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A systematic review of the effect of oral glucocorticoids on energy intake, appetite, and body weight in humans

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ABSTRACT

Obesity is a serious risk factor for chronic disease, and commonly prescribed oral glucocorticoids (OCS) may be contributing to the prevalence of obesity. The objective of this review was to assess the impact of OCS on obesity in humans through effects on body weight (BW), energy intake, appetite, and body composition. An electronic search of English language peer-reviewed studies from 1973 up to March 2012 was conducted using Medline, CINAHL, EMBASE, and Cochrane databases. Original studies that addressed the effects of OCS on appetite, energy intake, BW, or body composition in adults were considered eligible. Data from 21 studies with objectively measured outcomes were extracted and assessed for quality using standardized tools. The publication year varied from 1986 to 2013, and the sample size, from 6 to 189. Energy intake was measured in 6 studies; BW, in 19 studies; energy expenditure, in 3 studies; body composition, in 6 studies; and appetite was evaluated in 3 studies. Short-term oral glucocorticoid therapy may result in small increases in energy intake but does not appear to result in increased BW, possibly due to an increase in energy expenditure. Long-term therapy may result in clinically significant weight gain. Within-subject variation due to metabolism and physical activity levels confounds the relationship. A dose-response relationship of oral glucocorticoid therapy on energy intake, appetite, BW, or body composition was not found. Additional well-designed, double-blind, placebo-controlled clinical trials that use standardized doses of OCS and assess the effects on appetite, energy intake, BW, and composition are strongly justified to confirm the findings of this review.

1. Introduction

Obesity is a major risk factor for many serious and debilitating chronic diseases. Modifiable risk factors, which contribute to overweight and obesity, including prescription medications, are being targeted to reduce the burden of this now prevalent condition [1]. Oral glucocorticoids (OCS) are considered to have obesogenic effects [1]. However, it is unclear whether a dose-response relationship exists and whether effects on body weight (BW) are uniform across different conditions. The

Abbreviations: BW, body weight; BMD, bone mineral density; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DEX, dexamethasone; LBM, lean body mass; MeSH, Medical Subject Headings of the National Library of Medicine; NHMRC, National Health and Medical Research Council Australia; OCS, oral glucocorticoids; PE, prednisone equivalent; RCT, randomized controlled trial; RA, rheumatoid arthritis.

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short- and long-term effects of OCS on BW and body composition need to be described so that any associated risks can be communicated to patients, and suitable recommendations can be made to avoid such effects.

Oral glucocorticoid drugs are used both in the short and long terms for their anti-inflammatory properties in asthma, rheumatologic diseases, dermatological disorders, autoimmune diseases, and many other inflammatory disorders [2]. Although OCS are widely used, they are well known to have adverse effects, which are dose dependent and related to the half-life, frequency, and time of day administered and the route of administration of the drugs [2]. Short-term adverse effects include insomnia, constipation, bloating, mood changes, and hyperglycemia, whereas long-term treatment is associated with osteoporosis, bone necrosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, Cushing syndrome, cataracts, glaucoma, skin thinning, easy bruising, and muscle atrophy [3,4]. Authors of scientific articles commonly state that OCS are associated with increased appetite and/or BW [1] and cite historical studies including dialysis patients on long-term OCS [5] and terminally ill cancer patients [6]. Yet, the association of weight gain and appetite changes with OCS therapy in humans does not appear to be uniform and has not been well described.

Oral glucocorticoids have been shown to rapidly stimulate appetite in patients with cancer cachexia and are often prescribed for this purpose [7]. However, risk of adverse effects such as muscle wasting may outweigh the benefits of using OCS [8]. The effects of OCS on patients with cancer cachexia and other conditions where abnormalities in energy metabolism exist and where weight regain occurs as a result of treatment and recovery should not be generalized to all patient populations prescribed OCS. Indeed, OCS are not used clinically in patients with inflammatory conditions to cause weight gain. Lean tissue weight gain can be beneficial in terminally ill or cachectic patients [6], but gains in fat mass are undesirable and can be detrimental especially in conditions such as asthma, osteoarthritis, and diabetes [9]. Furthermore, the perceived association of OCS with obesity and weight gain can influence patients' compliance with their prescribed medications [1]. This review focuses on the effects of OCS in humans, as the treatment effects in humans are relevant to management and therapy in these conditions.

In the literature, OCS adverse effects, such as BW and appetite changes, are not often reported and when they are reported, rather than using objective pre and post measurements, most data are recall and self-reported by subjects postintervention. In addition, there is a bias toward reporting adverse effects following long-term rather than short-term interventions, and these adverse effects are not investigated as primary outcomes in OCS intervention studies [10]. Therefore, the objective of this review was to identify whether OCS have clinically relevant effects on BW, appetite, energy intake, and body composition in humans. The review will assess the literature to identify clinically significant effect sizes including energy intake changes of greater than or equal to 2 MJ/d and a 5% change in BW and whether a relationship exists between glucocorticoid dose, duration, and effect size in subjects with inflammatory conditions and healthy subjects. For this purpose, Medline, CINAHL, EMBASE, and Cochrane databases were searched for relevant studies using keywords relating OCS and diet, appetite, BW, and composition until May 2012 and by reviewing the reference lists from retrieved articles.

2. Methods for the selection of literature reviewed

2.1. *Search strategy*

English language articles from 1973 up to March 2012 were searched in electronic health and medical databases using keywords and Medical Subject Headings of the National Library of Medicine (MeSH) in Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE (Excerpta Medical Database), Cochrane Database, Australian digital thesis program, and Dissertation and Abstracts. A further author search was performed to identify updated versions of retrieved studies. Cited reference searches of retrieved articles through Web of Science database and hand searching of reference lists of retrieved studies were also conducted. The MeSH search terms were adult, BW, obesity, weight gain, adiposity, glucocorticoids, prednisone, methylprednisolone, dexamethasone (DEX), prednisolone, immunosuppressive agent, DEX isonicotinate, satiety response, satiation, appetite stimulants, appetite regulators, energy intake, diet, food habits, eating, leptin, leptin receptors, adiponectin, ghrelin, ghrelin receptors, respiratory function tests, forced expiratory volume, inflammation, and inflammatory mediators.

2.2. *Article inclusion criteria*

An a priori review protocol was designed with criteria to include studies with human adult participants 18 years or older taking OCS that objectively measured and reported at least one of the following outcomes: BW (kilograms), dietary intake or body composition (percentage of body fat or percentage of lean body mass [LBM]), or appetite. Study designs included were both short- and long-term randomized controlled trials (RCTs), quasi-experimental studies, cohort studies, case-control studies, observational studies, and systematic reviews. Exclusion criteria were animal studies, pregnancy, children (<18 years old), transplant patients, Cushing syndrome, Addison disease, and associated conditions with cortisol production abnormalities and cachexia and studies using OCS therapeutically to increase appetite in terminally ill or cancer patients. Studies using intravenous, intramuscular, and topical glucocorticoids or progesterones, mineralocorticoids, nonsteroidal immunosuppressive drugs, steroidal eye drops, anabolic steroids, and steroid hormones were excluded. Case study, reviews, and narrative study designs were excluded.

2.3. *Data extraction and analysis*

All studies retrieved by the search strategy were initially appraised by the principal reviewer (BB) for relevance to the review according to the article title and either excluded or included. Further appraisal of the remaining articles was based on the article title, abstract, and keywords by the principal and second reviewer (LMW). Articles deemed not