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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.

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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

relevant based on abstract were excluded, and reason for exclusion was recorded. All remaining abstracts that appeared to meet the inclusion criteria were retrieved in full. If there was any doubt as to whether an article met the inclusion criteria based on the title, abstract, keywords, and MeSH, the full article was retrieved for clarification. Retrieved articles were assessed for exclusion criteria and subjected to a second appraisal by the second reviewer. Upon disagreement on the inclusion of an article, a third independent reviewer decided whether the study was to be included (LW). All full-text articles were then appraised for methodological quality using a standardized critical appraisal checklist designed by the American Dietetic Association [11]. The tool addressed the reliability, validity, and feasibility of included studies. Studies of negative or neutral methodological quality as judged by the critical appraisal tool were excluded from the review.

Study details were extracted and recorded using a standardized data extraction tool developed for this review. Each study was also assessed by the National Health and Medical Research Council, Australia (NHMRC) levels of evidence hierarchy, which assigns a level of evidence according to the

study design [12]. A summary of the evidence was created using narrative summaries and tables summarizing the evidence. Oral glucocorticoid dosages and study outcomes such as energy intake were converted to similar units to allow comparison. Prednisone equivalent (PE) dosages were calculated for studies that used OCS other than prednisone or prednisolone, by a glucocorticoid conversion calculator [13].

3. Findings of oral glucocorticoid effects on energy intake, BW, body composition, and appetite

Articles were identified using an initial and secondary database search strategy and via cited reference searches and hand searching reference lists of retrieved articles (Fig.). After excluding duplicate articles and reviewing titles, abstracts were retrieved and reviewed, and relevant full-text articles were retrieved. Data extraction and methodological quality checks were performed on all full-text articles that met inclusion criteria. Articles were excluded due to poor methodological quality.

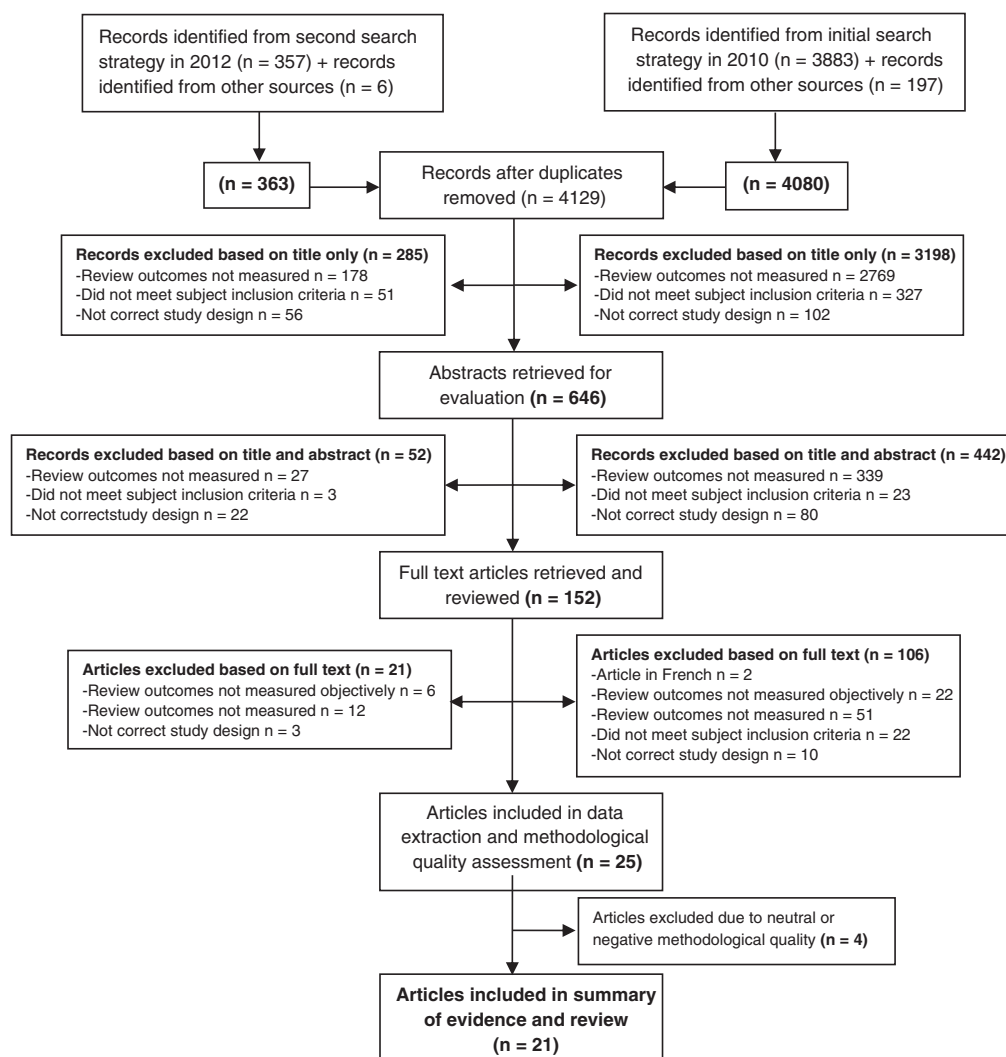


Fig. – Articles for inclusion in a systematic review of the impact of oral corticosteroids on BW, dietary intake, appetite, and body composition in humans.

Table 1 – Design of studies not included in the review due to poor methodological quality

	Methodology issues ^a	Level of evidence ^b	Study design	Blinding	Study duration/ follow-up
Berneis et al [14]	Subject selection, and inclusion/exclusion criteria not described, no blinding	II	RCT	Nil	7 d
Kyle and Hazleman [15]	Inclusion/exclusion criteria and subject demographics not described, study groups not compared, no blinding	II	RCT	Nil	2 mo/68 wk
Melzer and Souhrada [16]	Subject selection, recruitment and inclusion/exclusion criteria not described, no control group	IV	Cross-sectional analysis	N/A	N/A
Roubenoff et al [17]	Inclusion/exclusion criteria not described and no control group	IV	Case series: pretest/posttest	Nil	12 d

^a American Dietetic Association critical appraisal checklist.

^b National Health and Medical Research Council levels of evidence.

3.1. Description of excluded studies

Studies excluded due to poor methodological quality indicated by the quality criteria checklist included studies in healthy subjects [14], subjects with polymyalgia rheumatic and giant cell arteritis [15], asthmatics and healthy controls [16], and rheumatoid arthritis (RA) subjects [17] (Table 1). The median intervention period of excluded studies was 9.5 days, ranging from 7 to 12 days. Reasons for exclusion were study groups not compared at baseline, inclusion/exclusion criteria and recruitment methods not described, participants and researchers not blinded to study allocation, and no control group used.

3.1.1. Description of included studies

Of the 21 included studies, there were 14 RCTs, 1 pseudo-RCT, 3 non-RCTs, 1 observational cross-sectional study, and 2 case series with pretest/posttest measures (Table 2). Twenty studies with a total of 1236 participants used an experimental design with a median intervention period of 21 days, ranging from 24 hours to 2 years. The publication year varied from 1986 to 2013. The methodological quality of all included studies was positive.

3.1.2. Subject population of included studies

The characteristics of included studies are presented in Table 3. Among the included studies, the total number of subjects was 1254. Eight studies with a total of 98 participants (7.8% of total review subjects) were performed with subjects from healthy populations [18,20,22,23,31,32,37,38]; 4 studies and 45% of subjects had RA [24,26,29]; and other subjects had Grave ophthalmopathy [19], chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [25], asthma [33,39], Crohn disease [27,36], Wegener granulomatosis [21], sarcoidosis [28], and cystic fibrosis [35].

3.1.3. Study arms (treatment/control) of included studies

Of the 20 intervention studies, 15 included a treatment and placebo/control arm, and 3 studies compared routine OCS treatment with another OCS drug and regimen [25,27,28]. Eight intervention studies included a true placebo group, whereas 5 studies used a cross-over design with subjects acting as their own control in the placebo phase [18,20,31,32,35]. Three intervention studies did not include

control subjects [21,37,38], and the cross-sectional study compared Crohn disease subjects on OCS to healthy controls not taking OCS [36].

3.2. Glucocorticoids and dosages used in included studies

The most commonly used glucocorticoids were prednisone (n = 361) and prednisolone (n = 609), which were used in 17 studies; DEX was used in 2 studies (n = 45), and betamethasone, methylprednisolone, and hydrocortisone were each used by 1 study. The average daily dose used by the intervention studies was 40 mg (median, 40 mg) PE, and ranged from 5 to 267 mg PE per day.

3.3. Effects of OCS on energy intake

Energy intake was reported in 5 short-term intervention studies with cumulative OCS doses ranging from 75 to 420 mg PE (Table 3). Compared with placebo or baseline, energy intake was increased in 1 study [22], decreased in 1 study [18], and was not different in 3 studies [20,31].

Tataranni et al [22] measured energy intake of healthy males on OCS and placebo, via analysis of 4-day food and drink intake, and reported energy intake was significantly increased in subjects taking 50 mg/d methylprednisolone for 4 days compared with placebo. This RCT allowed the 15 participants to eat ad libitum from an automated vending machine, while energy intake was measured by calculating the energy/nutrient content of all meals and snacks before consumption minus leftovers for 4 days during OCS and placebo phases [22].

A study by Askari et al [18] measured energy intake during 24-hour controlled inpatient feeding and reported decreased energy intake in 6 subjects after 1 day of hydrocortisone (75 mg PE) therapy compared with placebo. Energy intake was measured by a dietitian weighing meals before and after serving and calculating nutrient content [18]. While on OCS, subjects consumed significantly less energy than when on placebo.

Udden et al [37] compared energy intake using 48-hour food recalls and an eating behavior monitor before and after prednisolone 25 mg/d for 7 days in 12 healthy females. There was no difference in energy intake (MJ) between meals eaten pre-OCS and post-OCS as measured by 48-hour recalls before

Table 2 – Design and primary outcome of studies included in the review

Reference	Level of evidence ^a	Study design	Blinding	Study duration/ follow-up	Primary outcomes
Askari et al [18]	II	Randomized cross-over controlled trial	Unclear	2 × 24 h periods/ 2-wk wash out	Blood glucose, insulin, cortisol, and leptin
Prummell et al [19]	II	RCT	Double	6 mo	Clinical efficacy: NOSPECS score
Rieth et al [20]	II	Randomized cross-over controlled trial	Double	2 × 1 wk periods 3-wk wash out	Energy intake and adipokines
Wung et al [21]	II	RCT	Double	1 y	Disease control, BW
Tataranni, 1996 [22]	II	RCT	Double	4 days	Energy intake, RMR, EE
Brotman et al [23]	II	RCT	Double	5 d	HR, BP, lipids
Van Everdingen et al [24]	II	RCT	Double	2 y	Efficacy: grip strength, disease modifying properties
Van Schaik et al [25]	II	RCT	Double	32 wk/20 wk	Efficacy: clinical remission
Capell et al [26]	II	RCT	Double	2 y/6 mo	Efficacy: radiological and clinical changes
Campieri et al [27]	II	RCT	Double	8 wk	Efficacy and safety of budesonide
Rizzato et al [28]	II	RCT	Nil	2 y/4 y	Efficacy and safety of deflazacort
Wassenberg et al [29]	II	RCT	Double	2 y	Efficacy: radiological (Ratingen score)
Kirwan [30]	II	RCT	Double	2 y	Efficacy: radiological damage and erosion to hands
Jollin et al [31]	II	Randomized cross-over controlled trial	Double	7 d	Adipokines, BW, body composition, and dietary intake
Wolthers et al [32]	III-2	Pseudo-randomized cross-over controlled trial	Double	2 × 4 d periods 10-d wash out	REE, catecholamines, thyroid function, and leptin
Nishimura et al [33]	III-2	Nonrandomized, controlled experimental trial	Nil	12 mo	BMD, BMC, body composition
Lazenby et al [34]	III-2	Nonrandomized, controlled experimental trial	Single	2 × 7 d periods	Efficacy: esophageal acid contact time, GORD symptoms.
Pantin et al [35]	III-2	Nonrandomized, cross-over controlled experimental trial	Single	2 × 3 wk periods 1 wk tapered	Efficacy: lung function, MRC breathlessness score, 6MW
Mingrone et al [36]	III-2	Case-control	–	–	Energy intake, body comp, EE
Udden et al [37]	IV	Case series: pretest/posttest	Nil	7 d	Energy intake, leptin, insulin, glucose, eating behavior
Chong et al [38]	IV	Case series: pretest/posttest	Nil	21 d	RMR, TEE, body composition

Abbreviations: HR, heart rate; BP, blood pressure; REE, resting energy expenditure; BMC, bone mineral content; GORD, gastroesophageal reflux disease; MRC, medical research council; 6MW, 6-minute walk test; EE, energy expenditure; RMR, resting metabolic rate; TEE, total energy expenditure.

^a National Health and Medical Research Council levels of evidence.

and after treatment, although intake was not compared with a placebo group. Food intake was also measured by a universal eating monitor that weighed the participant's meal before and after eating, which found that food intake in grams increased postprednisolone treatment [37]. Rieth et al [20] reported no difference in energy intake of 8 healthy males on prednisolone 60 mg/d for 7 days compared with placebo. Energy intake was measured by 3-day food records, before and after OCS and placebo phases [20]. Energy intake was not different to placebo in 17 healthy females following 50 mg/d prednisone for 7 days in an RCT by Jollin et al [31]. Food intake was measured with 3-day food records kept in the last 3 days of each treatment phase.

A cross-sectional study by Mingrone et al [36] compared energy intake between subjects with Crohn disease on an average oral prednisone dose of 29 ± 18 mg/d to energy intake of healthy controls not taking OCS, through analysis of the

consumed portion of 24 hours of inpatient meals prepared by a dietitian. Crohn subjects on OCS had greater energy intake than healthy controls not on OCS. There was no significant difference in their body mass index, although significant fecal nutrient losses were shown in this group of Crohn subjects.

3.4. Effects of OCS on energy expenditure

Three short-term studies included in the review examined energy expenditure during OCS therapy. The intervention by Chong et al [38] measured energy expenditure in healthy females using doubly labeled water, finding that energy expenditure increased from baseline after OCS treatment (11.73 MJ/24 h to 14.74 MJ/24 h; $P < .05$), although subjects' BW increased despite the concurrent increase in energy expenditure. Tataranni et al [22] measured energy expenditure in healthy males via indirect calorimetry and also reported

Table 3 – Subject population, OCS cumulative dose, and results of short-term (<3 months) studies included in the review

Intervention studies	Subjects	CD ^a	Δ	Energy intake	Δ	BW
Campieri et al [27]	177 Crohn	1400 mg			+	Budesonide Δ + 1 kg Pred Δ + 2.1 kg; P = .0001
Pantin et al [35]	20 CF	420–630 mg			~	Pre: 49 kg (32–76) Post: No change
Rieth et al [20]	8 Healthy M	420 mg	~	Pred = 9.18 ± 0.57 MJ/d Placebo = 9.85 ± 1.11 MJ/d; P > .05	~	Pre: 68.6 ± 2.8 kg, FM = 14.5% ± 1.3% Post: 68.9 ± 3.0 kg, FM = 14.3% ± 1.2%
Lazenby et al [34]	20 Asthma	420 mg			~	Pre: 99.7 ± 6.5 kg Post: 100.4 ± 6.9 kg; P = .08
Jollin et al [31]	17 Healthy F	350 mg	~	Pred: Pre: 6.62 ± 0.46 MJ/d Post: 7.35 ± 0.43 MJ/d; P > .05 Placebo: Pre: 6.53 ± 0.37 MJ/d Post: 6.68 ± 0.39 MJ/d; P > .05	~	Pred: Pre: 60.8 ± 1.4 Post: 61.8 ± 1.2; P > .05 Placebo: Pre: 61.1 ± 1.4 Post: 61.7 ± 1.5; P > .05
Tataranni et al [22]	15 Healthy M	200 mg	+	Meth: 27.68 ± 7.55 MJ/d Placebo: 20.78 ± 3.91 MJ/d; P < .05 ^b	~	Meth: Δ + 2.8 ± 1.1 kg Placebo: Δ + 2.3 ± 0.9 kg P = .17 ^c
Wolthers et al [32]	8 Healthy M	200 mg			~	LBM: Placebo Δ -0.4 ± 0.9 kg Pred Δ -0.7 ± 0.9 kg; P > .05
Brotman et al [23]	25 Healthy M	200 mg			+	DEX Δ + 1.3 ± 1.5 kg; P = .006 Placebo Δ -0.02 ± 0.7; P = .008
Udden et al [37]	12 Healthy F	175 mg	~	Pre: 7.13 ± 0.62 MJ/d Post: 7.39 ± 0.51 MJ/d; P > .05 Food intake (g): Pre: 221 ± 36, Post: 264 ± 44; P < .05	~	Pre: 80.1 kg, Post: 79.9 kg FM Pre: 41.9%, Post: 42.2%
Chong et al [38]	7 Healthy F	175 mg			+	Pre: 70.4 kg, Post: 71.6 kg; P < .05 FM: Pre: 26.7 kg, Post: 28.2 kg; P < .05
Askari et al [18]	6 Healthy (3 M, 3F)	75 mg	-	HC group = 10.41 ± 0.90 MJ/d Saline = 12.58 ± 0.97 MJ/d; P = .005		
Observational study						
Mingrone et al [36]	7 Crohn, 11 HC	29.0 ± 17.8 mg/d		Pred = 9.61 ± 0.88 MJ/d Control = 7.76 ± 0.52 MJ/d; P = .005		

Abbreviations: CD, cumulative dose of oral corticosteroids taken during study period in PEs; F, female; HC, healthy control; M, male; CF, cystic fibrosis; FM, fat mass; +, significantly increased from baseline or greater than placebo/control; ~, no change from baseline or no significant difference between active drug and placebo/control; -, significantly decreased from baseline or lower than placebo/control; Δ, change from baseline.

^a Prednisone equivalent of dosage used in study.

^b Subjects allowed to eat ad libitum 24 h/d from automated vending machine Meth group energy intake significantly increased from baseline and significantly higher than placebo after 4 days of treatment.

^c Meth and placebo groups significantly increased weight from baseline (P < .05), although weight change from baseline in Meth group was not significantly different to placebo.

increased energy expenditure in the OCS group greater than the increase in placebo group, which may explain how subjects remained weight stable despite significantly increased energy intake from food. Wolthers et al [32] reported that energy expenditure (measured by indirect calorimetry) was not different in 8 healthy males while on OCS or placebo, with no corresponding change in BW during either phase.

3.5. Effects of OCS on BW

Weight gain as an adverse effect of OCS treatment is often reported in the literature with no reference to initial body-weight, the actual change in BW, or whether weight gain was clinically or statistically significant. These studies have used OCS therapy in various conditions, both in the short [40–48] and long terms [15,49–59] with various study designs, and have not been included in the summary of evidence for this review as no objective measure was reported for the effect on BW.

Nineteen studies in the review measured BW, of which 4 studies measured and reported energy intake. Studies have

been divided into short (<3-month duration) and long terms (≥3-month duration) to distinguish the effects on BW.

Nine studies were long term, of which 4 studies reported no difference in BW compared with control or baseline (Table 4). Increased BW in the OCS group compared with control or baseline was seen in most (5) of the longer duration studies (6 months to 2 years) with high cumulative OCS doses (2800–9984 mg PE) [19,21,24,28,29]. Dietary energy intake was not measured in these 5 studies.

In a 2-year RCT by Rizzato et al [28], after 4 years, 36 sarcoidosis subjects on prednisolone (12.5–40 mg/d) gained 3.7 kg, whereas there was no change from baseline in the deflazacort (12.5–40 mg/d PE) group (36 subjects). However, when the groups were compared after 1 year of treatment, the prednisolone and deflazacort groups had gained a similar amount of BW. There was no placebo or true control group in this study. Van Everdingen et al [24] described an RCT in 81 subjects with RA that used a prednisone dose of 10 mg/d for 2 years and reported a 3 kg weight gain in the treatment group with no change in the placebo group. Another RCT in RA by

Table 4 – Subject population, OCS cumulative dose, and results of long term (≥ 3 months) studies included in the review

Intervention studies	Subjects	Cumulative dose ^a	Δ	BW
Rizzato et al [28]	69 Sarcoidosis	9984 mg	+	DFZ: BL: 70.1 ± 0.4 , 1 y: 72.1 ± 0.5 , 4 y: 70.0 ± 0.6 kg; $P = .202$ Pred: BL: 69.9 ± 0.4 , 1 y: 72.0 ± 0.5 , 4 y: 73.6 ± 0.8 kg; $P = .001$
Van Everdingen et al [24]	81 RA	7300 mg	+	Pred Pre: 77 ± 19 kg, Post: 80 ± 20 kg; $P = .001$, Placebo: no change
Van Schaik et al [25]	40 CIDP	6425 mg	~	DEX -0.38 kg (-1.2 , 2.4) 95% CI Pred + 1.4 kg (-1.5 , 4.4) 95% CI; $P = .28$
Kirwan [30]	128 RA	5475 mg		Pred Pre: 71 ± 11.1 , no change Placebo: 67.4 ± 15.4 , no change
Capell et al [26]	167 RA	5110 mg	~	Pred Pre: 68 kg, Post: 72 kg; $P < .001$ Placebo Pre: 69 kg, Post: 72 kg; $P = .031$ Difference between groups; $P > .05$
Wung et al [21]	157 WG	3900-7900	+	3.9 ± 6.9 kg/4.4% increase at 1 y 24% of patients increased by 11.2 kg/13.5%
Wassenberg et al [29]	189 RA	3650 mg	+	Pred: $\Delta + 5$ kg Placebo: $\Delta + 0.3$ kg
Prummel et al [19]	56 GO	2800 mg	+	Pred Pre: 71 kg (95% CI 67-75) Post: 73 kg (68-78) at 24 wk; $P = .002$ Placebo: no change
Nishimura et al [33]	23 Asthma F 17 HC	1825-3650 mg	~	No change in weight (kg), FM, or LBM (%)

Abbreviations: DFZ, deflazacort; BL, baseline; WG, Wegener granulomatosis; GO, Graves ophthalmopathy; +, significantly increased from baseline or greater than placebo/control; ~, no change from baseline or no significant difference between active drug and placebo/control; Δ , change.

^a Prednisone equivalent of dosage used in study.

Wassenberg et al [29] with a prednisolone dose of 5 mg/d for 2 years in 189 subjects reported a 5 kg weight increase compared with 0.3 kg increase in placebo. In 157 Wegener granulomatosis subjects, Wung et al [21] examined the effects of 3 to 12 months of prednisone therapy on BW and reported a 3.9 kg (4.4%) increase in BW in all subjects. Subjects with the highest OCS cumulative dose had the smallest weight gain (3.2% BW), whereas subjects with the lowest dose gained the most weight (5.1% BW); thus, weight gain did not correlate with OCS dose. Furthermore, 24% of subjects gained 10 kg or more after 1 year, with a mean increase of 11.2 kg (13.5% BW). Prummel et al [19] reported a 2 kg increase in BW compared with no change in the placebo group in 56 subjects with Grave ophthalmopathy in a 6-month RCT with a prednisone average dose of 33.3 mg/d.

Four long-term studies reported no change in BW compared with baseline or control following OCS treatment [25,26,30,33]. In a 2-year RCT of prednisone 7.5 mg/d by Kirwan [30], BW did not change in either the prednisone or placebo group in subjects with RA. Van Schaik et al [25] found after 8 months in CIDP subjects that weight gain in the prednisolone group (<120 mg/d) was not different to the weight loss in the DEX group (267 mg/d PE). However, this was not compared with a placebo or true control, and the findings did not indicate if the weight gain in the prednisolone group was significant. There was no change in weight from baseline after 12 months of 5 to 10 mg/d prednisone in asthmatic subjects [33], and in subjects with RA, both the prednisone (7 mg/d) and placebo groups had a significant increase in BW after 2 years, although there was no difference in the weight change between groups [26].

Three short-term studies (5 days to 8 weeks) reported weight gain compared with baseline or controls [23,27,38], whereas most short-term studies (7) reported no change in BW (Table 3) [20,22,31,32,34,35,37]. Campieri et al [27] found that after 8 weeks of treatment, subjects with Crohn disease on prednisolone less than 40 mg/d gained 2.1 kg compared with subjects in the budesonide group who gained 1 kg. This

study did not include control group. An RCT by Brotman et al [23] describes a 5-day intervention in 25 healthy males on a DEX dose of 40 mg/d PE in which subjects in the treatment group increased BW by 1.5 kg, compared with a loss in the placebo group. Chong et al [38] reported 7 healthy females with a betamethasone dose of 8.3 mg/d PE for 21 days, increased BW by 1.2 kg, although the study did not include a control group.

Udden et al [37] reported no change in BW in healthy subjects while on prednisolone 25 mg/d for 7 days despite an increase in food intake. However, this increase in food intake was only seen by the universal eating monitor not the 48-hour food recall. Similarly, Tataranni et al [22] found in 15 healthy males after 4 days treatment that although energy intake increased in the methylprednisolone group (50 mg/d PE) compared with placebo, weight change was not different between the 2 groups. A study by Lazenby et al [34] in 20 subjects with asthma on prednisone 60 mg/d for 7 days reported no difference in BW compared with baseline, whereas a study by Pantin et al [35] in cystic fibrosis also saw no change in BW following 4 weeks of prednisolone 20 to 30 mg/d. Rieth et al [20] reported that there was no difference in BW or energy intake in 8 healthy males between 7 days of prednisolone 60 mg/d and the placebo phase. There was also no difference in BW change and energy intake in 17 healthy females after 7 days of prednisone 50 mg/d compared with placebo in an RCT by Jollin et al [31].

3.6. Effects of OCS on body composition

Body composition was measured in 5 studies, using whole-body dual-energy x-ray absorptiometry [22,33], bioelectrical impedance [32], skinfold thickness [20], and oxygen¹⁸ dilution measurement of total body water [38]. These studies were mainly in healthy populations with durations of 4 days to 12 months, using prednisone and prednisolone, of which 2 studies measured energy intake [20,37]. Four studies reported

no change in body composition [20,32,33,37], and 1 reported an increase in fat mass [38]. Chong et al [38] measured fat mass and fat-free mass derived from oxygen¹⁸ dilution measurement of total body water in 7 healthy females before and after 21 days of betamethasone (8.3 mg/d PE) and reported increased fat mass, accompanied by an increase in BW with no change in fat free mass. An RCT in 8 healthy males by Rieth et al [20] reported no change in percentage of fat mass and LBM after prednisone (60 mg/d) for 7 days. In a cross-over controlled trial by Wolthers et al [32], change in LBM was measured via bioelectrical impedance in 8 men, before and after 4 days of 50 mg/d PE and placebo, and reported no difference. A 12-month experimental trial reported no changes in percentage of fat mass or LBM after 5 to 10 mg/d OCS, although only 10 of 23 asthmatic subjects were taking OCS and energy intake was not measured in this study [33].

3.7. Effect of OCS on appetite

Increased appetite during or after OCS therapy is commonly presented as a self-reported adverse effect in the literature [40,48,53,60] and in 1 short-term and 1 long-term study included in this review [23,25]. In the 6-month RCT by Van Schaik et al [25], a structured questionnaire was used at each visit during the treatment phase in weeks 8, 16, 24, and 33 and the follow-up phase in weeks 42 and 52. The questionnaire collected information on increased appetite and whether it was minor or severe. During the treatment phase, minor increased appetite was reported by 8 subjects (33%), and severe increased appetite, by 1 subject (4%) in the DEX group and 3 (19%) and 5 (31%) subjects, respectively, in the prednisolone group ($P = .95$) [25]. Broman et al [23] used a structured postintervention survey to assess unblinding and self-reported effects, and increased appetite was reported in 2 DEX-treated subjects and 1 placebo-treated subject ($P > .99$). In a short-term study, Udden et al [37] measured appetite objectively using visual analog scales for “hunger” and “desire to eat” before meals and “fullness” after meals in 12 healthy postmenopausal women. There was no difference in visual analog scale scores after 7 days of prednisolone 25 mg/d or placebo [37].

3.8. Effect size and significance

Statistically significant changes in energy intake were reported in 4 short-term studies [18,22,36,37], whereas clinically significant energy intake changes were seen in only 2 of these studies ($\Delta > 2$ MJ/d, able to cause a > 0.5 -kg weight change in 1 week) [18,22]. The only study that showed a clinically significant increase in energy intake by Tataranni et al [22] did not show a statistically or clinically significant weight gain. Body weight gain is considered clinically significant when it is greater than or equal to 5% of initial BW [61,62]. The average increases in BW reported by 3 short-term [23,27,38] and 3 long-term studies were not considered clinically significant [19,23,24,38]. Three long-term studies, however, reported increases in BW that were clinically significant. Rizzato et al [28] reported a 5.3% increase at 4-year follow-up after 2 years of OCS therapy and greater than 5% increase in BW was reported by Wassenberg et al [29] after 2 years. Although

Wung et al [21] did not see a clinically significant effect size within the whole cohort, they found that 24% (38/157) of subjects gained 10 kg or more with an average increase of 13.5% in BW at 1-year follow-up after a minimum of 6 months of OCS therapy. Hence, it appears that long-term OCS therapy may induce some weight gain.

4. Analysis of clinical data

The objective for this review was to examine the effects of OCS on energy intake, BW, body composition, and appetite in healthy subjects and in subjects with inflammatory conditions that are managed using OCS. Objective evidence demonstrating that glucocorticoids have an impact on BW, energy intake, or appetite is limited. We have identified studies that suggest that short-term OCS use is unlikely to lead to increased energy intake, although they may increase energy expenditure. Hence, if increases in appetite/energy intake do occur due to short-term OCS use, energy balance does not appear to be disturbed. This is supported by our observation that BW was not significantly increased with short-term OCS use in most studies, and increases in BW were not clinically significant. However, it appears that clinically significant increases in BW may result from long-term OCS use. From the studies that measured body composition, it appears that glucocorticoids do not have a significant impact on fat and lean mass in treatment periods lasting 7 days or less. Some investigators suggest that any weight gain as a result of OCS therapy is due to an increase in total body water [23]; however, a 21-day study in 7 healthy females suggests that excess body fat is responsible for any weight gain that occurs post-OCS treatment [38]. Although there is some evidence presented in the literature, which suggests adverse body composition changes are associated with long-term OCS therapy [63,64], the long-term studies included in the review did not examine effects on body composition.

The studies included in this systematic review are heterogeneous in nature, with diverse primary outcomes, glucocorticoid regimens, and study duration. However, the evidence level of most included studies is above the NHMRC level 3 evidence, indicating that most of the study designs used are able to adequately answer the research question. Several of the included studies aimed to measure clinical efficacy of OCS use and were not designed to evaluate changes in BW, energy intake, or appetite; thus, these were recorded mainly as adverse effects, not as primary outcomes. Many other studies have described increased BW as an adverse effect of OCS therapy, although BW was not measured objectively [40,41,46–48,51,53,65–67]. Studies with only self-reported weight gain were excluded from the review (Fig.).

The body of evidence for the review was generated mainly by medium-term investigations of glucocorticoid safety and efficacy studies in subjects with inflammatory conditions. Other studies exist where changes in BW as a result of OCS have been recorded. However, the subject populations have metabolic disorders and include conditions associated with weight loss; hence, effective treatment with OCS leads to a desirable weight regain. For example, treatment of some cancer and transplant patients with OCS may lead to weight

regain as part of the recovery process, rather than a direct effect of OCS on BW. Hence, such studies were not included in this review. This review examines OCS used in healthy controls, and therapeutically, for their anti-inflammatory actions, where weight gain is considered an adverse effect. Taking into account the body of evidence for the effects of OCS on BW and the self-reported data from many studies, it is likely that OCS cause clinically significant increases in BW, especially after long-term therapy.

Weight gain and obesity occur as a result of energy imbalance where greater kilojoules are consumed than are expended, over a period [10]. Even a small long-term energy imbalance can result in BW changes over time. For example, energy intake of just 2 MJ more than required (equal to the energy in a chocolate bar plus a soft drink or a hamburger) can result in clinically significant weight gain over a 10-week period [62]. Increased energy intake generally precedes weight gain and obesity as the consequence of an increased appetite. Increased appetite is commonly reported as an unwanted adverse effect of OCS therapy; however, like energy intake, it is generally not measured in interventions. Furthermore, to determine whether changes in BW are a result of changes in energy intake and appetite, physical activity and energy expenditure need to be assessed. Studies in this review did not control for energy expenditure or dietary intake when weight changes were considered. There was, however, some evidence that OCS use was associated with increased energy expenditure [22,38].

Although it is unlikely short-term OCS lead to adverse effects on body composition, changes in whole-body composition were not measured in the long-term studies included in the review. Body composition changes such as the redistribution and accumulation of fat in the face and dorsocervical region leading to appearance of a “moon face” and buffalo hump known as lipodystrophy have been reported after long-term use (>3 months) in subjects with inflammatory conditions, dialysis patients, and after organ transplantation [5,64,68–70]. Endogenous hypercortisolism known as Cushing syndrome is associated with central fat accumulation—particularly visceral fat—with decreased bone mineral density (BMD) and LBM [71]. The effects of exogenous hypercortisolism on body composition resulting from OCS therapy are different to those seen in Cushing syndrome [63]. In a study comparing the body composition of subjects with Cushing syndrome and RA and healthy controls, Resmini et al [63] found that chronic endogenous hypercortisolemia had greater effects on body composition than long-term maintenance prednisone treatment. Subjects with Cushing syndrome had greater total and percentage of body fat and trunk fat, greater LBM, and lower BMD than RA subjects [63]. There was no difference in body mass index in the 3 subject groups; however, both subjects with Cushing syndrome and RA had higher waist-hip ratios than controls [63].

Some research suggest that the metabolic effects of glucocorticoids are dose dependent, with low doses exhibiting anabolic effects and high doses producing catabolic effects, associated with decreased BW and food intake [68,72]. An acute response to high-dose OCS over 24 hours in a group of 6 healthy subjects demonstrated decreased energy and fat intake compared with placebo [18]. This evidence, coupled

with that from animal studies, demonstrates that OCS are likely to stimulate appetite and dietary intake at low doses yet inhibit appetite when high doses are given [72,73]. However, evidence from this review does not indicate any dose response pattern in relation to dietary intake or weight gain.

Animal studies on the effects of glucocorticoid treatment on food intake and BW show conflicting results. Experiments administering DEX peripherally to rats and mice reported dose-dependent decreased food intake and diminished rate of weight gain compared with controls [72,74–77]. Two studies have shown that when DEX is administered centrally through intracerebroventricular infusion for 3 days, food intake and BW gain increase [76,78]. Other investigations in rodents that have used intracerebroventricular injections or adrenalectomised rats [79] are not directly comparable with glucocorticoid therapy in humans where drug administration is oral and thus acts peripherally and whose hypothalamic-pituitary-adrenal axis remains intact. Notwithstanding the evidence existing in animal models, this evidence does not exist in human studies, demonstrating the need for well-designed human studies examining the effects of clinically relevant dosage regimens.

Future studies that measure BW as an outcome of OCS therapy should measure dietary intake using appropriate dietary assessment tools, such as food records, and also measure physical activity, as both are confounders of weight change. The ability of OCS to cause weight gain also depends on the metabolic background, which is known to vary in different disease states. Hence, resting metabolic rate and energy expenditure should be considered in any future examination of the effects of OCS on BW.

The review included studies performed in healthy controls and subjects with inflammatory conditions as well as studies of short duration. It is important to include these studies, as in conditions such as asthma, subjects experience acute and sometimes chronic inflammation, although they may be metabolically healthy and similar to healthy controls. In these subjects, OCS are prescribed for limited periods of generally 3 to 10 days, which means it is important to describe the short-term effects of OCS. Short-term studies are also important to investigate whether dose-response relationships exist. Although there are some studies that have examined energy intake during short-term OCS therapy, these studies have been performed in healthy subjects. Thus, there is a paucity of evidence on the effects of long-term OCS on energy intake and also energy expenditure in chronic disease states, which may differ metabolically from healthy subjects. Most studies contributing to the body of evidence for the review were in inflammatory conditions; thus, the findings of the review may not reflect the physiological functions of OCS. Conclusions of this review are mainly based upon effects from the use of synthetic OCS, which may be expected to produce different effects to physiological glucocorticoids due to the effects and pharmacodynamics of large OCS doses.

A systematic literature review designed to synthesize the current objective scientific evidence for effects of OCS on dietary intake, BW, body composition, and appetite faces 2 major limitations. First is the diversity of numerous features of the studies under investigation from the study populations, aims, study design, and outcome variables. For example, although most studies examined physiological effects of OCS on dietary

intake, almost 50% of the studies were designed to determine clinical efficacy of OCS use in inflammatory conditions. This creates a difficulty in pooling study findings, making it impossible to more precisely synthesize the studies into a meta-analysis. Second, another problem relates to the nature of trying to measure changes in BW without measuring energy intake, physical activity, and energy metabolism. Only 3 studies measured weight change and energy intake, and none of the studies in this review have addressed the need to account for physical activity level. Furthermore, most studies in the review have not considered the impact of fluid distribution on BW changes. In longer term studies without a placebo control, it is difficult to establish what the normal trajectory of BW would follow in comparison with the OCS-treated group.

Like all systematic reviews, the findings of this study depend on other factors, for example, the nature of the search strategy, the inclusion and exclusion criteria, and data extraction. In addition, the limited availability of relevant studies in the literature with objective assessment of BW and dietary intake is a limitation to this review. Therefore, although adverse effects associated with OCS use may be observed, it is their measurement and recording, which is required to make definitive conclusions on their impact.

5. Summary and future research

In summary, this review has demonstrated that currently, there is insufficient objective evidence to conclude that short-term use of OCS causes clinically significant changes in energy intake, BW, body composition, or appetite in healthy controls or subjects with inflammatory conditions such as RA or asthma. Although long-term use of OCS may contribute to clinically significant increases in BW, effects on appetite and dietary intake are not known. Further studies are needed in a range of patient populations to elucidate the effects of OCS on energy intake and expenditure, BW, and appetite with validated, sensitive tools, in well-designed and adequately powered RCTs. This is important for the future clinical management of subjects in whom OCS are routinely used to manage inflammation and obesity may contribute to adverse patient outcomes.

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