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Vitamin D and Glucocorticoid Sensitivity in Obesity-Associated Asthma: A Narrative Review

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Abstract: Vitamin D restores glucocorticoid sensitivity in vitro, but this effect has not been demonstrated clinically in obese patients with asthma. This narrative review analyses experimental and clinical data from 2006–2026 on the links between obesity, vitamin D deficiency and corticosteroid insensitivity. Obese asthma patients show reduced corticosteroid efficacy and lower vitamin D levels. In vitro, vitamin D restored dexamethasone-induced IL-10 secretion and MKP-1 expression; observationally, higher vitamin D levels were associated with better lung function and steroid response. However, high-dose vitamin D3 did not reduce treatment failure in the VIDA trial. An individual participant data meta-analysis showed fewer exacerbations requiring systemic corticosteroids, particularly with severe deficiency, whereas a 2023 Cochrane update did not confirm an overall benefit. A blunted response to supplementation in obesity may partly explain these discrepancies. Trials in obese asthma with weight-adjusted dosing, monitoring of serum levels and corticosteroid response as the primary outcome are needed.

Keywords: asthma, obesity, vitamin D, corticosteroid insensitivity, inhaled corticosteroids, IL-10, MKP-1.

Introduction

Although inhaled corticosteroids (ICS) are the cornerstone of asthma treatment, their efficacy is substantially reduced in obese patients. Obesity increases the risk of asthma in a dose-dependent manner [1] and is associated with more severe disease [2]. In a pooled analysis of five clinical trials including 1,242 patients, obese patients treated with fluticasone or fluticasone/salmeterol were less likely to achieve asthma control than patients of normal weight [3]. The clinical response to beclomethasone also declined with increasing body mass index (BMI) [4].

Vitamin D deficiency is common in obese individuals and is associated with more severe asthma. Because experimental studies have shown that vitamin D enhances glucocorticoid (GC) signalling, it has been proposed as an inexpensive and safe agent that may partly overcome obesity-related GC insensitivity. However, the results of clinical studies are conflicting, and evidence specific to obese patients is very limited.

Aim of the review — to analyse the mechanisms linking obesity, vitamin D deficiency and reduced GC sensitivity, to evaluate the clinical evidence on vitamin D supplementation from the perspective of obese asthma, and to define requirements for future research.

Literature Search Strategy

This narrative review was prepared in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria.

Parameter	Description
Databases	PubMed/MEDLINE, Scopus, Cochrane Library, Google Scholar
Period	January 2005 – October 2026
Search terms	(asthma) AND (vitamin D OR cholecalciferol OR 25-hydroxyvitamin D) AND (corticosteroid OR glucocorticoid OR steroid resistance OR steroid response) AND/OR (obesity OR body mass index)
Inclusion	Experimental (in vitro, ex vivo) studies, observational studies, RCTs and meta-analyses published in English or Russian
Exclusion	Studies conducted exclusively in children (except mechanistic studies) and case reports

Reduced Glucocorticoid Sensitivity in Obesity

Reduced GC efficacy in obese patients with asthma has been demonstrated at the clinical, functional and cellular levels.

Table 1. Key studies demonstrating reduced GC response in obesity

Study	Design, n	Main finding
Peters-Golden et al., 2006 [4]	Post hoc analysis of RCTs	Clinical response to beclomethasone decreased with increasing BMI
Boulet and Franssen, 2007 [3]	Analysis of 5 RCTs, 1,242	Obese patients were less likely to achieve control with ICS or ICS/LABA
Sutherland et al., 2008 [6]	Cross-sectional; asthma and control groups	Higher BMI was associated with a blunted in vitro response to dexamethasone; no such association in subjects without asthma
Telenga et al., 2012 [5]	4 cohorts, 423 (GC response assessed in 118)	After a 2-week course of GCs, FEV1 increased by 1.7% in obese and by 6.3% in normal-weight patients

Mechanisms

• **Inflammatory phenotype.** Obese patients may have less eosinophilic and more neutrophilic airway inflammation; neutrophilic inflammation responds poorly to GCs [5].

• **Systemic metabolic inflammation.** TNF-α, IL-6 and leptin produced by adipose tissue impair GC signalling pathways, whereas levels of the anti-inflammatory adipokine adiponectin are reduced [2].

• **Impaired GC signalling.** In obese patients with asthma, dexamethasone-induced expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) is reduced, leading to persistent activity of pro-inflammatory kinases [6].

• **Mechanical factors.** Reduced lung volumes and closure of small airways cause symptoms that are independent of inflammation and therefore unresponsive to GCs.

Thus, reduced GC responsiveness in obesity involves several mechanisms. Vitamin D may influence only some of them, namely GC signalling and immune regulation.

Vitamin D, Obesity and Glucocorticoid Signalling

Vitamin D Metabolism in Obesity

Obese individuals have lower serum 25(OH)D concentrations and a blunted response to vitamin D supplementation. In a secondary analysis of the large VITAL RCT, after 2 years of supplementation total 25(OH)D increased by a mean of 13.5 ng/mL in participants with BMI <25 kg/m², but by only 10.0 ng/mL in those with BMI ≥35 kg/m²; free and bioavailable vitamin D also increased less [7]. This attenuation persisted after adjustment for baseline vitamin D status.

Proposed explanations include sequestration of this fat-soluble vitamin in adipose tissue, less sun exposure among obese individuals and impaired hepatic vitamin D metabolism in obesity. In addition, GCs themselves may accelerate vitamin D catabolism [9].

Mechanisms by Which Vitamin D Enhances GC Action

Table 2. Key experimental evidence on the interaction between vitamin D and GCs

Study	Model	Main finding
Xystrakis et al., 2006 [8]	CD4+ T cells from GC-resistant and GC-sensitive patients; oral vitamin D3 in healthy volunteers and 3 patients	Adding vitamin D3 restored dexamethasone-induced IL-10 secretion to the level seen in GC-sensitive patients; vitamin D3 prevented dexamethasone-induced down-regulation of GC receptor expression; oral vitamin D3 enhanced the response to GCs
Sutherland et al., 2010 [9]	Cross-sectional, 54 adults with asthma	Each 1 ng/mL increase in vitamin D was associated with an FEV1 approximately 22.7 mL higher; airway hyperresponsiveness was greater in those with levels <30 ng/mL; in ICS-naïve participants, dexamethasone-induced MKP-1 expression increased with vitamin D level; vitamin D levels were lower in those with higher BMI

Based on these data, three main mechanisms by which vitamin D increases GC sensitivity have been proposed:

1. **Induction of IL-10-secreting regulatory T cells** — together with GCs, vitamin D enhances production of the anti-inflammatory cytokine IL-10 [8].

2. **Preservation of GC receptor expression** — vitamin D prevents the dexamethasone-induced reduction in GC receptor numbers [8].

3. **Enhanced MKP-1 induction** — MKP-1 dampens inflammatory signalling via p38 MAP kinase [9].

Reduced MKP-1 induction in obesity [6] and low vitamin D levels [9] may act as mutually reinforcing factors. For this reason, obese patients with asthma are of particular theoretical interest as the group most likely to benefit from vitamin D supplementation.

Clinical Evidence

RCTs and meta-analyses of vitamin D supplementation have not fully confirmed the experimental findings.

Table 3. Key clinical evidence on vitamin D supplementation

Study	Design, n	Intervention	Main finding
VIDA, Castro et al., 2014 [10]	Double-blind RCT, 408 adults, 25(OH)D <30 ng/mL	Vitamin D3: 100,000 IU once, then 4,000 IU/day for 28 weeks, added to ciclesonide	No change in the rate of first treatment failure (28% vs 29%; HR 0.9). Slightly lower ciclesonide dose required to maintain control (difference 14.9 µg/day)
Jolliffe et al., 2017 [11]	Individual participant data meta-analysis of 7 RCTs, 955	Vitamin D2 or D3, various doses	Fewer exacerbations requiring systemic GCs (aIRR 0.74); stronger effect in those with 25(OH)D <25 nmol/L (aIRR 0.33); no subgroup difference by BMI
Williamson et al., Cochrane, 2023 [12]	Meta-analysis of RCTs	Vitamin D or its hydroxylated metabolites	No reduction in exacerbations requiring systemic GCs (OR 1.04; rate ratio 0.86, 10 studies, 1,599 participants); no improvement in asthma control

Interpretation from the Perspective of Obese Patients

The very name of the VIDA trial (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) reflected the hypothesis that vitamin D enhances GC sensitivity, and randomisation was stratified by BMI (≤25 vs >25 kg/m²) [10]. However, no BMI-specific effect was reported. The investigators later noted that only about 82% of participants reached sufficient levels after supplementation, meaning that in some patients, possibly obese ones, vitamin D did not rise to the target level.

The discrepancy between the meta-analyses is also important [11, 12]. Patients with severe asthma and those with profound vitamin D deficiency (<25 nmol/L) were poorly represented in the Cochrane review, so a benefit in these particular groups cannot be excluded [12]. Obese patients with asthma frequently exhibit both of these characteristics.

Thus, the benefit of vitamin D supplementation has not been demonstrated in the general asthma population, but patients with coexisting obesity, profound deficiency and GC insensitivity have not been studied separately.

Knowledge Gaps and Future Research

The gap between experimental and clinical findings defines clear directions for future research.

1. **No RCTs specific to obese asthma.** In existing RCTs, obese patients were either not analysed separately or their numbers were insufficient for subgroup analysis.

2. **Dosing.** The blunted response to supplementation in obesity [7] suggests that standard doses are insufficient for obese patients. Strategies of weight-adjusted dosing and maintaining a target 25(OH)D level (e.g., ≥30 ng/mL) should be tested.

3. **Outcome measures.** Clinical RCTs have mainly assessed exacerbations. Direct measures of GC sensitivity — for example, dexamethasone-induced MKP-1 expression, FEV1 response to a course of ICS, or the ICS dose required to maintain control — would test the hypothesis more precisely.

4. **Patient selection.** Enrolling obese patients with profound vitamin D deficiency (<20 ng/mL) and a documented poor response to GCs would increase the likelihood of detecting an effect.

5. **Regional data.** There are no data from Central Asia, including Uzbekistan, on vitamin D status in obese patients with asthma or its relationship with GC response.

Proposed Design for a Future RCT

Element	Recommendation
Population	BMI ≥30 kg/m², 25(OH)D <20 ng/mL, uncontrolled asthma despite medium- or high-dose ICS
Intervention	Vitamin D3 at a weight-adjusted dose, with monitoring of 25(OH)D levels
Control	Matching placebo
Blinding	Double-blind
Duration	At least 6 months
Primary outcome	GC sensitivity (FEV1 response to a course of ICS or dexamethasone-induced MKP-1 expression)
Secondary outcomes	ACQ/ACT, exacerbations, ICS dose required to maintain control, FeNO, IL-10, hs-CRP, 25(OH)D level
Stratification	BMI category, sex, baseline 25(OH)D

Conclusions

1. GC efficacy is reduced in obese patients with asthma at the clinical, functional and cellular levels.

2. In vitro, vitamin D increases GC sensitivity by inducing IL-10-secreting regulatory T cells, preserving GC receptor expression and restoring MKP-1 induction.

3. RCTs in the general asthma population and the latest Cochrane review have not confirmed a clinical benefit of vitamin D supplementation; any benefit may be limited to patients with profound deficiency.

4. The response to vitamin D supplementation is blunted in obesity, which may partly explain the lack of effect at standard doses.

5. The effect of vitamin D on GC sensitivity in obese patients with asthma remains an open question that should be addressed in dedicated RCTs using weight-adjusted dosing and GC response as the primary outcome.

References

1. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007;175(7):661–666. doi:10.1164/rccm.200611-1717OC
2. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169–1179.
3. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med. 2007;101(11):2240–2247.
4. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J. 2006;27(3):495–503.
5. Telenga ED, Tideman SW, Kerstjens HA, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67(8):1060–1068.
6. Sutherland ER, Goleva E, Strand M, et al. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med. 2008;178(7):682–687.
7. Tobias DK, Luttmann-Gibson H, Mora S, et al. Association of body weight with response to vitamin D supplementation and metabolism. JAMA Netw Open. 2023;6(1):e2250681.
8. Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest. 2006;116(1):146–155. doi:10.1172/JCI21759
9. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DYM. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med. 2010;181(7):699–704. doi:10.1164/rccm.200911-1710OC
10. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. JAMA. 2014;311(20):2083–2091. doi:10.1001/jama.2014.5052
11. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017;5(11):881–890. doi:10.1016/S2213-2600(17)30306-5
12. Williamson A, Martineau AR, Sheikh A, Jolliffe D, Griffiths CJ. Vitamin D for the management of asthma. Cochrane Database Syst Rev. 2023;2(2):CD011511. doi:10.1002/14651858.CD011511.pub3