculates an increase in fracture risk of 15% for major osteoporotic fracture and 20% for hip fracture risk [30].

Table 6. Fracture risk categories in glucocorticoid treated patients

| Fracture risk      | Adults ≥ 40 years of age                              | Adults < 40 years of age |
|--------------------|-------------------------------------------------------|--------------------------|
| High fracture risk | Prior osteoporotic fracture(s)                        | Prior osteoporotic fracture(s) |
|                    | Hip or spine bone mineral density                     |                          |
|                    | 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%   |                          |
| Moderate fracture risk | FRAX (GC-adjusted) 10-year risk of major osteoporotic fracture* 10% ~ 19% | Hip or spine bone mineral density Z score < –3 |
|                    | FRAX (GC-adjusted) 10-year risk of hip fracture >1% and <3% | or rapid bone loss (≥10% at the hip or spine over 1 year) and Continuing GC treatment at ≥7.5 mg/day for ≥6 months |
| Low fracture risk  | FRAX (GC-adjusted) 10-year risk of major osteoporotic fracture* <10% | None of above risk factors other than GC treatment |
|                    | FRAX (GC-adjusted) 10-year risk of hip fracture <1%   |                          |

FRAX: https://www.shef.ac.uk/FRAX/tool.jsp. GC-adjusted: increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is > 7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%). *Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus. Adapted from Buckley et al. Arthritis Care Res (Hoboken) 2017;69:1095-110 [16], with permission of the American College of Rheumatology.
Fracture risk assessment

1) Initial fracture risk assessment

The initial fracture risk assessment should be performed as early as possible in patients with long-term GC treatment. It is appropriate to assess the fracture risk within 6 months of the initiation of long-term GC treatment, and to consider the calculated risks when selecting the specific GC treatment (Figure 2). The most important factors in the initial assessment are the dose, duration, and method of administration of GCs, and history of previous fracture, fall, and frailty. The current nutritional status, weight loss, and the possibility of secondary OP, including thyroid disease, need to be evaluated carefully. In particular, it is necessary to investigate the variables included in FRAX (history of previous fracture, comorbidities, smoking history, alcohol consumption, family history of fracture) in patients ≥ 40 years of age. Adjusting FRAX for GC dose and BMD testing are also necessary. If a patient < 40 years of age has risk factors for fracture (previous osteoporotic fracture, malnutrition, thyroid disease, weight loss, secondary hyperparathyroidism, hypogonadism, family history of femoral fracture, smoking, alcohol consumption, etc.), it is important to conduct a BMD early in treatment to assess fracture risk further.

2) Reassessment of fracture risk

If GCs are used continuously, it is necessary to reassess the risk of fracture every 12 months (Figure 3). For adults ≥ 40 years of age who continue GC treatment and are not treated with OP medications beyond calcium and vitamin D, FRAX and BMD should be performed every one to three years. FRAX and BMD are recommended every year if the initial GC dose is prednisolone ≥ 30 mg/day, if the cumulative dose is greater than 5 g in the previous year, or if osteoporotic fractures have occurred.

For adults ≥ 40 years of age who are at high risk of fracture (initial GC dose of prednisolone ≥ 30 mg/day, cumulative dose ≥ 5 g/year, osteoporotic fracture occurring ≥ 12 months after beginning OP medications, poor medication adherence or absorption, or other significant OP risk factors) who are taking OP medications with GC treatment, BMD testing should be completed every two to three years and is recommended as early as possible. BMD testing should be performed at intervals as soon as

![Figure 2. Initial fracture risk assessment. A clinical fracture risk assessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (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) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient’s age. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is > 7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available. Adapted from Buckley et al. Arthritis Care Res (Hoboken) 2017;69:1095-110 [16], with permission of the American College of Rheumatology.](https://www.shef.ac.uk/FRAX/tool.jsp)
Figure 3. Reassessment of fracture risk. A clinical fracture risk reassessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (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) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient’s age. Very high dose GC treatment was defined as treatment with prednisone ≥ 30 mg/day and a cumulative dose of > 5 g in the past year. Reliability of FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) after OP treatment is debated, but FRAX calculation can be repeated in adults age ≥ 40 years who have not received treatment. It is recognized that in some cases, bone mineral density (BMD) testing may not be available. Adapted from Buckley et al. Arthritis Care Res (Hoboken) 2017;69:1095-110 [16], with permission of the American College of Rheumatology.

possible, even after discontinuation of OP medication.

For adults < 40 years of age who have moderate or high risk and are receiving continuous GC treatment, BMD testing should be conducted every 2 ~ 3 years.

Treatment and follow-up of GIOP

1) KQ1: Is non-pharmacological treatment beneficial for the prevention and treatment of GIOP in adults taking glucocorticoids?

Non-pharmacological treatments such as exercise, good nutrition, smoking cessation, and avoiding alcohol abuse are recommended for all adults taking glucocorticoids. Because there is insufficient evidence for the effects of these treatments in GIOP, it is recommended that treatment be based on data from these treatments in postmenopausal OP patients [III/B].

Because there are limited data on effects of non-pharmacological treatments in the prevention and treatment of GIOP, it is recommended that treatment be based on the established non-pharmacological treatment of postmenopausal OP patients. Although the effects of these lifestyle modifications on fracture risk have not been established for patients with GIOP, non-pharmacological treatments such as weight-bearing exercise, good nutrition, smoking cessation, and avoiding alcohol abuse is recommended for all adults taking GCs [III/B].

2) KQ2: Which pharmacological treatments are effective for prevention and treatment of GIOP in adults < 40 years of age?

There are few randomized controlled trials comparing the effects of drugs on prevention of bone mass loss and
fracture for this age group. This is because adults <40 years of age have relatively high BMD and fewer fractures than postmenopausal women. However, it is reported that long-term use of GCs in premenopausal women <40 years of age may cause changes in bone structure and weaken bone strength [31,32]. Initial pharmacologic treatment for adults <40 years of age is summarized in Figure 4.

(1) KQ2-1: Is calcium and vitamin D supplementation effective in the prevention and treatment of GIOP in adults <40 years of age?

- **Calcium and Vitamin D and lifestyle modifications**
  - **Low risk**
    - No further treatment
      - Monitor with yearly clinical fracture risk assessment with BMD testing every 2~3 years depending on risk factors
  - **Moderate/high risk**
    - <40 years of age
      - 1. History or osteoporotic fracture(s) OR
      - 2. Z score <-2 at hip or spine and prednisolone ≥7.5 mg/day OR
      - 3. ≥10%/year loss of BMD at hip or spine and prednisolone ≥7.5 mg/day OR
      - 4. Very high dose GCs and ≥30 years
    - ≥40 years of age
      - 1. History or osteoporotic fracture(s) OR
      - 2. Men ≥50 years and postmenopausal women with BMD T score ≤-2.5 at hip or spine OR
      - 3. FRAX (GC-adjusted) 10-year risk for major osteoporotic fracture ≥10% OR
      - 4. FRAX (GC-adjusted) 10-year risk for hip fracture >1% OR
      - 5. Very high dose GCs
- **Women of childbearing potential (not planning a pregnancy during period of OP treatment)**
  - Treat with an oral bisphosphonate
    - Second-line therapy: teriparatide
- **Women not of childbearing potential and men**
  - 1. Bisphosphonate. Oral bisphosphonates preferred. If oral bisphosphonate are not available, intravenous bisphosphonates
  - 2. Teriparatide
  - 3. Denosumab
  - 4. SERM: If bisphosphonates, teriparatide and denosumab are not available in postmenopausal women

**Figure 4.** Initial pharmacologic treatment for adults. Recommended doses of calcium and vitamin D are 1,000~1,200 mg/day and 600~800 IU/day (serum level ≥ 20 ng/mL), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1~2 alcoholic beverages/day. Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone ≥ 30 mg/day and a cumulative dose of > 5 g in the past year. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is > 7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available. SERM: selective estrogen receptor modulator. Adapted from Buckley et al. Arthritis Care Res (Hoboken) 2017;69:1095-110 [16], with permission of the American College of Rheumatology.
Glucocorticoids reduce intestinal absorption and renal reabsorption of calcium, and increase calcium excretion into the urine [33]. Therefore, calcium and vitamin D are recommended for adults < 40 years of age who are taking prednisolone ≥ 2.5 mg for ≥ 3 months [II/B]. However, calcium alone is not effective in the prevention and treatment of GIOP [34-36], it is more effective to take calcium and vitamin D together. Patients receiving vitamin D3 (cholecalciferol) [37,38] or activated vitamin D (calcitriol, alphacalcidol) [39,40] in combination with calcium showed an inhibitory effect on bone loss compared to calcium alone or no treatment. Adequate intake of calcium (1,000 ~ 1,200 mg) and vitamin D (800 IU) are recommended to maintain vitamin D concentration (≥ 20 ng/mL) [expert consensus/B]. The use of supplements may be considered if the intake of calcium and vitamin D through meals is insufficient [expert consensus/B].

(2) KQ2-2: Is bisphosphonate effective in the prevention and treatment of GIOP in adults < 40 years of age?

1. Oral bisphosphonates are recommended for adults < 40 years of age with moderate to high risk of fracture [II/A].
2. If oral bisphosphonates are not appropriate intravenous bisphosphonate is recommended [II/A].

Bisphosphonates are recommended for women without childbearing potential and men < 40 years of age at moderate to high fracture risk [II/A]. Alendronate was effective in prevention of bone loss and fractures in premenopausal women with high-dose GC therapy [41]. Subgroup analysis of adults < 40 years of age has been done in several previously published studies on GIOP treatment. These studies have shown that bisphosphonates such as alendronate [41-46], risedronate [47-49], zoletronic acid [50] increased BMD and decreased fracture risk compared to placebo or calcium/vitamin D. Oral bisphosphonates, which have a relatively short half-life, are preferred. If oral bisphosphonates are not appropriate, intravenous bisphosphonate is recommended.

(3) KQ2-3: Is teriparatide effective in the prevention and treatment of GIOP in adults < 40 years old?

Teriparatide is recommended for adults < 40 years old with moderate to high risk of fracture [II/A].

Teriparatide is recommended for women without childbearing potential and men < 40 years of age at moderate to high fracture risk [II/A]. Among patients taking prednisolone ≥ 5 mg/day for ≥ 3 months, teriparatide treatment led to significantly higher spine BMD than alendronate treatment in both postmenopausal and premenopausal women [51].

(4) KQ2-4: Is denosumab effective in the prevention and treatment of GIOP in adults < 40 years of age?

Denosumab is recommended for adults < 40 years of age?

Recommendations for calcium and vitamin D supplementation in adults ≥ 40 years of age are the same as for adults < 40 years of age. Calcium and vitamin D are recommended for adults ≥ 40 years of age who are taking prednisolone ≥ 2.5 mg for ≥ 3 months [II/B]. Sufficient calcium (1,000 ~ 1,200 mg) and vitamin D (800 IU) intakes are recommended, and adequate vitamin D concentrations (≥ 20 ng/mL) should be maintained [Expert consensus/B].

3) KQ3: Which pharmacological treatments are effective for the prevention and treatment of GIOP in adults ≥ 40 years of age?

Initial pharmacologic treatment for adults ≥ 40 years of age is summarized in Figure 4.

(1) KQ3-1: Is calcium and vitamin D supplementation effective in the prevention and treatment of GIOP in adults ≥ 40 years of age?

1. Calcium and vitamin D are recommended for all adults taking prednisolone ≥ 2.5 mg/day for ≥ 3 months [II/B].
2. Sufficient calcium (1,000 ~ 1,200 mg) and vitamin D (800 IU) intakes are recommended, and adequate vitamin D concentrations (≥ 20 ng/mL) should be maintained [Expert consensus/B].
3. The use of supplements should be considered when the intake of calcium and vitamin D through meals is insufficient [Expert consensus/B].
4. The adequate dosage should be considered, because high doses of calcium and vitamin D supplementation may increase the risk of gastrointestinal side effects and renal stones [Expert consensus/B].
The use of supplements should be considered when the intake of calcium and vitamin D through meals is insufficient [expert consensus/B]. The adequate dosage should be considered, because high doses of calcium and vitamin D supplementation may increase the risk of gastrointestinal side effects and renal stones [53] [expert consensus/B]. There are concerns about increased risk of cardiovascular disease due to calcium intake, but a recent meta-analysis reported that calcium intake did not increase cardiovascular outcomes and mortality, regardless of the combination of vitamin D agents [54].

(2) KQ3-2: Is bisphosphonate effective in the prevention and treatment of GIOP in adults ≥40 years of age?

| Oral bisphosphonates are recommended for adults ≥40 years of age with moderate to high risk of fracture [I/A]. |
| If oral bisphosphonates are not appropriate, intravenous bisphosphonate is recommended [I/A]. |
| There is no evidence of increased side effects such as atypical femoral fractures or osteonecrosis of the jaw caused by bisphosphonates in patients with GIOP. However, when planning long-term bisphosphonates use in patients with GIOP, the risk-benefit ratio should be considered [Expert consensus/B]. |

Oral bisphosphonates are recommended for adults ≥40 years of age with moderate to high risk of fracture. If oral bisphosphonates are not appropriate, intravenous bisphosphonate is recommended [I/A]. Alendronate and risedronate can be used as oral bisphosphonates, and the effects of alendronate [42-46,55,56] and risedronate [47-49,57-59] on the prevention and treatment of GIOP have been demonstrated through several studies. Ibandronate, an oral bisphosphonate, has been shown to increase spine and hip BMD and decrease bone turnover markers compared to placebo in postmenopausal women taking GCs for rheumatic diseases [60]. However, evidence for the use of ibandronate for GIOP prevention is still insufficient. Zoledronic acid was superior to risedronate as an intravenous bisphosphonate for the prevention and treatment of GIOP [50,61]. Bisphosphonates are associated with osteonecrosis of the jaw [62-64] or atypical femoral fracture [65-70], but there is no evidence of increased side effects caused by bisphosphonates in patients with GIOP. However, when planning long-term bisphosphonate use in patients with GIOP, the risk-benefit ratio should be considered [expert consensus/B].

(3) KQ3-3: Is teriparatide effective in the prevention and treatment of GIOP in adults ≥40 years of age?

Teriparatide is recommended for adults ≥40 years of age with moderate to high risk of fracture [I/A]. When comparing the use of teriparatide with that of estrogen for 12 months in postmenopausal women with GIOP, spine and hip BMD were significantly increased in the teriparatide group, and there was no difference in forearm BMD between the two groups [71]. In addition, the use of teriparatide for 18 months or 36 months led to a significant increase in the spine and hip BMD, and reduction of vertebral fracture risk, compared with the use of alendronate. However, there was no difference in the reduction effect of non-vertebral fracture risk between the two groups [51,72,73].

(4) KQ3-4: Is denosumab effective in the prevention and treatment of GIOP in adults ≥40 years of age?

Denosumab is recommended for adults ≥40 years of age with moderate to high risk of fracture [I/A]. For patients with rheumatoid arthritis taking methotrexate and prednisolone ≥2.5 mg/day for ≥3 months, the effects of denosumab on BMD and bone turnover were compared with placebo. Denosumab treatment increased spine and hip BMD and reduced bone turnover markers for 12 months [74]. Recently, in a randomized, double-blind, comparative study of denosumab and risedronate in patients ≥19 years of age taking prednisolone ≥7.5 mg/day for ≥3 months, denosumab significantly increased spine and femoral BMD compared to risedronate [52].

(5) KQ3-5: Is SERM effective in the prevention and treatment of GIOP in postmenopausal women?

In the treatment of GIOP, selective estrogen receptor modulating agents have not been sufficiently proven to be effective in the prevention of fractures. However, if bisphosphonates, teriparatide, and denosumab are not available to postmenopausal women with moderate to high risk of fracture, SERM should be considered [II/B].

In the treatment of GIOP, selective estrogen receptor modulating agent (SERM) has not been sufficiently proven to be effective in the prevention of fractures. However, if bisphosphonates, teriparatide, and denosumab are not available to postmenopausal women with moderate to high risk of fracture, SERM should be considered [II/B].

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mab are not available in postmenopausal women with moderate to high risk of fracture, SERM should be considered [II/B]. For postmenopausal women taking prednisolone ≤ 10 mg/day for ≥6 months, 12 months of raloxifene treatment significantly increased lumbar spine and hip BMD and decreased bone turnover markers [75].

4) KQ4: Is it safe to use OP medications in women planning to have a pregnancy?

① Oral bisphosphonates are preferred for women with moderate to high risk of fracture who are planning to have a pregnancy [Expert consensus/C].
② Teriparatide is considered in women with moderate to high risk of fracture who are planning to have a pregnancy [Expert consensus/C].
③ Because of lack of evidence of fetal safety, intravenous bisphosphonate and denosumab are not recommended [Expert consensus/C].
④ OP medications except calcium and vitamin D are not recommended for use during pregnancy [Expert consensus/C].

Women who plan to become pregnant should be cautious in the use of OP medication [expert consensus/C]. Oral bisphosphonates are preferred, and teriparatide is also considered for women with moderate to high risk of fracture. However, intravenous bisphosphonate and denosumab are not recommended because of lack of evidence of fetal safety. OP medications except calcium and vitamin D are not recommended for use during pregnancy. When bisphosphonates were used in pregnant rats in vivo, abnormal ossification and calcification of the offspring skeletal system were found at birth [76]. However, in pregnant women exposed to bisphosphonates before or during pregnancy, there were no differences in pregnancy outcomes or birth defects when compared to unexposed pregnant women [77,78].

5) KQ5: How should response to treatment be monitored in patients with GIOP using physical measurements, imaging, and biochemical methods?

① Annual BMD and fracture risk assessment using FRAX are recommended in patients taking continuous GCs. The simple spine x-ray examination is recommended to evaluate vertebral fractures [Expert consensus/B].
② Regular follow-up is recommended to assess compliance with OP medication [Expert consensus/B].
③ There is insufficient evidence for biochemical monitoring of treatment response in patients with GIOP [Expert consensus/I].
④ Annual BMD and fracture risk assessment using FRAX are recommended in patients taking continuous GCs [expert consensus/B]. BMD is measured at the lumbar spine and hip by dual energy X-ray absorptiometry (DXA). A simple spine X-ray is recommended to evaluate vertebral fractures radiographically [expert consensus/B]. Regular follow-up is recommended to assess compliance with OP medications [expert consensus/B]. There is insufficient evidence for biochemical monitoring of treatment response in patients with GIOP [expert consensus/I].

6) KQ6: Should discontinuation of OP medication be considered if the fracture risk is reassessed to be low during GIOP treatment?

When glucocorticoid treatment is discontinued in patients with GIOP and low fracture risk, discontinuation of OP medication may be considered. Discontinuation of OP medication should be individualized, taking into consideration the risk-benefit ratio [Expert consensus/B].

When GC treatment is discontinued in patients with GIOP and the result of fracture risk reassessment is low (low fracture risk), discontinuation of OP medication may be considered [expert consensus/B]. Discontinuation of medication should be individualized, considering the risk-benefit ratio [expert consensus/B]. For adults ≥40 years of age, when glucocorticoid treatment was discontinued, discontinuation of OP medication was considered if the patient had a follow-up BMD T-score > -2.5, a 10-year risk of major osteoporotic fracture < 10%, or a 10-year risk of hip fracture < 1% after FRAX adjustment for GCs dose. For adults < 40 years of age, when glucocorticoid treatment was discontinued, discontinuation of...
OP medication was considered if there were no risk factors such as low BMD (Z score < -3.0), history of previous fracture, and low body weight. When fracture risk is moderate to high, OP medication should be continued even if GCs are discontinued.

7) KQ7: How should initial treatment failure be defined for GIOP?

① For adults ≥ 40 years of age, initial treatment failure is defined as follows: Osteoporotic fractures occur more than 2 times after initiation of oral bisphosphonate treatment or osteoporotic fractures occur or there is significant BMD reduction (≥ 10% /year) after 12 months of treatment initiation. Switching to another OP medication is recommended [Expert consensus/B].

② When fracture risk reassessment is moderate to high after five years of oral bisphosphonate treatment, active OP treatment is recommended [Expert consensus/B].

If osteoporotic fractures occur more than 2 times after initiation of oral bisphosphonate treatment or osteoporotic fractures occur after 12 months of treatment initiation, or if there is significant BMD reduction (≥ 10% /year) at follow-up, this is defined as initial treatment failure. Switching to another OP medication is recommended [Expert consensus/B].

When fracture risk reassessment is moderate to high after oral bisphosphonate treatment for 5 years in adults ≥ 40 years of age, active OP treatment is recommended [expert consensus/B]. In this case, bisphosphonates could be used continuously without a drug holiday, and medications could be changed to intravenous bisphosphonate or other OP medications depending on the patient’s drug compliance and treatment response.

DISCUSSION

The aim of developing this guideline was to promote effective treatment of GIOP by presenting standardized recommendations for prevention and treatment of GIOP for all clinicians treating patients who use or plan to use GCs. The primary implication of this guideline is that all clinicians treating patients with GCs should be aware of the risk of GIOP, identify those at high risk of fracture, and provide appropriate treatment. While OP treatment is currently given primarily to patients whose decreased bone mass was solely determined by BMD, this new guideline recommends that fracture risk should be assessed generally so that patients with moderate to high risk of fracture could receive OP treatment. Considering the pathophysiological characteristics of GIOP, it is clinically important to prevent the reduction of bone mass by glucocorticoids.

To develop this guideline, the KSBMR and the KCR jointly formed a development committee and a working committee with experts in the field. These committees used systematic literature searches and adapted previously-published guidelines, following guidelines for the development of CPGs by NECA. This new guideline includes recommendations for the assessment and monitoring of fracture risk, as well as the treatment and prevention of fractures during the period of GC administration for adults ≥ 19 years of age.

This guideline recommends the use of oral bisphosphonates as first line therapy for GIOP in adults ≥ 40 years of age [I/A]. Other guidelines for OP primarily recommend the use of intravenous bisphosphonate, teriparatide, and denosumab for high-risk groups such as GIOP [79]. However, the major published clinical studies show that oral bisphosphonates have the highest evidence level when considering fracture reduction, safety, and cost.

This guideline has several limitations and many further studies are needed. First, since domestic clinical studies on GIOP have been scarce, this guideline was developed by adapting guidelines published in other countries. Unfortunately, the guidelines published in other countries also suffer from limited clinical and epidemiological data on GIOP-induced fractures. Clinical trials assessing fracture as a primary outcome in patients taking GCs are especially needed. Notably, both GIOP and non-GIOP clinical trials show similar effects of OP medications on relative fracture risk. Therefore, results of non-GIOP clinical trials could be generalized to patients with GIOP. However, these estimates are not accurate in estimating clinical benefits from practical treatment. Second, this guideline accepts treatment criteria of FRAX, used in the United States. According to FRAX, OP treatment should be considered if the risk of major osteoporotic fractures over 10 years is > 10% or hip fracture risk over 10 years is > 1%. If these treatment criteria are calculated in reverse by FRAX, we can estimate the range of BMD corresponding to treatment targets according to age. For example, FRAX would recommend treatment in the following...
patients: Korean women with a body mass index of 25 kg/m² when there is no other risk factor except taking GCs; and T-score of the hip BMD ≤−2.0 in all adults ≥40 years of age, ≤−1.5 in adults ≥50 years of age, ≤−1.0 in adults ≥60 years of age, and any T-score in adults ≥80 years of age. However, FRAX criteria specific to Koreans should be established to overcome the limitations of FRAX and to assess the risk of fracture more precisely. Third, there have been few studies of fractures in adults <40 years of age and, therefore, there are no means to assess fracture risk. Because of these limitations, the levels of evidence of most of the recommendations in these guidelines were moderate (II) or expert consensus.

This guideline recommends that calcium and vitamin D could be administered to patients with GIOP, as it is to postmenopausal OP patients, but the evidence is not sufficient. Although there is a concern for cardiovascular risk due to calcium and vitamin D supplementation, adequate calcium intake might be more important because GCs increase urinary calcium excretion in patients taking GCs. Hence, it is necessary to investigate the appropriate calcium and vitamin D supplementation for patients taking GCs. Additional studies in patients taking GCs are needed to investigate the differences of fracture risk according to age and gender, the role of the simple spine X-ray to assess fracture risk, fetal safety of OP medication in women with childbearing potential, and the effects of pharmacological treatment in children.

In Korea, OP medication is recognized as an insurance benefit only when the T-score is ≤−2.5 in BMD testing or when osteoporotic fracture is detected at the time of radiography. However, as described above, because the risk of glucocorticoid-induced fracture increases before a significant reduction in bone mass occurs [3], many patients’ fracture risk could be underestimated if the decision to treat GIOP is made solely from the results of BMD. Therefore, gradual institutional improvement is needed to expand the insurance coverage of OP medications to patients at high risk of fracture, such as those taking GCs long-term and previous fracture history. Additionally, an efficient quality index should be developed to assess the effectiveness of this guideline in the prevention and treatment of GIOP.

**CONCLUSION**

In conclusion, GIOP is a problem that all clinicians should be interested in, and patients should also be aware of the risks. Clinicians should evaluate the risk of fracture for all patients taking GCs and actively prevent reduction of bone mass.

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**CONFLICT OF INTEREST**

Yoon-Kyung Sung has received financial support for clinical research sponsored by Pfizer within the last 2 years. Dong Ah Park has participated in the development of headache clinical practical guidelines for methodology consultation. The other authors declare no conflict of interest. If a committee member receives research funding from a company, that member does not participate in discussions or votes concerning that company’s drug.

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한국인 글루코코르티코이드 유발 골다공증 진료지침

소영주, 김규현, 김영민, 김담, 김혜영, 정홍연, 김혜연, 김진호, 이은주, 이성호, 이성욱, 이성숙, 이성률, 이상도, 이성주, 이성하, 이성현, 이성구, 이성연, 이성득, 이성복, 이성호, 이성상, 이성원, 이성환

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목적
한국인의 글루코코르티코이드 유발 골다공증의 예방과 치료를 위한 진료 지침과 권고안을 개발하고자 하였다.

방법
대한골대사학회와 대한류마티스학회는 한국보건의료연구원에서 작성한 임상진료지침 개발 매뉴얼에 따라 공동으로 진료지침을 개발하였다. 국내 연구 결과가 제한적인 점을 고려하여, 기존에 개발된 근거 중심 진료지침을 수용 개작하였다. 핵심 질문 선정과 진료지침의 체계적 고찰이 수행되었으며 질평가를 통해 선정된 진료지침을 대상으로 핵심 질문에 대한 대답과 권고안이 동료 검토를 통해 도출되었다.

결과
본 진료지침의 적용 대상은 글루코코르티코이드를 사용하거나 사용할 계획인 19세 이상의 성인이며, 소아 및 청소년은 포함하지 않았다. 골절 위험도의 초기 평가는 글루코코르티코이드 시작 6개월 내에 이루어져야 하며, 장기간 사용시 12개월마다 골절 위험도를 평가해야 한다. 골절 위험도는 글루코코르티코이드의 용량을 보정한 FRAX와 과거 골절력에 의한 골절력, 골밀도 결과 등으로 평가한다. 매일 프레드니솔론 2.5mg을 3개월 이상 복용하는 경우 적절한 칼슘과 비타민D를 투여할 것을 권고한다. 중등도 이상의 골절 위험이 있는 환자들의 경우 골다공증 약제를 두어야 한다. 가임기 여성은 골다공증 약제 사용에 주의가 필요하다. 글루코코르티코이드를 지속적으로 두어야하는 환자들에게 매년 골밀도, FRAX를 이용한 골절위험도 평가 및 척추 단순 엑스선 검사를 시행할 것을 권고한다.

결론
임상의들을 위한 글루코코르티코이드 유발 골다공증의 예방과 치료에 대한 진료지침이 개발되었다.
표 1. 백신질문

백신질문1. 글루코코르티코이드를 사용하는 환자에서 비약물적 치료가 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

백신질문2. 40세 미만 성인에서 어떤 약물 치료가 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
2-1. 40세 미만 성인에서 칼슘과 비타민D 보충은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
2-2. 40세 미만 성인에서 비스포소네이트(bisphosphonate) 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
2-3. 40세 미만 성인에서 테리파라티드(teriparatide) 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
2-4. 40세 미만 성인에서 탄수화물(deoxanomab) 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
백신질문3. 40세 이상 성인에서 어떤 약물 치료가 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
3-1. 40세 이상 성인에서 비타민D 보충은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
3-2. 40세 이상 성인에서 비스포소네이트 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
3-3. 40세 이상 성인에서 테리파라티드는 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
3-4. 40세 이상 성인에서 탄수화물 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
3-5. 폐경 후 여성에서 선택적 에스트로겐 수용체 조절제 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

방 법

진료지침의 적용 대상은 글루코코르티코이드를 사용하거나 사용할 계획인 19세 이상의 성인이며 소아 및 청소년과 사구체 여과율이 30 mL/minute 미만인 경우 포함하지 않았다. 글루코코르티코이드 유발 골다공증 진료지침을 개발하기 위해 내분비내과와 전문의, 류마티스내과 전문의, 정형외과 전문의 및 방법론 전문가를 포함한 다양한 전문가 및 다기관으로 구성된 개발위원회와 실무위원회가 구성되었으며, (부록 1) 이를 통해서 체계적 문헌고찰을 통한 진료지침의 선정과 체계적 진료지침 선정 절차를 통해서 최종적으로 선택된 진료지침을 수용 개정 하였다. 본 진료지침은 5년 이내 개정을 검토할 계획이며, 해당 질환에 대한 신약이 승인되거나 근거가 크게 변경되면 초기 개정이 필요할 수 있다.

진료지침 작성방법

진료지침의 작성은 한국보건의료연구원(National Evidence-Based Healthcare Collaborating Agency, NECA)에서 작성한 임상진료지침 개발 매뉴얼(Guidance for develop-
핵심 질문(Key question, KQ)의 선정
글루코코르티코이드 유발 골다공증 임상진료지침의 핵심 질문을 선정하기 위하여 총 9명의 위원으로 구성된 실무위원회에서 미국, 프랑스, 스페인, 일본, 브라질, 그리고 국제골다공증재단-유럽골대사학회(International Osteoporosis Foundation-European Calcified Tissue Society, IOF-ECTS)에서 개발된 진료지침 총 6개를 검토하여 일차적으로 14가지의 관련 주제를 선정하였다. 개발위원회에서 이 주제들을 검토 후 임상적 중요성과 국내 실정을 고려하여 최종적으로 주제를 선택하였다. 이에 대해 인구 집단(P, patient population), 중재법(I, intervention), 비교 중재법(C, comparator), 중재 결과(O, outcome) 등의 내용을 포함하여 최종적으로 7가지의 핵심 질문을 결정하였다(표 1).

**진료지침의 검색과 선별**
관련 문헌의 검색은 두 명의 실무위원이 진료지침 검색어를 활용하여 포괄적으로 검색을 시행하였다. 주요 정보원은 PubMed와 OVID-EMBASE의 국외 정보원, KoreaMed와 KMbase의 국내 정보원, 그리고 National Guideline Clearinghouse, Guidelines International Network, Korean Medical Guideline Information Center (KoMGI) 등의 진료지침 등록 사이트를 검색하였다. 검색과 검색된 2010년 이후 출간된 문헌은 총 309편이었다. 제목과 초록을 검토하여 27개의 문헌을 선택하였고, 이에 대한 원문 검토를 통해 1) 핵심질문과 일치하는 PICO를 포함하는 진료지침 2) 근거기반 진료지침(체계적 문헌검색의 보고가 있고, 권고와 지지 근거 사이에 명확한 연계가 있는 것) 3) 동료검토가 이루어진 진료지침, 4) 한국어 또는 영어로 출판된 진료지침으로 최종 7개가 선정되었다(표 1, 부록3,4).

**진료지침의 최종 선정 과정**
체계적 문헌고찰과 선정기준 및 배제기준을 통해서 선정된 7개의 진료지침서에 대한 평가를 통해서 최종적으로 수용, 계층할 진료지침을 선정하였다(표 2). 진료지침의 최종 과정은 Appraisal of Guidelines for Research and Evaluation II(이하 AGREEII)를 통해 시행하였고, 종합평가 이외에 범위와 목적, 개발의 엄격성, 이해 당사자의 참여, 명확성과 표현, 적용성 및 편집 독립성에 대해 평가하였다. AGREEII를 이용한 진료지침 평가는 진료지침
표 2. 1차 AGREE 평가를 위해 선택된 글루코코르티코이드 유발 골다공증 임상진료지침

| 제목 | 국가 | 기관 | 년도 | 참고문헌 |
|------|------|------|------|---------|
| 1 American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis [21] | 미국 | American College of Rheumatology | 2010 | Arthritis Care Res. 2010 Nov;62 (11):1515-26 |
| 2 A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis [22] | 해당 없음 | Joint IOF-ECTS GIO Guidelines Working Group | 2012 | Osteoporos Int. 2012 Sep;23(9): 2257-76 |
| 3 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary [23] | 캐나다 | Scientific Advisory Council of Osteoporosis Canada | 2010 | J Bone Miner Metab. 2014 Jul;32(4):337-50 |
| 4 2014 update of recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis [24] | 프랑스 | Bone Section of the French Society for Rheumatology (SFR) and Osteoporosis Research and Information Group (GRIQ) | 2014 | Joint Bone Spine. 2014 Dec;81(6): 493-501 |
| 5 Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis [25] | 브라질 | Committee for Osteoporosis and Bone Metabolic Disorders of the Brazilian Society of Rheumatology; Brazilian Medical Association; Brazilian Association of Physical Medicine and Rehabilitation | 2012 | Rev Bras Reumatol. 2012 Aug;52(4):580-93. |
| 6 Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update [26] | 일본 | Japanese Society for Bone and Mineral Research | 2014 | Reumatismo. 2016 Jun 23;68(1):1-39. |
| 7 Guidelines for the diagnosis, prevention and management of osteoporosis [27] | 이탈리아 | The Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS) | 2016 | |

표 3. 2차 AGREE 평가를 위해 추가된 임상진료지침

| 제목 | 국가 | 기관 | 년도 | 참고문헌 |
|------|------|------|------|---------|
| 1 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [16] | 미국 | American College of Rheumatology | 2017 | Arthritis Care Res. (Hoboken). 2017 Sep 21. [Epub ahead of print] |
| 2 UK clinical guideline for the prevention and treatment of osteoporosis [29] | 영국 | National Osteoporosis Guideline Group (NOGG) | 2012 | Arch Osteoporos. 2017 Dec;12(1):43. |

당 3명의 실무위원이 담당하였으며, 실무위원간 일정 점수 이상의 차가 나는 항목에 대해서는 재검토와 합의 (consensus)의 과정을 거쳤다. 진료지침의 선정에는 특히 개발의 엄격성을 고려하였으며, 이를 통하여 미국(2010 년), IOF-ECTS, 캐나다, 프랑스의 진료지침 4개가 선정되었다[21-24]. 진료지침을 선정하는 동안 영국의 국가 골다공증 진료지침 그룹(National Osteoporosis Guideline Group, NOGG)과 미국류마티스학회(American College of Rheumatology, ACR)에서 글루코코르티코이드 유발 골다공증의 진료지침이 발표되었다[16,29] 따라서, 2010 미국류마티스학회 진료지침은 2017 미국류마티스학회 진료 지침으로 대체하여(표 3).
표 4. 근거 수준 정의

| 근거수준 | 표현 | 의미 |
|----------|------|------|
| I        | 높음 (High) | 다른 연구가 효과 추정에 대한 신뢰를 바꾸는 경우가 거의 없음 (무작위대조시험, 무작위대조시험의 체계적 검토) |
| II       | 중등도 (Moderate) | 다른 연구가 효과 추정에 대한 본 위원회의 신뢰에 중요한 영향을 미칠 수 있으며 추정에 대한 신뢰 정도가 변할 수 있음 (I에 해당되지 않으나, 전향적 디자인의 관찰 연구, 환자-대조군 연구가 있는 경우) |
| III      | 낮음 (Low) | 다른 연구가 효과 추정에 대한 본 위원회의 신뢰에 매우 중요한 영향을 미칠 수 있으며 추정에 대한 신뢰 정도가 변할 수 있음 (후향적 디자인의 관찰 연구, 환자-대조군 연구) |
| IV       | 매우 낮음 (Very low) | 본 위원회의 추정값에 대한 신뢰 정도를 확신하지 않음 (해당 연구 없음) |
| EC       | 전문가의 합의 (Expert consensus) | 근거 문헌은 없으나 본 위원회 전문가의 공식적 합의를 통해 현재수준에서 합시적으로 적용하기에 적합함 |

표 5. 권고 등급 정의

| 권고등급 | 표현 | 의미 |
|----------|------|------|
| A        | 시행하는 것을 권고함 (recommended) | 해당 중재는 원하는 효과에 대한 충분한 근거가 있어 시행할 것을 권고함 |
| B        | 조건부로 시행하는 것을 권고함 (conditionally recommended) | 해당 중재는 원하는 효과에 대한 근거는 중등도와 높은 근거 사이임. 중재의 실행은 선택적으로 제공하거나, 전문가의 판단에 따라 특별한 개인에게 시행할 것을 권고함 |
| C        | 시행하지 않는 것을 권고함 (not recommended) | 해당 중재의 효과가 있거나 없다는 것에 대한 근거는 부족분하고, 효과에 대한 추가적인 연구가 필요함. 해당 중재의 효과에 대한 확신도가 매우 낮음. 권고등급 결정 자체가 의미가 없다고 판단함 |
| I        | 권고 없음 (no recommendation) | 해당 중재의 효과가 있거나 없다는 것에 대한 근거는 부족분하고, 효과에 대한 추가적인 연구가 필요함. 해당 중재의 효과에 대한 확신도가 매우 낮음. 권고등급 결정 자체가 의미가 없다고 판단함 |

결과

대상 환자의 골절 위험도 예측과 분류

골절 위험도를 기반한 치료 결정에 있어서 대상 환자를 골절 위험도 예측에 따라 분류하는 것이 중요하다. 골절 위험도 예측을 위하여 2017 ACR 진료지침을 비롯한 많은 글루코코르티코이드 유발 골다공중 진료지침에서 널리 사용되고 있는 FRAX를 사용하기로 하였다. FRAX 이용에도 환자의 골질력, 골밀도 검사 결과, 그리고 골루코르티코이드 용량 등 독립적인 위험인자도 반영하여 환자의 골절 위험도를 예측하고 분류하였다(표 5). 특히 연령은 많은 골다공중 연구가 50세 이후로 진행되고 있으나, 이는 FRAX의 계산식에 이미 반영되는 측면이 있어, FRAX의 사용이 가능한 40세 이상 성인과 그렇지 않은 40세 미만 성인
표 6. 글루코코르티코이드 치료 중인 환자들의 골절 위험도에 따른 분류

| 골절 위험         | 40세 이상 | 40세 미만 |
|------------------|----------|----------|
| 높은 위험도       | 이전 골다공증 치료력 | 이전 골다공증 치료력 |
|                  | 대퇴골 또는 척추골밀도 | 대퇴골 또는 척추골밀도 |
|                  | 50세 이상의 나이성 패턴 구분 후 T-값 ≤ −2.5 | 대퇴골 또는 척추골밀도 Z-값 < −2.5 또는 월드 글로벌 스코어의 12.5% 미만 |
|                  | FRAX* (글루코코르티코이드 용량 보정값 †) | FRAX* (글루코코르티코이드 용량 보정값 †) |
|                  | 10년 내 주요 골다공증 골절 위험도 ≥ 20% | 10년 내 주요 골다공증 골절 위험도 ≥ 20% |
|                  | 10년 내 대퇴골 골절 위험도 ≥ 3% | 10년 내 대퇴골 골절 위험도 ≥ 3% |
| 중등도 위험도     | FRAX* (글루코코르티코이드 용량 보정값 †) | FRAX* (글루코코르티코이드 용량 보정값 †) |
|                  | 10년 내 주요 골다공증 골절 위험도 ≥ 10~19% | 10년 내 주요 골다공증 골절 위험도 ≥ 10~19% |
|                  | 10년 내 대퇴골 골절 위험도 > 1% 그리고 < 3% | 10년 내 대퇴골 골절 위험도 > 1% 그리고 < 3% |
| 낮은 위험도       | FRAX* (글루코코르티코이드 용량 보정값 †) | FRAX* (글루코코르티코이드 용량 보정값 †) |
|                  | 10년 내 주요 골다공증 골절 위험도 < 10% | 10년 내 주요 골다공증 골절 위험도 < 10% |
|                  | 10년 내 대퇴골 골절 위험도 ≤ 1% | 10년 내 대퇴골 골절 위험도 ≤ 1% |

*https://www.shef.ac.uk/FRAX/tool.jsp. †글루코코르티코이드 사용량이 프레드니솔론 사용량을 기준으로 7.5 mg/일을 초과한 용량을 사용할 경우에는 FRAX로 산출한 값이 10년 주요 골절 위험도 20% 이상일 경우에만 적용 

그림 2. 초기 골절 위험도 평가. 임상적 골절 위험도 평가는 글루코코르티코이드 사용력(용량, 기간, 사용 패턴), 낙상, 골절, 다른 골다공증 위험 인자들 (영양 불량, 급격한 체중 감소 또는 체중 증가, 성장기능저하증, 이차 부합상성기능저하증, 잡상신경질환, 대퇴골 골절의 가족력, 유전자 항체 검사(백혈증, 캐노길, 그리고 피, 몸무게, 근력평가, 그리고 잡상신경질환의 척추절, 경추절, 그리고 하부 간비뼈와 상부 골반 사이의 좁은 공간)를 포함하는 신체 검진을 포함한다. 글루코코르티코이드 사용량이 프레드니솔론 사용량을 기준으로 7.5 mg/일을 초과한 용량을 사용할 경우에는 FRAX (https://www.shef.ac.uk/FRAX/tool.jsp.)을 이용하여 산출한 10년 내 주요 골절 위험도에 1.15를, 10년 내 대퇴골 골절 위험도에 1.2를 곱한다. (예를 들어, FRAX로 산출된 10년 내 주요 골절 위험도가 2.0%라면, 2.2%로 증가한다.) 어떤 경우에는 골밀도 검사가 가능하지 않을 수 있으므로, 원저[16]의 허락을 받아 제시하였다.

그림 2. 초기 골절 위험도 평가. 임상적 골절 위험도 평가는 글루코코르티코이드 사용력(용량, 기간, 사용 패턴), 낙상, 골절, 다른 골다공증 위험 인자들(영양 불량, 급격한 체중 감소 또는 체중 증가, 성장기능저하증, 이차 부합상성기능저하증, 잡상신경질환, 대퇴골 골절의 가족력, 유전자 항체 검사(백혈증, 캐노길, 그리고 피, 몸무게, 근력평가, 그리고 잡상신경질환의 척추절, 경추절, 그리고 하부 간비뼈와 상부 골반 사이의 좁은 공간)를 포함하는 신체 검진을 포함한다. 글루코코르티코이드 사용량이 프레드니솔론 사용량을 기준으로 7.5 mg/일을 초과한 용량을 사용할 경우에는 FRAX (https://www.shef.ac.uk/FRAX/tool.jsp.)을 이용하여 산출한 10년 내 주요 골절 위험도에 1.15를, 10년 내 대퇴골 골절 위험도에 1.2를 곱한다. (예를 들어, FRAX로 산출된 10년 내 주요 골절 위험도가 2.0%라면, 2.2%로 증가한다.) 어떤 경우에는 골밀도 검사가 가능하지 않을 수 있으므로, 원저[16]의 허락을 받아 제시하였다.
골절 위험도 평가 시기
1) 골절 위험도의 초기 평가
골절 위험도의 초기 평가는 글루코코르티코이드를 장기간 사용하는 환자에게 일찍 시행하는 것이 필요하다. 즉, 사용 시작 6개월 내에 골절 위험도를 평가하여, 산출된 위험도에 따라서 약제를 선택하는 것이 적절하다(그림 2).

초기평가에서 가장 중요한 것은 사용하고자 하는 글루코코르티코이드의 용량, 기간, 두어 방법과 과거의 골절력, 낙상 및 최악의 유무 등을 들 수 있다. 현재의 영양 상태 및 체중 감소, 갑상선 질환을 비롯한 2차 골다공증의 발생 가능성이 높아지기 때문에 이를 파악할 수 있다. 특히 40세 이상 환자에서 FRAX에 포함되어야 할 변수들(골절력, 과거 질환 및 동반 질환, 홍역력, 응력구, 골절력의 과거력과 가족력 등)에 대한 조사가 필요하다. 물론 FRAX를 통한 골절 위험도의 계산, 글루코코르티코이드 용량을 반영한 보정값(Adjusted value)과 골밀도 검사가 필요하다.

그림 3. 골절 위험도 평가. 임상적 골절 위험도 평가는 글루코코르티코이드 사용력(용량, 기간, 사용 면제), 낙상, 골절, 다른 골다공증 위험 인자들(영양 불량, 급격한 체중 감소 또는 저체중, 성신장기능저하증, 2차 부갑상선기능항진증, 갑상선신선반응중, 대퇴 골절의 가족력, 운동 및 응주력 등)을 고려한 골절 위험요인을 있을 경우에는 골밀도 검사를 초기에 실시하여 위험도를 판단하는 것이 중요하다.

2) 골절 위험도의 재평가
글루코코르티코이드를 지속적으로 사용하는 경우에는 매 12개월마다 골절 위험도를 재평가 하는 것이 필요하다(그림 3).

40세 이상 성인 환자에서 글루코코르티코이드를 지속적으로 사용하고 있으나 칼슘과 비타민D이외에 다른 골다공증 약제를 사용하지 않은 경우에는 FRAX와 골밀도 검사를 실시해야 하고, 이들의 1~3년마다 시행한다. 만일 초기용량이 하루 30 mg 이상의 고용량의 글루코코르티코이드를 복용 중이거나 지난 1년간의 누적 용량이 5 kg 이상인 경우, 혹은 골다공증 환자가 있었던 경우에는 매년 실시하는 것이 바람직하다. 40세 이상 성인으로서 글루코코르티코이드를 지속적으로 사용하는 경우는 매 1~3년마다 골밀도 및 FRAX를 통해 재평가하는 것이 필요하다(그림 3).

40세 미만 성인 환자에서 환자가 높은 골절 위험도를 가진 경우, 즉 골다공증성 골절이 의심되는 경우 뿐 아니라 영양 부족, 갑상선 질환, 저체중 감소, 2차 부갑상선기능항진증, 성신장기능저하증, 대퇴 골절의 가족력, 운동 및 응주력 등을 고려한 골절 위험요인을 있을 경우에는 골밀도 검사를 조기에 실시하여 위험도를 판단하는 것이 중요하다.
글루코 kort이드 유발 골다공증의 치료와 추적 관찰

1) 핵심질문: 글루코 kort이드를 사용하는 환자에서 비약물적 치료가 글루코 kort이드 유발 골다공증 예방과 치료에 효과적일까?

글루코 kort이드를 사용하는 모든 환자에게 운동, 식이 조절, 금연, 금수 등의 비약물적 치료를 권장한다. 글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다. 글루코 kort이드 유발 골다공증 환자에서 생활습관 개선과 골절 위험 감소효과는 명확하지 않다. 그러나, 글루코 kort이드와 함께 골다공증 약제를 복용하고 있는 경우에는 높은 위험도를 가진 경우(초기 글루코 kort이드 용량 30 mg이상, 연간 5g 이상의 글루코 kort이드 사용, 골다공증 약제 두어 시작 후 12개월 이내 발생한 골다공증 발생, 약물 부작용 혹은 화상 감소가 의심되거나 다른 골다공증 위험 요인을 갖는 경우) 2~3년 간격의 골밀도 검사를 하는 것이 바람직하다. 골다공증 약제를 복용하다가 현재는 중단한 경우에도 최대한 빠른 간격으로 골밀도 검사를 시행하는 것이 권유된다.

40세 미만 성인 환자에서 중등도 및 높은 위험도를 가지 고 있으며 글루코 kort이드 치료를 지속하는 경우에는 2~3년에 한차례씩 골밀도 검사를 실시하는 것이 추천된다.

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이해의 한계

글루코 kort이드 유발 골다공증의 치료와 추적 관찰

1) 핵심질문: 글루코 kort이드를 사용하는 환자에서 비약물적 치료가 글루코 kort이드 유발 골다공증 예방과 치료에 효과적일까?

글루코 kort이드를 사용하는 모든 환자에게 운동, 식이 조절, 금연, 금수 등의 비약물적 치료를 권장한다. 글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

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이해의 한계

글루코 kort이드 유발 골다공증의 치료와 추적 관찰

1) 핵심질문: 글루코 kort이드를 사용하는 환자에서 비약물적 치료가 글루코 kort이드 유발 골다공증 예방과 치료에 효과적일까?

글루코 kort이드를 사용하는 모든 환자에게 운동, 식이 조절, 금연, 금수 등의 비약물적 치료를 권장한다. 글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

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이해의 한계

글루코 kort이드 유발 골다공증의 치료와 추적 관찰

1) 핵심질문: 글루코 kort이드를 사용하는 환자에서 비약물적 치료가 글루코 kort이드 유발 골다공증 예방과 치료에 효과적일까?

글루코 kort이드를 사용하는 모든 환자에게 운동, 식이 조절, 금연, 금수 등의 비약물적 치료를 권장한다. 글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.

글루코 kort이드 유발 골다공증 예방과 치료를 위한 비약물적 치료의 근거가 충분하지 않으므로 폐경 후 골다공증 환자의 비약물적 치료에 준하여 치료할 것을 권장한다.
로우로코르티코이드를 사용하는 모든 화자에게 체중부하 운동, 균형 잡힌 식사, 곤란, 곰중 등의 비약물적 치료를 권고 한다[III/B].

2) 핵심질문: 40세 미만 성인에서 어떤 약물 치료가 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
40세 미만 성인의 글루코코르티코이드 유발 골다공증 화자를 대상으로 약제의 골밀도 감소 및 골절 예방 효과를 비교한 무작위 대조시험 연구는 매우 드물다. 이는 40세 미만 성인은 폐경 여성이들과 비교하여 골밀도가 비교적 높고, 골절 발생이 드물기 때문이다. 하지만 40세 이상의 폐경 후 여성에서도 글루코코르티코이드를 장기적으로 복용하면 골구조의 변화를 일으켜 골강도를 약화시킬 수 있다고 알려져 있다[31,32].

40세 미만 성인에서 초기 약물 치료는 그 린 4에 정리하였다(그림 4).

(1) 핵심질문-1: 40세 미만 성인에서 골소화 혹은 골소화 D 보충은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

1) 하루 2.5 mg 이상의 프레드니솔론을 3개월 이상 복용 중인 모든 성인은 갈슘과 비타민 D 보충을 권고한다 [II/B].
2) 충분량의 갈슘 (1000~1200 mg)과 비타민 D(800 IU)를 섭취하고, 적절한 비타민 D 농도 (20 ng/mL)을 유지하도록 권고한다[전문가 합의/B].
3) 식사를 통해 갈슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려할 수 있다[전문가 합의/B].
4) 고용량의 갈슘과 비타민D 보충은 위장관 부작용 및 신장성의 위험성을 증가시킬 수 있으므로 적절한 용량의 사용을 고려해야 한다[전문가 합의/B].

글루코코르티코이드는 갈슘의 장내흡수와 신장 재흡수를 감소시키고, 소변으로 갈슘 배출을 증가시킨다[33]. 따라서, 2.5 mg 이상의 프레드니솔론을 3개월 이상 복용 중인 40세 미만의 성인에서 갈슘과 비타민 D 복용을 권고한다 [II/B]. 그러나, 갈슘만 단독으로 복용하는 경우는 글루코코르티코이드 유발 골다공증 치료의 효과가 부족하고[34-36], 갈슘과 비타민 D 보충제를 함께 복용하는 것이 보다 효과적이다. 비타민 D3제제는 피트체의 호르몬 D3 (cholecalciferol)[37,38] 혹은 활성화된 비타민 D (calcitriol, alphacalcidol)[39,40] 모두 갈슘과 함께 복용하는 것이 갈슘 단독 복용 혹은 어떤 치료도 시행하지 않은 군에 비하여 골소실 억제효과가 있었다. 충분량의 갈슘 (1000~1200 mg)과 비타민 D (800 IU)를 섭취하고, 적절한 비타민 D 농도 (20 ng/mL)를 유지하도록 한다[전문가 합의/B]. 식사를 통해 갈슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려할 수 있다[전문가 합의/B].

(2) 핵심질문-2: 40세 미만 성인에서 비스포스포네이트 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
1) 40세 미만 성인에서 중증도 이상의 골절 위험이 있을 경우, 경구 비스포스포네이트 사용을 권고한다 [II/A].
2) 경구 비스포스포네이트 사용이 불가능한 경우, 주사 비스포스포네이트 사용을 고려할 수 있다 [II/A].

40세 미만의 임신 가능성 없는 여성과 남성에서 중증도 이상의 골절 위험을 있을 경우, 비스포스포네이트 사용을 고려할 수 있다 [II/A]. 알렌드로네이트(alendronate)는 고용량의 글루코코르티코이드 치료를 하는 폐경 후여성에서 골소실 예방효과와 골절 감소 효과가 있었다[41]. 지금까지 발표되었던 글루코코르티코이드 유발 골다공증 치료 효과에 대한 여러 연구들에서 40세 미만 성인에 대한 하위 그룹 문헌이 축적되지 않았다. 이 연구들은 동일한 알렌드로네이트[41-46], 리드로네이트(isedronate)[47-49], 콜레도르산(choledronic acid)[50] 등의 비스포르네이트가 위약군 혹은 골절, 비타민 D 제제 복용군 대비 골밀도 증가 및 골절 감소효과가 있음을 증명하였다. 비스포스포네이트의 경우, 반감기가 비교적 짧은 경우 비스포스포네이트를 우선적으로 사용한다. 만약, 경구 비스포스포네이트 사용이 불가능한 경우에는, 대신 주사 비스포스포네이트 사용을 고려할 수 있다.

(3) 핵심질문-3: 40세 미만 성인에서 테라피러티드 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

40세 미만 성인에서 중증도 이상의 골절 위험을 있을 경우, 테라피러티드 사용을 권고한다 [II/A].

40세 미만의 임신 가능성 없는 여성과 남성에서 중증도 이상의 골절 위험을 있을 경우 테라피러티드 사용을 고려할 수 있다 [II/A]. 프레드니솔론 5 mg/일 이상을 3개월 이상 복용하고 있는 환자들을 대상으로 알렌드로네이트와 테라피러티드의 치료효과를 비교하였을 때, 폐경 후 여성과 폐경 전 여성 모두에서 테라피러티드 사용 시 착근 골밀도가 더욱 크게 증가하였다[51].

(4) 핵심질문-4: 40세 미만 성인에서 테노수맙(denosumab) 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

40세 미만 성인에서 중증도 이상의 골절 위험을 있을 경우, 테노수맙 사용을 고려할 수 있다 [II/A].

40세 미만의 임신 가능성 없는 여성과 남성에서 중증도 이상의 골절 위험을 있을 경우 테노수맙 사용을 고려할 수 있다 [II/A]. 최근, 프레드니솔론 7.5 mg/일 이상을 시작하거나 3개월 이상 복용하고 있는 19세 이상 환자들을 대상으로 시행된 테노수맙과 리드로네이트의 무작위의 이중

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맹검 비교 연구에서, 데노수맙이 리세드로네이트에 비해 척추와 대퇴골 골밀도를 유의하게 증가시켰다[52].

3) 핵심질문: 40세 이상 성인에서 어떤 약물 치료가 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
40세 미만 성인에서 초기 약물 치료는 그림 4에 정리하였다 (그림 4).
(1) 핵심질문 3-1: 40세 이상 성인에서 칼슘과 비타민 D 보충은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
① 하루 2.5 mg 이상의 프레드니솔론을 3개월 이상 복용 중인 모든 성인은 칼슘과 비타민 D 복용을 권고한다 [II/B].
② 충분량의 칼슘(1000~1200mg)과 비타민 D(800 IU)를 섭취하고, 적절한 비타민 D 농도(20 ng/mL)를 유지하도록 권고한다[전문가 합의/B].
③ 식사를 통한 칼슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려할 수 있다[전문가 합의/B].
④ 골절의 위험을 증가시킬 수 있으므로 적절한 용량의 식사를 통해 칼슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려해야 한다[전문가 합의/B].
40세 이상 성인에서 골절의 위험을 증가시킬 수 있으므로 적절한 용량의 식사를 통해 칼슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려해야 한다.

(2) 핵심질문 3-2: 40세 이상 성인에서 비스포스포네이트 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
① 40세 이상 성인에서 골절의 위험을 증가시킬 수 있으므로 적절한 용량의 식사를 통해 칼슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려해야 한다[전문가 합의/B].
② 경구 비스포스포네이트 사용이 불가능한 경우, 주사 비스포스포네이트 사용을 권고한다 [I/A].
③ 글루코코르티코이드 유발 골다공증 환자에서 비스포스포네이트 사용으로 인한 비정형 대퇴골 골절 및 턱뼈괴사 등의 부작용이 증가한다는 증례는 미흡하다. 그러나 글루코코르티코이드 유발 골다공증 환자에서 장기적인 비스포스포네이트 사용이 위험성에 대한 증례는 부족하다[50,51,62-64]. 비스포스포네이트 사용으로 인한 턱뼈괴사 및 비정형 대퇴골 골절 발생은 매우 적으나, 글루코코르티코이드 유발 골다공증 환자에서 비스포스포네이트 사용으로 인한 턱뼈괴사 및 비정형 대퇴골 골절 등의 부작용이 증가하는지는 미흡하다. 하지만 글루코코르티코이드 유발 골다공증 환자에서 장기적인 비스포스포네이트 사용을 계획할 때는 위험-이익 비율을 고려해야 한다[전문가 합의/B].
(3) 핵심질문 3-3: 40세 이상 성인에서 태리파라티드는 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?
40세 이상 성인에서 골절의 위험을 증가시킬 수 있으므로 적절한 용량의 식사를 통해 칼슘과 비타민D 섭취가 부족한 경우 보충제의 사용을 고려해야 한다.
라티드를 사용한 군에서 척추, 대퇴골 골밀도가 더 많이 증가하였고, 전방 골밀도는 두 군간 차이가 없었다[71]. 또한, 테리파라티드와 알렌드로네이트의 치료 효과를 비교할 때, 18개월, 36개월 추적 관찰한 결과 테리파라티드를 사용한 군에서 척추, 대퇴골 골밀도 증가가 있고, 적추골절 감소효과는 우월하였으나, 비추 척추 감소효과는 두 군 간 차이가 없었다[51,72,73].

(4) 핵심질문 3-4: 40세 이상 성인에서 데노수맙 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

40세 이상 성인에서 중등도 이상의 골절위험이 있을 경우, 데노수맙 사용을 권고한다[1/A]. 메트로트렉세이트 (methotrexate)와 허부 2.5 mg 이상의 프레드나솔론을 3개월 이상 복용하고 있는 류마티스 관절염 환자들을 대상으로 데노수맙과 위약군의 1년 후 골밀도 변화를 비교하였을 때, 데노수mát을 두약한 군에서 제주와 대퇴골 골밀도가 크게 증가하였고, 골체 표적자가 크게 감소하였다[74]. 최근, 프레드나솔론 7.5 mg/일 이상을 사용하거나 3개월 이상 복용하고 있는 19세 이상 환자들을 대상으로 한 데노수맙과 데노수맙의 무작위 이중 매일 비교 연구에서, 데노수맙이 투약요법에 비해 적추와 대퇴골 골밀도를 유의하게 증가시켰다[52].

(5) 핵심질문 3-5: 폐경 후 여성에서 선택적 에스트로겐 수용체 조절제 사용은 글루코코르티코이드 유발 골다공증 예방과 치료에 효과적인가?

글루코코르티코이드 유발 골다공증 치료에 있어서 선택적 에스트로겐 수용체 조절제의 골절 예방 효과는 근거가 충분하지 않으므로, 폐경 후 여성에서 중등도 이상의 골절 위험을 있으므로 비스포스포네이트, 테리파라티드, 데노수맙 사용이 불가능한 경우, 선택적 에스트로겐 수용체 조절제 사용을 고려할 수 있다[II/B].

선택적 에스트로겐 수용체 조절제는 글루코코르티코이드 유발 골다공증 치료에 있어서 골절 예방 효과 근거가 충분하지 않으므로, 폐경 여성에서 중등도 이상의 골절 위험이 있으면서 비스포스포네이트, 테리파라티드, 데노수맙 사용이 불가능한 경우, 선택적 에스트로겐 수용체 조절제 사용을 고려할 수 있다[II/B]. 프레드나솔론은 하루 20 mg 이하로 6개월 이상 사용하고 있는 폐경 여성에서 알로스피르 (raloxifene) 복용군과 위약군을 1년 추적 관찰하였을 때, 적추 골밀도와 대퇴골 전체 골밀도가 증가하였고, 골체 표적자가 의미 있게 감소하였다[75].

4) 핵심질문 4: 임신을 계획하고 있는 여성에서 골다공증 약제 사용은 안전한가?

임신을 계획하고 있는 여성에서는 골다공증 약제 사용에 주의해야 한다[전문가 합의/C]. 중등도 이상의 골절 위험이 있을 경우, 경구 비스포스포네이트를 우선적으로 사용할 수 있으며, 테리파라티드 사용도 고려할 수 있다. 하지만, 주사 비스포스포네이트, 데노수맙은 레이안에 대한 근거가 부족하므로 사용을 권고하지 않는다. 임신 중에는 칼슘과 비타민 D 체제를 제외한 골다공증 치료 약제 사용을 권고하지 않는다. 동물 실험에서 임신 중 가래 비스포스포네이트 사용을 하였을 때, 태생기동안 골격계의 형성과 석회화 과정에서 이상이 발생하였다[76]. 임신 중에는 임신 초기에 비스포스포네이트 사용이 필요한 경우는 매우 극소적이다. 임신여성의 출산기에는 골절 위험도가 증가하며, 비스포스포네이트는 출산기에는 사용하지 않는다[77,78].

5) 핵심질문 5: 글루코코르티코이드 유발 골다공증 환자에서 신체계/영상학적/생화학적 방법을 이용하여 얼마나 잘 치료받고 있는지 판단할 수 있는가?

① 글루코코르티코이드 치료를 지속하는 환자에서 매년 치료를 확인하는 간격은 적추 X-ray 검사를 1년마다 시행하는 것을 권고한다[전문가 합의/B].

② 골다공증 약제 복용을 정확하게 하는 것이 중요하다. 생화학적 방법을 이용한 치료 반응 평가는 골부위를 정확하게 판별할 수 있는 것이 중요하다. 치료 반응의 평가는 골밀도 검사 및，서 초음파 검사조직 등이 존재한다. 

글루코코르티코이드 치료를 지속하는 모든 환자에서 매년 치료를 확인하는 간격은 적추 X-ray 검사를 1년마다 시행하는 것을 권고한다[전문가 합의/B]. 치료 반응의 평가는 골밀도 검사 및 초음파 검사조직 등이 필요하다.
여 요추와 대퇴골 부위를 촬영한다. 이 때 척추 골절을 영상학적으로 평가하기 위하여 척추 단순 에스진 검사를 같이 시행할 것을 권고한다[전문가합의/B]. 골다공증 약제 복용의 순응도를 평가하기 위해서 정기적인 진료를 통한 경과 관찰을 권고한다[전문가합의/B]. 글루코코르티코이드 유발 골다공증 환자에서 골고정 표지자와 같은 생화학적 방법을 이용한 치료 반응 모니터링은 극히가 부족하다[전문가 합의/I].

6) 혈심 질문6: 글루코코르티코이드 유발 골다공증 치료 중 골절 위험도를 재평가하여 낮은 골절 위험도로 확인되었을 경우 골다공증 치료 약제 중단을 고려할 수 있는가?

치료 중인 글루코코르티코이드 유발 골다공증 환자에서 글루코코르티코이드 투여가 중단되고 재평가한 골절위험도가 낮을 때((low fracture risk) 골다공증 치료 약제의 중단을 고려할 수 있다. 골다공증 치료 약제의 중단은 환자의 위험-이익을 판단하여 환자마다 개별화되어야 한다[전문가 합의/B].

7) 혈심 질문7: 글루코코르티코이드 유발 골다공증 치료 실패를 어떻게 정의할 것인가?

① 40세 이상의 성인 환자에서 다음과 같은 경우 초기 치료 실패로 정의한다. 경구 비스포스포네이트 치료 시작 후 2년 이상의 골다공증 치료 과정이 발생하거나 치료 시작 12개월 후 골다공증 치료 효과를 해소할 수 없는 경우 또는 추적 관찰 결과에서 이미 있는 골절도 감소(≥10%/년)가 있는 경우 초기 치료 실패로 정의하고, 다른 종류의 약제로 변경을 고려할 수 있다[전문가 합의/B].

본 지침은 글루코코르티코이드를 사용하거나 사용할 계획인 환자들을 진료하는 모든 임상의들에게 글루코코르티코이드 유발 골다공증의 일차 예방 및 치료에 대한 표준화된 지침을 제시하여 효율적인 치료를 증진시킬 목적으로 개발되었다. 본 지침의 일차적인 의의는 글루코코르티코이드를 투여 받는 환자를 진료하는 모든 임상의들이 글루코코르티코이드 유발 골다공증의 위험성 그리고 치료 효과를 인지하고 치료 실패를 예방하여 적절한 치료를 받도록 하여야 한다.
개작의 과정이 시행되었다. 본 지침은 19세 이상의 성인을 대상으로 글루코코르티코이드를 투여받는 기간 동안의 골절 위험도의 평가와 모니터링, 골절 예방을 위한 치료에 대한 권고안을 포함하고 있다.

본 지침에서는 40세 이상에서 경구 비스포스포네이트가 일차 약제로 권고되었다(I/A). 일부 골다공증 지침에서는 글루코코르티코이드 유발 골다공증과 같은 고위험군에 대해 주사 비스포스포네이트나 테리파라티드, 테오노말의 사용을 일차적으로 권고하고 있다[79]. 하지만, 현재까지 발표된 다수 임상 연구들의 골절 감소 효과, 안전성, 비용 등을 고려할 때 경구 비스포스포네이트가 가장 높은 근거 수준을 가지고 있음을 알 수 있다.

본 진료지침은 많은 한계를 가지고 있으며 많은 추가 연구가 필요하다. 첫 번째로, 글루코코르티코이드 유발 골다공증에 대한 국내 임상 연구가 많이 부족한 실정이었으므로 본 지침은 외국 지침들을 수용 개작하는 방식으로 개발되었다. 하지만, 외국 지침들에서도 글루코코르티코이드 유발 골다공증에 대한 임상 연구가 매우 제한적이다. 특별로 글루코르티코이드를 투여받는 환자들을 대상으로 하여 골절을 일차 목표로 하는 임상 시험이 필요하다.

세 번째로, 지금까지 40세 미만 성인들에 대한 골절 연구는 거의 없으며 글루코코르티코이드 유발 골다공증 환자에게서는 치료가 필요하다. 따라서, 골다공증 환자에 대한 임상 연구를 통해 가장 적절한 치료를 찾아야 할 것이다.

결론적으로, 글루코코르티코이드는 모든 임상의들이 고려해야 하는 문제이며 환자들도 그 위험성을 인식해야 한다. 글루코코르티코이드를 두여받는 모든 환자들을 대상으로 골절 위험을 평가하여 체계적으로 골절의 감소를 예방하는 시도가 적극적으로 이루어져야 한다.

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CONFLICT OF INTEREST

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