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Review

Animal models for glucocorticoid-induced postmenopausal osteoporosis: An updated review

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ABSTRACT

Glucocorticoid-induced postmenopausal osteoporosis is a severe osteoporosis, with high risk of major osteoporotic fractures. This severe osteoporosis urges more extensive and deeper basic study, in which suitable animal models are indispensable. However, no relevant review is available introducing this model systematically. Based on the recent studies on GI-PMOP, this brief review introduces the GI-PMOP animal model in terms of its establishment, evaluation of bone mass and discuss its molecular mechanism. Rat, rabbit and sheep with their respective merits were chosen. Both direct and indirect evaluation of bone mass help to understand the bone metabolism under different intervention. The crucial signaling pathways, miRNAs, osteogenic- or adipogenic- related factors and estrogen level may be the predominant contributors to the development of glucocorticoid-induced postmenopausal osteoporosis.

Contents

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1. Introduction

Osteoporosis (OP), is a systemic skeletal disorder, characterized by decreased bone mass, microarchitectural deterioration and increased fragility as well as consequent increase in risk of bone fracture, which greatly affects people's life quality and even gives rise to the increased mortality, arousing extensive concerns among the population. OP is generally classified as the primary OP and secondary OP. Glucocorticoid (GC) intake is the most common cause of secondary OP, while menopause is one of the common cause of primary OP [1].

Epidemiological study showed up to 4.6% of postmenopausal women are taking oral GC [2]. GC intervention and menopause often simultaneously play roles in developing OP. Related study has reported that GCs aggravate the postmenopausal or aged osteoporotic status and impairment of skeletal metabolism [3], and thus increase the morbidity of OP and the risk of OP-related fractures. Therefore, more attention should be paid to the patients with glucocorticoid-induced postmenopausal osteoporosis (GI-PMOP), and more basic research related to GI-PMOP should be devoted to exploring its underlying mechanism and the potential therapeutic target, which requires suitable animal models simulating the population. However, available relevant studies are still inadequate, and how to successfully establish and correctly select an animal model of GI-PMOP are still an outstanding question.

To characterize GI-PMOP well, GCs were administered to ovariectomized animals. Ovariectomy (OVX) is a canonical means to create PMOP model. Combined with GCs treatment, ovariectomized animals not only rapidly develop OP, but also pertinently mimic glucocorticoid-induced postmenopausal osteoporosis (GI-PMOP) [4]. Therefore, we introduce this combined OP model by summarizing the advantages of its establishment, characteristics of animals selected, routine experimental protocols and evaluation of OP, and attempt to deduct the underlying pathogenesis of GI-PMOP on the basis of existing study.

2. Strengths and limitations of OVX and/or GC treatment

2.1. Ovariectomy

Varieties of OVX animals have been employed to investigate OP. In rats, bone loss occurs some days after OVX at different bone sites in both cancellous and cortical bone [5–7]. OVX causes enlarged bone marrow cavity, showing the similar pathological regression of bone in postmenopausal women. Therefore OVX has been regarded as an canonical protocol to create the OP model in animals. However, in the other species, such as rabbits and sheep, etc. OVX alone is incapable of developing sufficient osteoporosis [8–10].

2.2. Glucocorticoid treatment

Clinical studies have shown that patients who take GCs for 6 months or longer develop OP [11]. OP also occurs in animals like rat, rabbit, and sheep after GCs treatment due to enhanced bone resorption and reduced bone formation. Effects of GCs on bone metabolism had been extensively studied. Most of researches have demonstrated that GCs administration lead to bone loss [12,13]. However, paradoxical result that dexamethasone increased the bone mass had been revealed when treating rats with GC at relative low dose [14]. Additionally, high dose treatment of GC may cause additional detrimental effects (like osteonecrosis) on bone [15], even lead to animal's death [16] attributable to the increased risk of infection on account of immunosuppression of GC. Besides, although GCs causes a more progressive bone loss compared to OVX, the bone loss reverse after GC cessation [17]. These limitations increase the chance of failure establishing OP model.

2.3. Union of OVX and GC treatment

Due to the limitations of either OVX or GC treatment alone to induce osteoporosis, like insufficiency, inconsistency, and time consumption, combined methods including ovariectomy combined with deficient diet [18,19], OVX combined with hindlimb unloading [20], and with GCs treatment, have been applied to create OP models. While increasing researches preferred to combining OVX and GCs treatment due to the strengths. On the one hand, combination of OVX and GCs treatment rapidly and severely induced significant bone loss [21–23]. On the other hand, bone loss continues after GC treatment cessation [24,25], without rebound like that caused by GC intervention alone [26].

Altogether, OVX is a canonical means to produce PMOP model, whereas it cannot induce sufficient bone loss alone in common model animals such as rabbits and sheep. GC treatment can notably decreases cancellous bone in humans and large animals, but not consistently in rodents [27]. Moreover, GC-induced osteoporosis might show a reversal of bone loss after GC cessation. Compared with OVX or GC intervention alone, combination of them showed more potency in inducing OP and no reversal.

3. Creation of GI-PMOP model

3.1. Animals

Rodents, rabbits, sheep, goats, dogs, pigs and primates are familiar animals utilized to establish models for OP study. They have quite a few merits and respective characteristics in application. However, goats, dogs, pigs, and primates are not preferential in OP-related research due to their inherent shortcomings including high cost, inconvenience to feed and care, anatomical or physiological difference from human, etc. In contrast, rats, rabbits and sheep are most commonly used for OP models, particularly for GI-PMOP model. Therefore we focus on depicting characteristics of these three animals.

3.1.1. Rat

The satisfactory reproducibility is paramount in choosing the most proper animal model for the disease study. First, in adult humans, the prevailing activity of bone includes modeling and