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Glucocorticoid-induced Osteoporosis: From Pathogenesis to Treatment

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스테로이드 유발성 골다공증: 병인에서 치료까지

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정 윤 석

스테로이드에 의한 골다공증 (GIO)은 이차성 골다공증의 가장 흔한 원인이다. 그러나 아직까지 그 기전은 명확하게 밝혀지지 않았으며, 치료 또한 쉽지 않다. GIO의 병인기전은 표적기관에 초점을 둔 전통적 모델과 골세포에 초점을 둔 과학적 모델이 있다. 과거의 전통적 모델에서는 스테로이드는 장에서 칼슘 흡수를 억제하고 소변으로의 칼슘 배출을 촉진하여, 이러한 음의 칼슘 균형이 이차성 부갑상선기능항진증을 일으키는 것으로 설명하고 있다. 그러나 이러한 과거 모델에 대한 반론과 문제점이 제기되고 있다. 최근의 과학적 모델에서는 스테로이드가 초기 (투여 1년 이내) 가속화된 골소실에서 파골세포를 직접적으로 자극하고, 파골세포의 활성도와 생존을 증가시켜, 골전환을 증가시키고 골소실을 촉진한다. 후기 감속화된 지속적 골소실에서는 스테로이드는 조골세포를 직접적으로 억제할 뿐만 아니라 파골세포에 의해 매개된 조골세포 동원을 간접적으로 억제한다. 이에 따라 느린 골전환 및 골소실을 유도한다. 이 밖에 조골세포에 대한 스테로이드의 작용기전은 Runx2 발현, PPAR gamma 발현, Wnt / β-catenin 신호 등이 있다. 저자 등은 glycogen synthase kinase-3 β (GSK3 β)의 역할을 최근 보고한 바 있다.

GIO의 일반적 치료 지침과 생활 개선 요법으로 가능한 최소 용량의 스테로이드 사용, 짧은 기간의 스테로이드 사용, 국소 스테로이드 요법, 금연, 알코올 섭취 감소, 체중부하 운동, 적절한 칼슘 섭취, 비타민 D 섭취, 낙상 예방이 있다. 약물 치료는 성호르몬 요법, 칼시토닌, 비스포스포네이트, 부갑상선호르몬 요법이 있다. 비스포스포네이트는 염증 사이토카인에 의한 골흡수를 억제하고, 조골세포와 골세포에 대한 세포사멸 억제 효과를 보인다. 이를 통해 요추의 골밀도를 증가시키고 척추골절의 위험을 감소시키는 것으로 보고되고 있다. 부갑상선호르몬은 조골세포에 대해 동원, 활성화, 생존을 증가시키고, 파골세포를 억제하지 않아 비스포스포네이트보다 치료 효과가 좋을 것으로 예상된다. 부갑상선호르몬은 알렌드로네이트에 비해 요추 및 고관절 골밀도를 증가시키고, 척추골절을 감소시키는 것으로 보고되었다. 향후 가능성 있는 치료제로서 GSK3 β 억제제, Dickkopf 항체, Sclerostin 항체 등이 연구되고 있다.

중심단어: 조골세포, 파골세포, 골세포

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Glucocorticoid-induced osteoporosis (GIO) is the most common type of secondary osteoporosis. The mechanism is complicated and treatment is unsuccessful until now. The pathogenesis of GIO could be classified in two models. First one is a traditional model of GIO focusing on target organs. Second one is a scientific

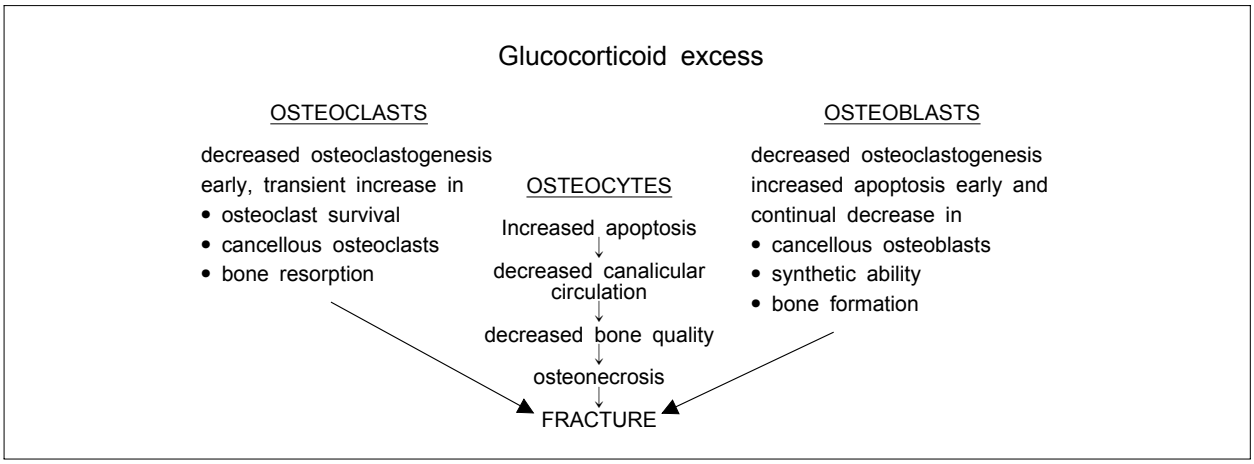

Fig. 1. Current scientific model of glucocorticoid-induced osteoporosis focused on roles of bone cells (adapted from reference 3).

model of bone cells.

PATHOGENESIS

The traditional model is as follows. Glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, and these negative calcium balance induce secondary hyperparathyroidism. On the other hand glucocorticoids affect muscle and bone directly. The traditional model of secondary hyperparathyroidism has been investigated and may not be true. For example, histomorphometric findings of GIO are associated with decreased osteoblast activities including decreased osteoblast number and bone formation, but in hyperparathyroidim osteoblastic activities are increased[1]. In terms of gonadal hormone study, glucocorticoid did not change serum testosterone, sex hormone blinding globulin (SHBG), or estradiol. Therefore, glucocorticoid may not have significant effect on sex hormones[2].

The recent model of scientific data highlighted on roles of bone cells including osteoclasts, osteoblasts, and osteocytes[3] (Fig. 1). Mechanism of early accelerated bone loss as follows[4,5]. Glucocorticoid increase mature osteoclast lifespan and activity. It happens in first 6 months (less than 1 year) of steroid treatment. Early accelerated bone loss could be induced by inflammatory cytokines or glucocorticoid itself probably via glucocorticoid receptor. Dexamethasone decreased caspase-3 activity of osteoclast, and this means reduced apoptosis and increased survival of osteoclast. In contrast, blocking glucocorticoid effect on osteoclast by 11 β-hydroxysteroid dehydrogenase (HSD) activation, anti-apoptotic effect disappeared[5]. Lee et al. studied the bone marrow transplantation patients, and showed that lumbar spine BMD had decreased more than 10% after glucocorticoid treatment. Bone resorption marker, type I collagen C-telopeptide (ICTP), significantly increased during the 6 months of bone marrow transplantation. Inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-6 (IL-6) increased during the early time after bone marrow transplantation and glucocorticoid treatment[6].

Late sustained bone loss after glucocorticoid treatment might have mechanism as follows[7]. The numbers and activities of osteoblasts decreased. Apoptosis of osteoblasts and osteocytes increased. The numbers and activities of osteoclasts decreased and these effects suppress osteoblasts indirectly. Kim et al. showed that actin ring of osteoclasts decreased after dexamethasone treatment, and these effect abolished by conditional knock out of glucocorticoid receptor on osteoclast. Suppression of osteoclast by glucocorticoid induced

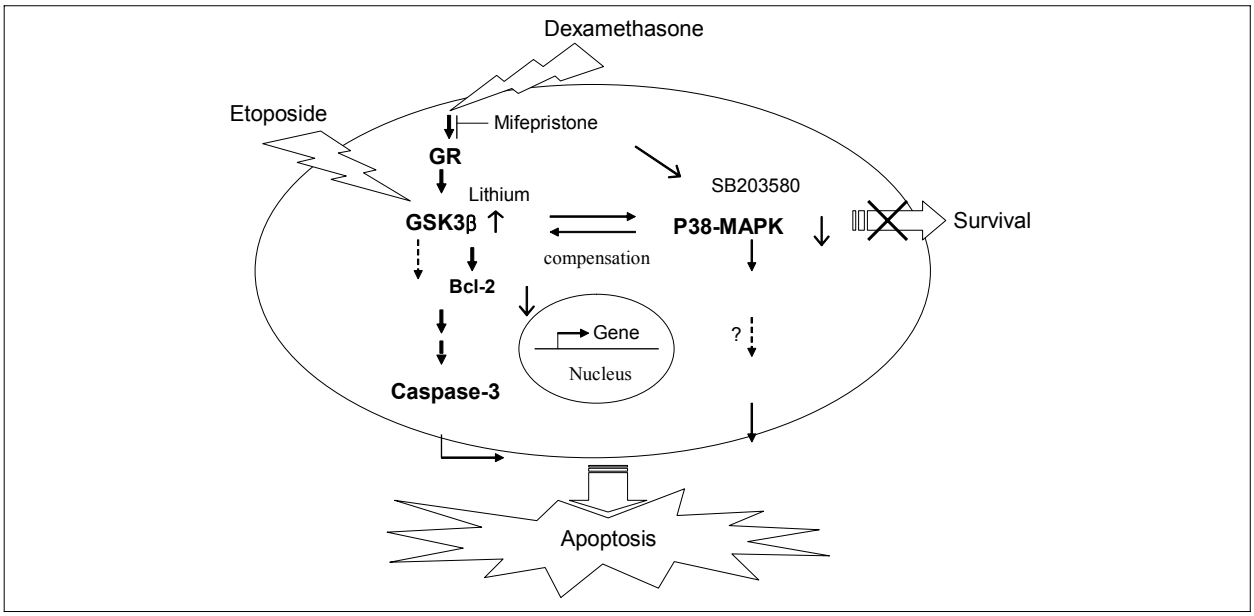

Fig. 2. Hypothesis of apoptosis induced by glucocorticoid in osteoblasts (modified from references 13 and 14).

significantly less bone formation and osteoblast activity measured by tetracycline labeling and serum osteocalcin[8].

More detailed action mechanism of glucocorticoid in osteoblasts may include (1) Runx2 expression, (2) PPAR gamma expression, and (3) Wnt β-catenin signal[9-12]. Yun et al. revealed that dexamethasone significantly decreased osteoblast cell number and increased apoptosis, and these effects were recovered by mifepristone (RU486), a glucocorticoid receptor antagonist. Dexamethasone induced osteoblast apoptosis, which mediated by glycogen synthase kinase-3 β (GSK3β), and rescued by lithium chloride[13]. GSK3β also a key component of etoposide-induced osteoblast apoptosis and rescued by lithium[14]. These results could be illustrated as follows. Dexamethasone exert its effect via glucocorticoid receptor, increase GSK3β activity, and finally induce caspase-3 leading to apoptosis (Fig. 2).

Histomorphometric data support that steroid-induced bone loss occur mainly due to suppression of osteoblasts and primarily affecting trabecular bone[15]. Bone biopsy study revealed that glucocorticoid decreased osteoid thickness, bone formation rate, and mineral apposition rate compared to postmenopausal osteoporosis[16]. Dexamethasone significantly increased apoptotic osteoblasts and osteocytes[17].

Summary of mechanism as follows. Early accelerated bone loss (within 1 year) in form of high bone turnover and rapid bone loss would occur by direct osteoclast stimulation, and by increased osteoclast activity and survival. Late decelerated continuous sustained bone loss in form of low bone turnover and slow bone loss would occur by direct osteoblast suppression, and by indirect osteoblast suppression by osteoclast-mediated osteoblast recruitment.

TREATMENT

Traditional general guidelines and life style modifications of GIO as follows. (1) As low as possible dose of glucocorticoids. (2) As short as possible duration of steroid administration. (3) Topical rather than systemic glucocorticoid, if possible. (4) Smoking cessation. (5) Alcohol reduction. (6) Weight- bearing exercise. (7) Adequate calcium and vitamin D intake. (8) Prevention

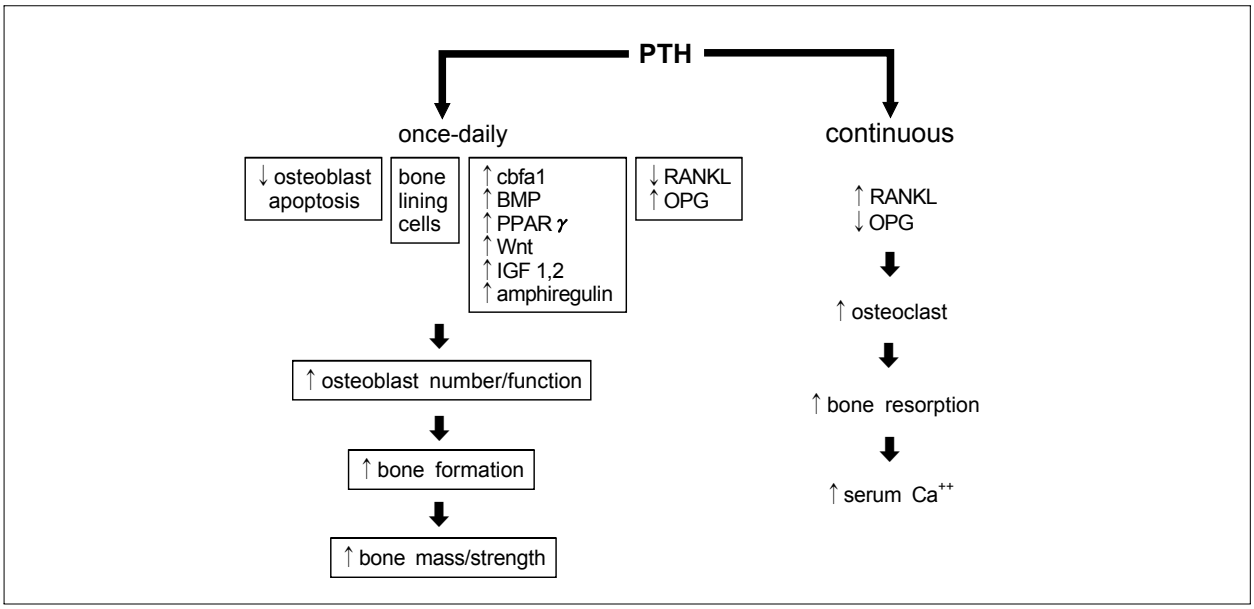

Fig. 3. Possible mechanism of action of parathyroid hormone on bone cells (information from reference 27).

of falls.

Medical treatment options for GIO are sex hormone, calcitonin, bisphosphonate, and parathyroid hormone. Sex (gonadal) hormone treatment as follows. Bone density increases in the spine when postmenopausal women taking long-term steroids are given estrogen/progestin therapy (EPT)[18,19]. There is no consistent data on the effect on the hip, and there are no trials large enough to assess the effect of EPT on fracture risk in patients taking glucocorticoids. Bone mineral density (BMD) of the spine increases when hypogonadal men receiving glucocorticoids are treated with testosterone for 1 year[20], but no hip or fracture data are available. Calcitonin treatment as follows. Calcitonin treatment may offer the additional benefit of relieving the pain associated with vertebral fractures[21], but larger studies are necessary to prove a fracture risk reduction.

Mechanism of actions of bisphosphonates in GIO are as follows. Bisphosphonates reduce early accelerated bone loss, prevent bone resorption by inflammatory cytokines, and demonstrate anti-apoptotic effects on osteoblasts and osteocytes. Risedronate in GIO mice model prevented bone resorption compared to placebo but also suppressed bone formation[22]. Kim and Cho showed that pamidronate increased lumbar spine BMD compared with control in steroid treated patients[23]. Bisphosphonates are proven to be effective with large scale randomized clinical trials. Two years treatment of alendronate increased BMD of the lumbar spine in patients receiving average daily doses of at least 7.5 mg of prednisone or equivalent compared to placebo[24]. One year therapy with risedronate in European with at least 6 months of 7.5 mg or greater prednisone equivalent, increased spine BMD compared to placebo[25]. Meta-analysis of the randomized clinical trials that included more than 50 patients in each treatment arm revealed that bisphosphonates significantly reduced the risk of vertebral fracture in GIO[26].

Theoretically, parathyroid hormone (PTH) could be a better treatment option than bisphosphonate, because PTH (1) target osteoblast, (2) increase osteoblast recruitment, activity, and survival, and (3) not suppress osteoclast (Fig. 3). PTH increase trabecular number and thickness rather than hypermineralize trabeculae. PTH treatment significantly increased lumbar spine BMD and total hip BMD compared to alendronate therapy in GIO

patients. PTH also significantly prevented vertebral fracture compared to alendronate group[27].

Future therapy of osteoblast-targeted as follows: (1) GSK3β inhibitor, (2) Dickkopf antibody, (3) Sclerostin antibody. Recent interesting study revealed that IG9402, namely amino-olpadronate, reduced osteoblast apoptosis similar to other bisphosphonates, but neither inhibited farnesyl pyrophosphate synthase (FPPS) nor induce apoptosis of osteoclasts, so, it could be a good candidate for GIO treatment[17]. These anti-apoptotic effects are mediated by connexin 43 of osteoblasts and osteocytes. As a result, connexin 43 conditional knock- out mice did not prevent apoptosis with bisphsphonate treatment[28].

Summary of treatment as follows. (1) Traditional treatment: Calcium, Vitamin D, Sex hormone, Calcitonin; (2) Randomized clinical trial (RCT) of evidence-based treatment: Bisphosphonates (alendronate, risedronate); (3) Mechanism-oriented treatment: PTH, Wnt pathway.

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■ ABSTRACT ■

Glucocorticoid-induced osteoporosis (GIO) is the most common type of secondary osteoporosis. However, the mechanism responsible for GIO and the appropriate treatment for this problem remain poorly understood. The pathogenesis of GIO can be explained by a traditional model and a scientific model of bone cells. According to the traditional model, glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, and the negative calcium balance induces secondary hyperparathyroidism. In the more recent scientific model of bone cells, glucocorticoids stimulate osteoclast cells directly and increase osteoclast cell activity and survival during early accelerated bone loss this activity induces high bone turnover and rapid bone loss. Glucocorticoids suppress osteoblast cell activity directly and suppress osteoblast cell activity indirectly by osteoclast-mediated osteoblast recruitment during late decelerated continuous sustained bone loss. This results in low bone turnover and slow bone loss. A more detailed action mechanism of glucocorticoids in osteoblasts may include: (1) Runx2 expression, (2) PPAR gamma expression, and (3) Wnt / β-catenin signaling. Glycogen synthase kinase-3 β (GSK3 β) also plays a role in osteoblast apoptosis. Traditional general guidelines and life style modifications for GIO are: (1) doses of glucocorticoids as low as possible (2) duration of steroid administration as short as possible (3) topical rather than systemic glucocorticoid treatment, if possible (4) smoking cessation (5) reduction of alcohol; (6) weight -bearing exercise (7) adequate amounts of calcium and vitamin D intake (8) and the prevention of falls. Medical treatment options for GIO are sex hormones, calcitonin, bisphosphonate, and parathyroid hormone. In some studies, estrogen/progestin therapy in postmenopausal women and testosterone therapy in hypogonadal men have shown a beneficial effect on bone mineral density (BMD) of the spine. Calcitonin treatment may have the additional benefit of relieving the pain associated with vertebral fractures. Bisphosphonates reduce early accelerated bone loss, prevents bone resorption by inflammatory cytokines, and demonstrates anti-apoptotic effects on osteoblasts and osteocytes. In many studies, bisphosphonates have shown significant increase in the BMD of the spine and reduction of the risk of vertebral fractures in GIO. Parathyroid hormone (PTH) might be a better treatment option than bisphosphonate therapy, because PTH (1) targets osteoblasts, (2) increases osteoblast recruitment, activity, and survival, and (3) does not suppress osteoclasts. PTH treatment significantly increased lumbar spine BMD and total hip BMD and prevented vertebral fractures compared to alendronate therapy in patients with GIO. Future therapy targeting osteoblasts include: (1) the GSK3 β inhibitor, (2)Dickkopf antibody, (3) Sclerostin antibody.

Key Words: Osteoblast, Osteoclast, Osteocyte