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Review

Long-term complications of past glucocorticoid use

Luciana P.C. Seguro [a], Cristina Rosario [b], Yehuda Shoenfeld [c,*]

[a] Rheumatology Division, Faculdade de Medicina da Universidade de Sao Paulo, Brazil
[b] Internal Medicine Department, Hospital de Pedro Hispano, Rua Dr. Eduardo Torres Matosinhos, Portugal
[c] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center (affiliated to Tel-Aviv University), Tel-Hashomer 52621, Israel

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ABSTRACT

Glucocorticoids (GC) are essential in the management of several medical conditions but its long-term use is associated with complications in diverse organs and systems. The aim of the present study is to review the long-term complications of past GC use.
Permanent damage related to GC can affect patient's life even years after its withdrawal. Classical examples are cataracts and esthetic problems like skin atrophy, striae, acne and obesity. Interestingly, for some complications, the risk of an incident event can persist for past GC use. Higher risks of osteoporosis, osteonecrosis, cardiovascular disease, infections and cancer have been associated with prior GC therapy. These evidences reinforce the importance of limiting our GC prescriptions at its lower possible dose.

Contents

1. Long-term complications of ever glucocorticoid use

1.1. Risks of complications persist after glucocorticoid withdrawal

Glucocorticoid (GC) therapy is essential in the management of patients with rheumatic and inflammatory diseases especially in cases with life threatening organ involvement. However, GC therapy is associated with several complications like osteoporosis, metabolic syndrome, cardiovascular disease, infections, osteonecrosis, and cataracts, among others [1].

Although the risk of side effects is time and dose dependent [1], even intermittent or low dose regiments have been associated with damage [2,3].

Most of the studies assess the complications associated with current GC therapy. The aim of the present study is to review the long-term complications of past GC use.

2. Glucocorticoids and bone disease

2.1. Glucocorticoids and osteoporosis

Deleterious effects of GC on bone are well known. There is an early, transient increase in bone resorption followed by a decrease in bone formation that persists throughout the duration of GC therapy. Indirect

* Corresponding author. Tel.: + 972 3 5302652; fax: +972 3 5352855.
E-mail address: shoenfel@post.tau.ac.il (Y. Shoenfeld).

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effects also occur as a result of hypogonadism, increased calcium loss from the intestine and kidney and vitamin D insufficiency [4].

The result is rapid bone loss and increased fracture risk early after therapy is initiated [5]. Fracture risk is dose dependent but it is increased even with low dose (2.5–7.5 mg of prednisolone or the equivalent) or intermittent regiments [2,6]. Fractures in GC induced osteopororosis (GIOP) can occur independently of bone mass density (BMD) [6] and can be found in up to 30–50% of patients [7].

After withdrawal of GC therapy, fracture risk returns partially back to baseline levels, unless the patient had substantial loss in bone mass due to high cumulative doses of GC [8]. A large United Kingdom study based in general practice showed that prior GC use confers a substantial increase in fracture risk [9]. In this regard, a meta-analysis of data from seven cohort studies of about 42,000 men and women showed that the ever use of GC was associated with an increased risk of any fracture at all ages. The risk was higher for osteoporotic fractures and for hip fracture alone. This increase in risk was not explained by differences in BMD and was independent of prior fragility fracture [10].

Besides high total medical and hospitalization costs [11], fractures are associated with significant morbidity including pain, disability and lower quality of life [12]. Also, higher mortality rates are described in patients with low BMD as well as in those with recent hip and vertebral fractures [13].

In recent years, efforts to reduce the incidence of GIOP and related fragility fractures have been done. Guidelines for the prevention and management and GIOP are available and indicate treatment with bone active drugs (like bisphosphonates and teriparatide) for high-risk patients [14–17]. All patients under current or past GC therapy should take calcium rich diet and vitamin D supplementation, unless contraindicated. Anyway, no evidence exists that there is a safe minimum dose or duration of glucocorticoid exposure and the lowest effective dose should be used in order to prevent OPIG [18].

2.2. Glucocorticoids and osteonecrosis

Glucocorticoids are the leading cause of nontraumatic osteonecrosis (ON). Up to 40% of patients can present osteonecrosis after long-term GC therapy [19]. The risk increases with higher doses and prolonged treatment but it may also occur with short-term exposure to high doses or after intra-articular injection. By inducing osteocyte apoptosis, GC decrease bone remodeling, disrupt the mechanosensory function of the osteocyte–lacunar–canalicular system and start the sequence of events leading to bone collapse [20].

Osteonecrosis can be asymptomatic, but some cases are dramatic with persistent joint pain and reduced range of motion with joint replacement indication. First symptoms of hip pain appear in average 33 months after initiation of GC, but several cases of osteonecrosis were noted early after the beginning of therapy [20].

Whether the risk persists after GC withdrawal is not known. In a populational-based case control study in the UK, the use of systemic glucocorticoids in the previous 2 years was an independent risk factor for osteonecrosis [21]. In a case–control study of HIV-infected patients, prior systemic GC use was strongly associated with osteonecrosis of the femoral head [22].

Once diagnosed, bisphosphonates are indicated to reduce pain, increase ambulation and delay bone collapse in patients with osteonecrosis [20].

2.3. Risks of bisphosphonate therapy for GIOP and GC related ON

It is worth mentioning that bisphosphonates use is also associated with bone complications, namely atypical fractures and osteonecrosis of the jaw, probably due to bone turnover suppression and consequent microdamage accumulation [23].

Atypical fractures are rare transverse stress fractures that occur in the cortical bone of the diaphysis, especially in the femur, and strongly relate to bisphosphonate use [24]. In a Swedish populational-based case control study, the risk increased with higher duration of bisphosphonate therapy but was not increased among GC users [25]. However, the absolute number of atypical fractures is low and it is estimated that 10 to 30 osteoporotic fractures are avoided to each atypical fracture that occurs after bisphosphonate therapy. The risk–benefit ratio clearly favors bisphosphonate therapy in patients with high risk of fracture [26,27].

Regarding osteonecrosis of the jaw, the risk is higher after the administration of endovenous bisphosphonates, especially for multiple mieloma and metastatic bone disease, probably due to higher doses administered and to effects of cancer itself. There are few case reports of these complications in osteoporotic patients [26]. Elective dentoalveolar procedures are not contraindicated in symptomatic patients receiving oral bisphosphonates. However, invasive dental procedures should be done prior to treatment with endovenous bisphosphonates. Dental infections must be treated promptly in patients on bisphosphonates therapy [26]. In patients with high risk of fractures, benefits with bisphosphonate use overweigh the potential risks [26].

3. Glucocorticoids and cardiovascular disease

Glucocorticoids contribute to a cluster of cardiovascular risk factors like obesity, insulin resistance, glucose intolerance, dyslipidemia and hypertension. Also, GC have direct effects on the heart, kidneys and blood vessels, influence vascular function, promote atherogenesis and affect vascular remodeling [28,29].

In fact, the risk for cardiovascular events is increased in patients under GC therapy. In an observational study of about 15,000 people, the relative risk for a cardiovascular event in patients receiving high-dose GC was 2.56 after adjustment for known covariates [30]. Also, patients under GC who presents features of iatrogenic Cushing's syndrome have an increased incidence of cardiovascular complications. In multivariate analyses, the relation between iatrogenic Cushing's syndrome and cardiovascular events was strong for coronary heart disease, for heart failure and for ischaemic cerebrovascular events [31].

Regarding previous use of GC, an ongoing excess risk is sustained after cessation of exogenous GC administration or cure of Cushing's disease and much of the risk is likely related to development of an exaggerated metabolic syndrome with its well-known adverse cardiovascular outcomes [32].

In a retrospective study of 30 Japanese children who had been treated with GC for nephrotic syndrome, the maintenance of high body mass index after CG withdrawal was related to the dose and duration of GC exposure and was associated with hyperlipidemia, which might enhance cardiovascular risk [33].

Also, a study of rheumatoid arthritis (RA) patients showed that previous exposure to prednisone or high yearly frequencies of pulsed GC administrations were independently associated with decreased insulin sensitivity. Since decreased insulin sensitivity is an independent risk factor for cardiovascular disease, GC may contribute to the excess cardiovascular event rates in RA [34].

Moreover, a populational based case–control study that evaluated more than 50,000 subjects found a significant association between ever use of oral glucocorticoids and any cardiovascular or cerebrovascular outcome. Although the association was stronger for the current use, past use of GC increased significantly the risk for heart failure [35]. This might be explained by the mineralocorticoid effects of administered GC since mineralocorticoid activation exacerbates heart failure by increasing sodium and fluid retention and by promoting remodeling through fibrosis of the atria and ventricles [36].

Patients exposed to GC need careful assessment of their cardiovascular risk profile. Treatment of individual factors, as well as the