Controversies related to determination of the glucocorticoid-induced osteoporosis intervention threshold: who are the patients?

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Abstract. Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis. The research demonstrates that oral administration of glucocorticoids often result in rapid bone loss and an increased risk of fractures during several months. The urgency of glucocorticoid-induced osteoporosis as a public health problem is caused by the frequent use of glucocorticoids by patients with various chronic diseases resulting in high level of osteoporosis. The glucocorticoid-induced osteoporosis develops due to the inhibition of bone formation, accompanied by an early but short-term bone resorption increase. An increase in the RANKL/OPG ratio, sclerostin expression growth, activation of PPARγR2, as well as hypogonadism, impaired absorption of calcium in the intestine, and a decrease of the insulin-like growth factor 1 production are among many mechanisms underlying the bone metabolism disorders caused by the long-term use of glucocorticoids. Despite available and effective preventive measures, the bone condition and risk of fractures for many patients who start or continue glucocorticoid therapy are not adequately assessed. The threshold values of daily doses of glucocorticoids (≥ 2.5 mg/day) and the duration of their administration (≥ 3 months) at which patients’ risk of fractures and the necessity of treatment with antiosteoporotic drugs should be assessed were identified. National guidelines for the management of glucocorticoid-induced osteoporosis offer different approaches to determination of the interventions threshold based on the use of various criteria. The 10-year probability of fractures based on the clinical risk factors, with or without bone mineral density assessment, is calculated and adjusted for regional fracture rate and mortality with the Fracture Risk Assessment Tool (FRAX). Despite limitations, this algorithm is the most effective in defining the interventions thresholds. The 2017 American College of Rheumatology guidelines indicate that the initial absolute risk of fractures should be assessed using the FRAX and taking into account the doses of glucocorticoids and bone mineral density test results no later than 6 months from the start of glucocorticoids therapy.

Keywords: glucocorticoid-induced osteoporosis; glucocorticoids; daily dose; pathogenesis; intervention threshold; fracture risk; FRAX; treatment; review

Glucocorticoids (GCs) belong to the only group of medications combining a vivid and fast anti-inflammatory and immunosuppressive effect; and thus making a multifaceted influence on the immunopathological processes accompanying rheumatologic and other conditions. GCs are widely used in treatment of numerous rheumatologic and other disorders. September 2018 marked a 70th anniversary of the first successful use of cortisol in a clinical practice. Despite an almost half a century long GC implementation, they are still considered primary anti-inflammatory actors [1].

Our understanding of the GC mechanisms has recently expanded. GCs were found to exercise their effect via genomic and non-genomic pathways. Most GC therapeutic effects realize themselves via genomic pathways, namely GC binding with GC cytosol-receptors (GCRs). Upon creation, GC/GCR complex translocates into a nucleus where it binds to specific transcription factors, which results in an induction/inhibition of specific transactivation and transrepression genes, respectively [2]. GC/GCR complex directly interacts with two transcription factors: activator protein 1 (AP-1) and nuclear factor NF-
dose of 7.5 mg per day and over [16]. Even a minimum few more than 2.5 mg per day, 2.59 times with a daily GC pression fractures rises 1.5 times with a daily GC dose of on GC dose. For instance, a relative risk of vertebral com considered that there is no absolutely safe GC dose; however, conditions, GC doses and regimens. Nowadays, it is con higher. A qualitative evaluation of this risk is impeded however, with (a history of) GC treatment it grows much ing age, the fracture risk grows both in men and women; a daily GC dose and fracture risk [15]. With an advanc mulative GC dose; a connection was also found between bone mineral density (BMD) loss correlates with a cu of GC-induced osteoporosis is an early and rapid loss an osteoporosis [14]. A principal distinguishing feature of GC-induced osteoporosis (OP) and related os the epidemiological data concern, mostly, an oral GC administration performed continuously during 3-6 months and longer. An Icelandic study reveals that 26 % of patients on GC treatment for > 6 months developed an osteoporosis [14]. A principal distinguishing feature of GC-induced osteoporosis is an early and rapid loss of bone mass after the beginning of GC therapy [9]. The bone mineral density (BMD) loss correlates with a cu-mulative GC dose; a connection was also found between a daily GC dose and fracture risk [15]. With an advanc ing age, the fracture risk grows both in men and women; however, with (a history of) GC treatment it grows much higher. A qualitative evaluation of this risk is impeded by significant discrepancies among patients, underlying conditions, GC doses and regimens. Nowadays, it is con-sidered that there is no absolutely safe GC dose; however, there are descriptions of existing fracture risk dependence on GC dose. For instance, a relative risk of vertebral com-pression fractures rises 1.5 times with a daily GC dose of fewer than 2.5 mg per day, 2.59 times with a daily GC dose of 2.5 - 7.5 mg per day, 5.18 times with a daily GC dose of 7.5 mg per day and over [16]. Even a minimum GC dose of 2.5 mg per day is associated with an increased fracture risk. A daily Prednisone dose of < 5 mg per day raises a fracture risk by 20 %, while a dose of 20 mg per day – by 60 % [9]. A meta-analysis was performed in order to summarize 42000 patients’ data obtained from 7 cohort studies. Its results show that an ongoing and pre-ceding GC treatment is an independent risk factor, ir-respective of the history of falls or measured BMD [15]. Any fracture’s odds ratio (OR) with GCs (compared to the subjects never treated with GCs) varies from 1.98 at the age of 50 years to 1.66 at the age of 85 years. For the vertebral fragility fractures OR fluctuates from 2.63 to 1.71, while for the femoral fractures – from 4.42 to 2.48 [15]. Another meta-analysis revealed a striking growth of fracture risk during 3-6 months after the beginning of oral GC treatment, irrespective of the principal complaint, age and sex [9].

M.A. Amiche et al. (2016) performed a Bayesian me-ta-analysis of fracture risks associated with an oral GC administration, taking into account the control data of clinical trials [17]. The subjects treated with GC during the previous 6 months had an annual frequency of verte-bral fractures of over 5.1 % [95 % credible intervals (CrI): 2.8-8.2] and extra-vertebral fractures of 2.5 % [95 % CrI: 1.2–4.2]. For the subjects treated with GC for longer than 6 months, the corresponding values were 3.2 % [95 % CrI: 1.8–5.0] and 3.0 % [95 % CrI: 0.8–5.0].

Using a large administrative database, A. Balasubramanian et al. (2016) studied initiation effects of a system-ic (oral or percutaneous) GC administration on fracture risks of patients with a rheumatoid arthritis (their mean age was 49 years) [18]. The fracture risk varied from 5 to 9/1000 person/years with a dose of <15 mg per day, 16 (11- 22.6) with a dose of ≥ 15 mg per day and 13.4 (10.7, 16.7) with a cumulative dose of ≥5400 mg (Prednisone converted). 60-182 days after the termination of GC treatment a fracture risk was 29 % lower even in those subjects still taking the GC treatment, and 12 months after that their fracture risk equaled the fracture risk of subjects never taking GCs.

The subjects treated with GC inhalers had a similarly increased risk of vertebral fractures; however, that effect was not as pronounced as in case of a systemic GC treat-ment [19], and as consistently documented. There is evi-dence of a high dose of GC inhalers being associated with an increased fracture risk [20-22]. When compared with control subjects, GC inhalers produced vertebral fracture and femoral fractures ORs of 1.15 (95 % CI: 1.10-1.20), 1.22 (95 % CI: 1.04-1.43) and 1.51 (95 % CI: 1.22-1.85), respectively. Vertebral fracture rate of subjects treated with Budesonide (OR = 0.95; 95 % CI, 0.85–1.07) and Fluticasone propionate (OR = 1.03; 95 % CI: 0.71–1.49) was similar to the one of subjects treated with Beclomethasone dipropionate [21]. It is interesting that a long-term administration of topical GC forms did not result in an increased fracture risk [23]. Skeletal fractures associated with GC use may have various localizations: vertebrae,
proximal femur, forearm, ribs, and long cortical shafts; however, most often they are fragility ones, producing no symptoms and revealed only through a targeted X-ray detection [8].

The earlier studies demonstrated that bone metabolism does not face significant changes due to the intermittent GC treatments, including a high-dose pulsed therapy. Those studies focused exclusively on the tran-sitory decrease of bone formation markers and their re-newal after 7–10 days following the pulsed therapy, as well as hypercalciuria [24-26]. Some studies also recorded an increased parathyroid hormone (PTH) and 1.25-hydroxyvitamin D levels after the first high-dose pulsed therapy session; however, those levels quickly returned to normal. It is nowadays considered that the fracture risk is associated with an intermittent GC treatment, high doses and high frequency of repeated treatment courses [27]. The oral GC treatment raises the vertebral fracture rate significantly, to the same extent as the inhaled GCs; however, with a continuous use, the fracture rate is much higher [28].

The suspension or cessation of GC use results in a significant reduction of fracture risk; however, it is unclear whether the fracture risk returns to the initial levels [28-30]. In a case-control study, the fracture risk did not return to the initial level after 1 year following the GC treatment cessation [31]. Another series of studies demonstrates an incomplete bone renewal after the GC treatment cessation [16]. These data prompt researchers to wonder about the duration of anti-osteoporotic treatment following the GC cessation. It is interesting that the FRAX algorithm used to evaluate the fracture risk includes any GC use in the past, even if it currently is suspended [32].

The varied GC side effects, namely bone loss and renewal rates, are well-known, though unclear. The pre-receptor modulation of glucocorticoid activity by 1β-hydroxysteroid dehydrogenase (11βHSD), an enzyme converting inactive and active cortisone/cortisol, may promote this variability through the anti-inflammatory cytokine effects [33, 34] and a genetic polymorphism of glucocorticoid receptors [35].

The GC-induced osteoporosis is characterized by a decreased bone formation with an added early, though short-term, increase in bone resorption (Fig.1). The reduced bone formation is a decisive process and a key link to the GC-induced osteoporosis, which is also a major distinction from postmenopausal osteoporosis, described by an increased bone turnover rate [36].

An initial increase of remodeling rate is accompanied by a reduced bone formation at the level of a separate basic multicellular unit (BMU); this combination of an increased bone turnover and negative remodeling balance leading to a rapid bone loss [37-39]. Due to a reduced bone formation, both at the level of bone tissue and at the BMU level, there occurs and later predominates a low bone turnover level. The GC’s direct influence on bone formation is mediated, mostly, by the peroxisome proliferator-activated receptor γ2 (PPARγ2)-activated gamma receptor 2 [40] and by the influence on Wnt/β-catenin signaling pathways [41]. The first mechanism promotes the pluripotent precursor cells being predominantly converted into adipocytes rather than osteoblasts, resulting in the latter’s reduction. The increased expression of sclerostin, being bound to Frizzled, Lrp4 and Lrp5 co-receptors, leads to the Wnt signaling pathway’s inhibition, and then, to a reduced differentiation of osteoblast precursors into the mature osteoblast cells and activated osteoblast and osteocyte apoptosis. It is well-known that the sclerostin (SOST) is an endogenous inhibitor of the canonic Wnt/β-catenin signaling pathway. In the sclerostin’s presence, the osteoblast precursors do not receive any Wnt signals, and the osteoblast differentiation gets suspended [42]. Besides inhibiting the osteoblast differentiation by repressing the Wnt/β-catenin signaling pathway, the GCs impede the osteoblast functioning in other ways, namely by reducing the bone morphogenetic proteins (BMPs), which also results in the inhibited differentiation [43].

The GCs have a direct effect on bone resorption, stimulating the macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-κ ligand (RANKL)’s production while repressing the osteoprotegerin (OPG)’s production by osteoblasts and osteocytes, as a result increasing both the osteoclast numbers and activity [44]. This effect runs out with time, possibly due to the reduction of osteoblast and osteocyte numbers.

In the recent years, there were several fundamental studies promoting a deeper understanding of molecular mechanisms behind the GC-induced osteoporosis’ pathogenesis. These mechanisms include the increased mature osteoblast and osteocyte apoptosis, osteoblast differentiation disorders and lengthening of osteoclast life cycle [1].

Besides a direct influence on the bone cells, the GCs play an indirect role in muscle functioning, calcium metabolism, bone mineralization by inducing hypogonadism, decreasing the growth hormone, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein (IGFBP)’s production [45]. The GC’s adverse influence on muscle mass and strength is proven. The so-called ‘steroid myopathy’ may indirectly increase the fracture risk by increasing the fall risk. Moreover, it is well-known that the GCs affect the bone metabolism by slowing down the Calcium intestinal absorption and inhibiting its re-absorption by the renal canals, provoking hypocalcaemia and secondary hyperparathyroidism [8]. It was also demonstrated that the GCs affect bone mineralization by two important messenger proteins’ transpression, i.e. osteocalcin and collagen type I’s [46]. It is worthy of note that the GCs are prescribed for treating inflammatory/autoimmune diseases, whose pathogenesis is associated with anti-inflammatory, pro-resorptive cytokines’ production, and further bone loss. By control-
ling the inflammation, the GCs may alleviate the negative inflammatory effect on bone; however, the recurrent primary complaint surges lead to an increased bone resorption and progressing bone loss.

Thus, using the GCs results in a rapid bone loss and increased fracture risk. The early osteoprotective interventions are required for a successful treatment of the GC patients.

**Whom to treat?**

Despite the GCs being a well-known and well-researched cause of secondary osteoporosis, most GC patients, taking an ongoing treatment or just starting it, are underexamined and underassessed in terms of their likely bone loss and fracture risk [47]. In case of the GC-induced osteoporosis, the terms of ‘prophylaxis’ and ‘treatment’ should be interpreted in a different way: prophylaxis refers to the instances of patients, never having taken GCs previously, are starting them now; treatment refers to the instances of patients taking GCs for more than 3 months. Moreover, despite a somewhat improved prophylaxis of GC-induced osteoporosis, its management is suboptimal: only 1 out of 4 patients, taking a long-term GC treatment, are on anti-osteoporotic medications and being regularly assessed by means of control densitometry tests [47]. Under these conditions, it is essential to single out those groups of patients with the highest fracture risk and determine an intervention threshold requiring an anti-osteoporotic treatment and thorough monitoring.

There are various guidelines for the GC-induced osteoporosis management, offered by various countries and regions and relying on epidemiological data. They are presented in Table 1. Nevertheless, their different interpretations, as well as local medico-economic discrepancies, led to the guidelines being published with divergent intervention thresholds. The criteria for their development progressed together with an assessment of fracture risk and creation of FRAX® algorithm.

Prior to the FRAX® algorithm implementation, the intervention thresholds involved the GC dose and duration of treatment, as well as BMD values. In terms of the GC dose, the threshold was set at 7.5 mg per day during 3 months. In 2000, a large-scale cohort study was published, showing an increased fracture risk with a dose of <5 mg per day. This study was, first and foremost, about the absence of any ‘safe’ GC doses and necessity of treatment and prophylaxis for all those patients on (or about to be on) a long-term oral GC treatment. Having revised the previous guidelines, the American College of Rheumatology (ACR) published a new version - ACR’2001- reducing the threshold daily GC dose to 5 mg [60]. In terms of T-score, the range was from -1.0 to -1.5 SD. Many national societies followed the ACR lead and reduced the threshold daily GC dose. According to the latest guidelines [61], the GC-induced osteoporosis is expected to develop if the daily GC dose is ≥2.5 mg (Prednisone converted) for 3 months and over. Those patients have a high risk of osteoporosis. At the same time, using only BMD as a reference for the high fracture risk has several disadvantages, namely a possible inaccuracy of bone quality assessment and age dependence [62].

With time, anti-osteoporotic treatment indications, in case of the GC-induced osteoporosis, started to veer towards an absolute fracture risk. It is suggested to use the FRAX® tool, calculating a 10-year probability of fractures according to the clinical risk factors, BMD or no BMD and calibrated for a regional fracture frequency and mortality. Based on the FRAX® algorithm, all patients receiving GCs in a daily dose of ≥2.5 mg (Prednisone converted) for 3 months and over are stratified into groups according to their fracture risks (Table 2).

While calculating a fracture probability, the GCs is considered at a dose of 2.5–7.5 mg per day and over, either at the current moment or in the past. It accounts for one of FRAX®’s limitations, namely introducing the oral GC treatment into the algorithm as a dichotomic risk factor (yes/no) with no account of a daily dose or duration (duration of less than 3 months is not considered at all) [27, 63]. For a long-term GC treatment of over 3 months, FRAX® suggests a medium dose (2.5–7.5 mg per day) and medium duration to be factored in a fracture risk calculation [15]. However, the doses higher than medium (≥7.5 mg per day) are associated with a higher fracture risk, while the doses of <2.5 mg are associated with a lower risk [12, 16, 27]. The population study data held in the Great Britain show that revision coefficients may be used to assess a 10-year probability of osteoporotic fractures depending on a daily GC dose (Table 3) [32]. For the daily dose of ≥2.5–<7.5 mg, an absolute fracture risk corresponds with the one calculated by FRAX®.

The FRAX® creators made an attempt of qualitative interpretation of the GC effect on the fracture risk extent [32]. They made a conclusion that those patients who take low GC doses (Prednisone converted - less than 2.5 mg per day) have a proximal femoral fracture risk reduced on average by 35 %, while a major osteoporotic fracture risk reduced by 20 %, taking into account the age-related variations. While taking FRAX® measurements, those patients who take a GC dose of 7.5 mg per day should have the fracture risks increased by 10–25 %, with account of localization and age [27].

Since right after the GC treatment the fracture risks fall dramatically, while calculating FRAX®, it is advised not to consider short-term GC treatments taken earlier. At the same time, recurrent (though short-term) GC treatments may cause a negative influence on BMD and raise the fracture risks; although the FRAX® is barely able to demonstrate this dependence numerically. Another FRAX®’s limitation is its inapplicability for fracture risk measurement of those patients already taking the anti-osteoporotic treatment. The FRAX® tool is not equipped to calculate vertebral fracture risks, and these are the
<table>
<thead>
<tr>
<th>Source of guidelines</th>
<th>Year of publication</th>
<th>Groups of patients</th>
<th>Intervention threshold</th>
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<tbody>
<tr>
<td>Royal College of Physicians, National Osteoporosis Society [48]</td>
<td>2002</td>
<td>All patients</td>
<td>GC treatment (expected or taken) during ≥3 months OR Age ≥ 65 years OR Previous osteoporotic fracture OR T-score ≤ -1.5 SD</td>
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<tr>
<td>Dutch Society for Rheumatology [49]</td>
<td>2004</td>
<td>Postmenopausal women and men &gt; 70 years Premenopausal women and men &lt; 70 years All patients</td>
<td>GC dose ≥ 7.5 mg per day OR GC dose ≥ 7.5 mg per day + T-score ≤ -2.5 SD GC dose ≥15 mg per day OR Previous osteoporotic fracture</td>
</tr>
<tr>
<td>Japanese Society for Bone and Mineral Research [50]</td>
<td>2005</td>
<td>All patients &gt; 18 years</td>
<td>GC dose ≥5 mg per day OR Previous osteoporotic fracture OR BMD &lt; 80% peak bone mass if the GC dose ≥ 10 mg per day</td>
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<tr>
<td>Belgian Bone Club [51]</td>
<td>2006</td>
<td>All patients</td>
<td>GC dose ≥7.5 mg per day during ≥3 months (expected or taken)</td>
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<tr>
<td>German osteology society (Dachverband osteoporosis – DVO) [52]</td>
<td>2009</td>
<td>All patients</td>
<td>GC dose ≥7.5 mg per day during ≥3 months (expected or taken)</td>
</tr>
<tr>
<td>American College of Rheumatology (ACR) [53]</td>
<td>2010</td>
<td>Postmenopausal women and men &gt; 50 years Premenopausal women of a non-reproductive age and men &lt; 50 years Premenopausal women with a reproductive potential</td>
<td>GC dose ≥7.5 mg per day during ≥3 months + low risk of major osteoporotic fractures (&lt;10 % by FRAX®) OR Any GC dose during the recent ≥3 months + medium risk of major osteoporotic fractures (10-20 % by FRAX®) OR High risk of major osteoporotic fractures (&gt;20 % by FRAX®) GC dose ≥5 mg per day during 1-3 months + osteoporotic fracture OR GC treatment ≥3 months (no-dose threshold) + osteoporotic fracture GC dose ≥7.5 mg per day (expected or taken) during ≥3 months + osteoporotic fracture</td>
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<tr>
<td>Scientific Advisory Council of Osteoporosis Canada [54]</td>
<td>2010</td>
<td>All patients</td>
<td>GC dose ≥7.5 mg per day during ≥3 months (expected or taken) + age &gt; 50 years</td>
</tr>
<tr>
<td>Committee for Osteoporosis and Bone Metabolic Disorders of the Brazilian Society of Rheumatology; Brazilian Medical Association; Brazilian Association of Physical Medicine and Rehabilitation. [55]</td>
<td>2012</td>
<td>Postmenopausal women Men at the initial stage of the GC treatment (prevention of the GC-induced osteoporosis) Men receiving the GC treatment (the GC-induced osteoporosis treatment)</td>
<td>GC dose ≥5 mg per day during ≥3 months (expected or taken) GC dose ≥5 mg per day during ≥3 months (expected or taken) + T-score ≥1.0SD GC dose ≥5 mg per day during ≥3 months (expected or taken) + T-score ≥1.5SD</td>
</tr>
<tr>
<td>International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) [56; 57]</td>
<td>2012</td>
<td>Postmenopausal women and men ≥50 years Premenopausal women and men &lt;50 years</td>
<td>GC dose ≥7.5 mg per day OR Age ≥70 years OR Osteoporotic fracture OR T-score ≤ -1.5SD OR Adjusted FRAX® is higher than the intervention threshold of general population GC treatment during ≥3 months + osteoporotic fracture</td>
</tr>
<tr>
<td>Bone Section of the French Society for Rheumatology (SFR) and Osteoporosis Research and Information Group (GRIIO) [58]</td>
<td>2013</td>
<td>Postmenopausal women and men ≥50 years Premenopausal women and &lt;50 years</td>
<td>GC dose ≥7.5 mg per day OR Age ≥70 years OR Osteoporotic fracture OR T-score ≥ -2.5SD OR Adjusted FRAX® is higher than the intervention threshold of general population GC treatment ≥3 months + osteoporotic fracture</td>
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most common type of fractures associated with the GC-induced osteoporosis; this fact also reducing the model’s efficacy [2]. The FRAX®’s use is age-restricted. It is indicated exclusively for people of 40 years old and older, while for children and younger adults the tool of choice is the BMD modified by the other risk factors, namely a history of fractures. This restriction may turn out critical for the group of rheumatologic patients who are predominantly young.

In the recent decade, there were several algorithms suggested for calculation of an absolute risk of fractures for an individual patient. They are based on the T-score of spine and hip BMD, as well as a daily GC dose (Prednisone converted). Among them there is Fracture in GIOP Score (FIGS) evaluating a 5- and 10-year osteoporotic risk, hip, vertebral and forearm fracture risks [64]. Although this model is more complicated than FRAX®; however, it has its advantages of taking into account the principal complaint, frequency of hospitalization relevant to it, fall risk and GC dose. These are the factors missing in the FRAX® algorithm. The risk is described in points: 30, 40 and 50 points corresponded with an absolute 5-year risk of 6.2, 15.3 and 35.2% respectively. A woman of 65 years old, with rheumatoid arthritis, a low BMI and a history of falls and fractures who took a daily GC dose of 15 mg (a general fracture risk of 54) had a 5-year fracture risk of 47% (while a man with a similar case record – 30.1%). A short-term high-dose GC treat-
ment (> or = 30 mg) was associated with only a slightly increased risk of osteoporotic fracture (OR 1.21; 95% CI 1.04-1.42).

Within the framework of an all-national program of osteoporosis screening, a cohort study was held in Taiwan from 2008 to 2011; its findings having been published in 2017 [65]. The study was aimed at developing and implementing the threshold intervention standards, based on FRAX®, for the GC patients. The Individual intervention threshold (IIT) was calculated according to an individual-specific FRAX® probability of a major osteoporotic fracture and compared with the subjects having had a previous history of fractures. 8704 participants were recruited for the study, among them the GC treated (n = 807) and controls (n = 7897). The clinical fracture risks, namely a previous hip fracture, a parents’ history of hip fractures, rheumatoid arthritis and secondary osteoporosis, were higher in the GC treated than in the controls. The GC treated also had a higher 10-year probability of hip fractures than controls. The percentage of GC treated with a

**Table 2. Stratification of the GC patients according to their fracture risks**

<table>
<thead>
<tr>
<th>Fracture risk level</th>
<th>Adult patients ≥ 40 years</th>
<th>Adult patients &lt; 40 years</th>
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<tr>
<td><strong>High fracture risk</strong></td>
<td>A history of osteoporotic fractures T-score ≤ -2.5SD at hip or lumbar spine In men ≥ 50 years and postmenopausal women. FRAX® (GC-treatment adjusted) 10-year risk of major osteoporotic fractures is ≥ 20%. FRAX® (GC-treatment adjusted) 10-year risk of femoral neck fractures is ≥ 3%.</td>
<td>A history of osteoporotic fractures</td>
</tr>
<tr>
<td><strong>Medium fracture risk</strong></td>
<td>FRAX® (GC-treatment adjusted) 10-year risk of major osteoporotic fractures is 10-19%. FRAX® (GC-treatment adjusted) 10-year risk of femoral neck fractures is &gt;1% and &lt;3%</td>
<td>Z-score &lt; -3.0 SD at hip and lumbar spine or a rapid bone loss (≥10% at hip or lumbar spine during 1 year). A long-term GC treatment at a dose of ≥ 7.5 mg per day for ≥ 6 months</td>
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<tr>
<td><strong>Low fracture risk</strong></td>
<td>FRAX® (GC-treatment adjusted) 10-year risk of major osteoporotic fractures is &lt;10%. FRAX® (GC-treatment adjusted) 10-year risk of femoral neck fractures is ≤1%</td>
<td>No above mentioned risk factors, but for GC treatment</td>
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Note: *FRAX – https://www.shef.ac.uk/FRAX/Tool.jsp

**Fig. 2. Initial (starting) evaluation of fracture risks and stratification of patients according to their risk groups.**

Clinical evaluation of fracture risks involves collecting the medical history in order to find out the GC treatment details (dose, duration, and regimen); fall, fracture, frailty and other osteoporotic risk factor evaluation (malnutrition, significant weight loss or low body mass index, hypogonadism, secondary hyperparathyroidism, thyroid disorders, family fracture history, history of alcohol consumption and smoking) and other clinical factors, as well as a physical examination, height and weight measurements, muscle strength; searching for clinical symptoms of an undiagnosed spinal fracture (namely, tenderness, deformation, height loss, reduction of lower intercostal and upper iliac wing space etc.). FRAX®’s major osteoporotic fracture risk indices should be multiplied by 1.15, while hip fracture risk indices should be multiplied by 1.2, if the Prednisone dose is over 7.5 mg per day.

Note: GC – glucocorticoids, BMD – bone mineral density.
Table 3. Revision coefficients to calculate a 10-year probability of proximal femoral and major osteoporotic fractures depending on GC dose (our adaptation of [32])

<table>
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<th>Dose</th>
<th>Prednisone converted (mg per day)</th>
<th>Mean revision for all ages</th>
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<tr>
<td></td>
<td></td>
<td>Proximal femoral fractures</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 2.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Medium</td>
<td>≥ 2.5—&lt; 7.5</td>
<td>No revisions</td>
</tr>
<tr>
<td>High</td>
<td>≥ 7.5</td>
<td>1.20</td>
</tr>
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A follow-up clinical fracture risk evaluation involves studying the GC treatment history (dose, duration, and regimen); fall, fracture, frailty and other osteoporotic risk factor evaluation (malnutrition, significant weight loss or low body mass index, hypogonadism, secondary hyperparathyroidism, thyroid disorders, family fracture history, history of alcohol abuse (over 3 units per day) and smoking) and other clinical factors, as well as a physical examination, height and weight measurements, muscle strength testing; searching for clinical symptoms of an undiagnosed spinal fracture (namely, tenderness, deformation, height loss, reduction of lower intercostal and upper iliac wing space etc.). A very high GC dose was determined as 30 mg of Prednisone per day and a cumulative dose of 5 g for the previous year. Reliability of FRAX after the anti-osteoporotic treatment is still under discussion; however, FRAX measurement may be re-taken after 40 years, is the subjects did not receive any anti-osteoporotic treatment.
10-year probability of major osteoporotic fractures higher than IIT exceeded the one of the controls (75.0 vs. 10.6%; P <0.001). However, only 20.3% of the GC treated and 30.5% of controls, whose fracture risk exceeded the IIT, reported taking anti-osteoporotic treatment. The researchers concluded the GC users should receive an active treatment according to their IIT, and not according to the BMD [65].

The study specifically mentions that the GC treated are under-assessed as to their fracture risks and do not receive an adequate anti-osteoporotic treatment, despite an increased Individual intervention threshold (IIT). This fact was also recorded by the previous papers [66]. The potential factors of a low compliance with the guiding principles of the GC-induced osteoporosis were young age, male sex, a lower GC dose, surgical and ENT prescriptions, and treatment at the minor clinical institutions [67].

Nowadays, the fracture risk assessment with the FRAX® algorithm is recommended by several guidelines on the GC-induced osteoporosis management, namely by the National Osteoporosis Guideline Group (NOGG) [68], the revised guidelines by the American College of Rheumatology (ACR) [61], and by the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) [56, 57].

Most guidelines on the GC-induced osteoporosis management concern postmenopausal women and men over 50 years old, who are taking (or about to take) a long-term (3 months and longer) GC treatment. The anti-osteoporotic treatment is to be prescribed to all patients with a history of fragility fractures. In these instances, the osteoporosis is diagnosed clinically, while the T-score (normal or over -1.5 SD) does not affect the diagnosis or prescriptions [63]. The indication of anti-osteoporotic treatment is also the patient’s age (70 years and older), as most patients of this age have a ‘red zone’ of intervention threshold for the oral GC treatment, according to FRAX®. The patients of 50-70 years taking high doses of GCs (≥7.5 mg per day) also require this treatment. In other instances, it is recommended to take the dual energy X-ray absorptiometry (DXA or DEXA) measurements; if the T-score is -1.5 SD and lower, osteoporosis is diagnosed and anti-osteoporotic treatment is prescribed. When all the above mentioned criteria are absent or the DEXA is unavailable, a 10-year fracture probability is calculated according to FRAX®. The Figure 2 presents an initial fracture risk evaluation and patients' stratification into risk groups, on a long-term GC treatment condition.

It should be noted that the GC risk stratification has been exclusively made for men and women over 50 years, while there were no respective criteria developed for children or young adults under 40. The 2017 guidelines by the American College of Rheumatology (ACR), ACR 2017, on the GC-induced osteoporosis management [61] were the first to suggest criteria of determining medium and low risk of osteoporotic fractures in the young adults of under 40. This is very important for the rheumatologic patients whose systemic connective tissue disease onset occurs at the young age, so that by 40 years they have a long history of the GC treatment and significant BMD losses [1, 69]. There is no doubt about one principal indication for the anti-osteoporotic treatment in the premenopausal women and men under 50 years, who have (or about to have) a long (3 months and over) GC treatment: the history of fragility fractures. In other cases, the decision on the GC prescription should be taken on an individual basis, as there is no conclusive evidence of the above-mentioned treatment’s necessity.

The ACR'2017 guidelines clearly state that for the adults of under 40 the initial absolute fracture risk should be evaluated by FRAX®, taking into account the GC dose and BMD, as early as possible (up to 6 months after the GC treatment start). For the patients over 40, the BMD should also be measured as early as possible. It is, first and foremost, about the patients with a history of fractures or other important osteoporosis risk factors. The ACR’2017 guidelines also set the time of initial fracture risk evaluation, i.e. up to 6 months after the GC treatment start or as early as possible. The follow-up evaluation should take place every 12 months, for all the patients taking the continued GC treatment. For patients who are ≥40 years, still taking the GC treatment with no anti-osteoporotic medications, other than Calcium and Vitamin D, the re-evaluation of fracture risk according to FRAX® and BMD measurements should be performed every 1-3 years. Those patients on the very high GC dose (≥30 mg per day, Prednisone converted, or a cumulative dose of 5 g for the previous year) or having a history of osteoporotic fractures should have a follow-up evaluation even earlier than that. In the above-mentioned age range, the BMD testing is appropriate only for those subjects who take the lower GC doses and do not have any other osteoporosis risk factors [1, 61].

The inadequate treatment of the GC-induced osteoporosis is due to the underestimated risk of probable fractures, and that’s a well-known fact [70, 71]. A population study of adult subjects ≥20 years determined a split between the BMD testing and anti-osteoporotic treatment prescribed for patients on a long-term GC treatment to be 90 days or longer [72]. Overall, during the first 6 months after the GC treatment start only 6 % had a DEXA measurement, 22 % received an anti-osteoporotic treatment and 25 % had both. The lack of adequate examination and treatment was recorded mostly for the young subjects, males and the patients treated by the family doctors (by comparison with rheumatologists). Similar results were revealed by the study using the National database of the state medical insurance system of France: only 8 % of patients on a long-term GC treatment have a BMD measurement, 18 % take a combined Calcium and Vitamin D treatment, and 12 % take bisphosphonates [73]. While analyzing the Canadian cohort of patients of 66 years and older, on a long-term GC treatment, they found only 13
% who took an anti-osteoporotic treatment [74]. The underestimated osteoporosis and fracture risk with a long-term GC treatment was aggravated by a lack of willingness to prescribe the bisphosphonates, a lack of control and compliance. In this case, a stratification of patients who require treatment is certainly vital.

Conclusions

Today, the GC-induced osteoporosis is considered one of the most common secondary osteoporosis causes and is associated with an increased fracture risk. The GC treatment causes an increased osteoblast and osteocyte apoptosis, along with a prolonged osteoclast activity, reduction of bone density and depreciation of its micro-architecture. In the recent years, the underlying GC-induced osteoporosis mechanisms were deciphered, among which the RANKL / OPG system and Wnt signaling pathway are considered the most prominent ones. New guidelines and new tools for evaluation of absolute fracture risks among individual patients may improve the identification of patients with an increased fracture risk and promote a quality and timely treatment.

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Дискусійні питання визначення порога втручання при глукокортикоїдіндукованому остеопорозі: кого лікувати?

Резюме. Глюкокортикоїдіндукований остеопороз є найпоширенішою причиною вторинного остеопорозу. Після початку перорального прийому глукокортикоїдів протягом декількох місяців відзначається швидка втрата кісткової маси і зростання ризику переломів. Важливість глукокортикоїдіндукованого остеопорозу як проблеми охорони здоров’я асоціювана з частим застосуванням глукокортикоїдів пацієнтами з різними хронічними захворюваннями та високим рівнем остеопорозу, виявленого в цих груп пацієнтів. Розвиток глукокортикоїдіндукованого остеопорозу пропонують різні підходи до визначення порога втручань, базуючись на використанні різних критеріїв. Алгоритм FRAX® розраховує 10-річну ймовірність переломів за клінічними факторами ризику та тестуванням мінеральної інтенсивності кістки. Національні керівництва з менеджменту глукокортикоїдіндукованого остеопорозу пропонують різні підходи до визначення порогу втручання, базуючись на використанні різних критеріїв. Алгоритм FRAX® розраховує 10-річну ймовірність переломів за клінічними факторами ризику та тестуванням мінеральної інтенсивності кістки. Незважаючи на обмеження, цей інструмент є найефективнішим у виразному порогу втручання, але короткострокові зміни розраховує 10-річну ймовірність переломів з тестуванням мінеральної інтенсивності кістки виразним порогу втручання.

Ключові слова: глукокортикоїдіндукований остеопороз; глукокортикоїди; добова доза; патогенез; порог втручання; ризик переломів; FRAX®; лікування; обзор
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**Дискуссионные вопросы определения порога вмешательства при глюкокортикокоидиндуцированном остеопорозе: кого лечить?**

**Резюме.** Глюкокортикокоидиндуцированный остеопороз является наиболее распространенной причиной вторичного остеопороза. После начала перорального приема глюкокортикокоидов в течение нескольких месяцев отмечается быстрая потеря костной массы и увеличение риска переломов. Важность глюкокортикокоидиндуцированного остеопороза как проблемы здравоохранения ассоциирована с частым применением глюкокортикокоидов пациентами с различными хроническими заболеваниями и высоким уровнем остеопороза, обнаруженного у этих групп пациентов. Развитие глюкокортикокоидиндуцированного остеопороза обусловлено ингибиторным воздействием на процесс образования кости, сопровождающимся ранним, но кратковременным увеличением резорбции кости. Среди многочисленных механизмов, лежащих в основе нарушения костного метаболизма при длительном приеме глюкокортикокоидов, необходимо отметить увеличение соотношения RANKL/OPG, повышение экспрессии склеростина, активацию PPARγR2, а также гипогонадизм, нарушение всасывания кальция в кишечнике и снижение выработки инсулиноподобного фактора роста 1. Несмотря на доступные и эффективные профилактические меры, многие пациенты, начинающие или получающие глюкокортикокоидную терапию, недостаточно оценены в плане состояния костной ткани и риска переломов. Установлены пороговые значения суточных доз глюкокортикокоидов (≥ 2,5 мг/сутки) и длительность их приема (≥ 3 мес.), при которых пациенты должны быть обязательно подвергнуты оценке риска переломов и необходимости проведения лечения антиosteoporотическими препаратами. Национальные руководства по менеджменту глюкокортикокоидиндуцированного остеопороза предлагают различные подходы к определению порога вмешательства, базируясь на использовании различных критериев. Алгоритм FRAX® рассчитывает 10-летнюю вероятность переломов по клиническим факторам риска с тестированием минеральной плотности кости или без него и калибруется для региональной частоты переломов в регионе. Несмотря на ограничения, этот инструмент является наиболее эффективным в определении порога вмешательств. В рекомендациях ACR — 2017 указывается, что начальный абсолютный риск переломов следует оценивать с использованием алгоритма FRAX® с учетом доз глюкокортикокоидов и тестирования минеральной плотности кости как можно быстрее (до 6 мес. от начала приема глюкокортикокоидов).

**Ключевые слова:** глюкокортикокоидиндуцированный остеопороз; глюкокортикокоиды; суточная доза; патогенез; порог вмешательства; риск переломов; FRAX®; лечение; обзор