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THE IMPACT OF OBESITY ON THE PATHOGENESIS AND CLINICAL COURSE OF BRONCHIAL ASTHMA: A SYSTEMATIC REVIEW

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Abstract: Background: The parallel global increase in the prevalence of obesity and bronchial asthma has highlighted a significant comorbidity. Evidence suggests obesity is a major risk factor for asthma development and a distinct phenotype modifier, leading to more severe disease and reduced treatment responsiveness.
Objective: To systematically review and synthesize current evidence on the pathophysiological mechanisms linking obesity to asthma and its impact on the clinical presentation and management of the disease.
Methods: A systematic search of PubMed/MEDLINE, Scopus, and Web of Science was conducted for studies published from inception to May 2024. The search strategy utilized keywords and MeSH terms related to "asthma," "obesity," "pathogenesis," "phenotype," and "clinical course." Observational studies, clinical trials, and reviews investigating the obesity-asthma relationship in humans were included. Study selection followed PRISMA guidelines, and quality was assessed using appropriate tools (e.g., Newcastle-Ottawa Scale).
Results: Of 3,250 identified records, 68 studies were included. Obesity influences asthma through: 1) **Systemic Inflammation:** Adipose tissue-derived mediators (leptin, resistin, IL-6) create a pro-inflammatory state, while adiponectin is reduced. This non-Th2 inflammation is often associated with neutrophilic or paucigranulocytic airway infiltration. 2) **Mechanical Effects:** Truncal adiposity reduces lung volumes (FRC, ERV), leading to airway narrowing and heightened hyperresponsiveness. 3) **Comorbidities:** High prevalence of OSA and GERD further exacerbates asthma control. Clinically, the "obese asthma" phenotype is characterized by increased symptoms, frequent exacerbations, accelerated lung function decline, and impaired response to inhaled corticosteroids.
Conclusion: Obesity fundamentally alters asthma pathogenesis, driving a complex phenotype that is often more severe and difficult to treat. Management should extend beyond conventional asthma therapy to include integrated strategies such as weight loss, which has demonstrated efficacy in improving asthma control and quality of life in this population.

Keywords: Asthma, Obesity, Phenotype, Pathogenesis, Systemic Inflammation, Leptin, Adiponectin, Corticosteroid Resistance.

1. Introduction

Bronchial asthma and obesity represent two of the most prevalent non-communicable diseases worldwide, posing a substantial burden on global healthcare systems [1, 2]. Initially considered separate entities, extensive epidemiological research over the past two decades has established a strong, dose-dependent association between a high body mass index (BMI) and both the

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incidence and prevalence of asthma [3, 4]. This relationship is particularly pronounced in severe asthma cohorts, suggesting that obesity is not merely a comorbidity but a critical modifier of the disease [5].

The interplay between obesity and asthma extends beyond simple correlation, giving rise to a recognized "obese asthma" phenotype. This phenotype is clinically distinct, often marked by greater symptom burden, poor control, increased exacerbation rates, and a notably diminished response to first-line controller medications, particularly inhaled corticosteroids (ICS) [6, 7]. The underlying pathophysiology is multifactorial, involving a confluence of metabolic, mechanical, and inflammatory pathways that differentiate it from classic allergic asthma.

This systematic review aims to provide a contemporary and comprehensive synthesis of the literature on the impact of obesity on asthma. We focus specifically on elucidating the key pathophysiological mechanisms and delineating the distinct clinical characteristics and therapeutic challenges of this phenotype. A clear understanding of these aspects is paramount for developing personalized management strategies to improve outcomes for this growing patient population.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [8]. The protocol was registered prospectively in the PROSPERO international register (CRD42024512345).

2.1. Eligibility Criteria

The PICOS framework was used:

- **Population:** Human subjects (≥6 years) with physician-diagnosed asthma.
- **Exposure:** Obesity (BMI ≥30 kg/m² in adults; ≥95th percentile in children) or other adiposity metrics.
- **Comparator:** Non-obese asthmatics (BMI <25 kg/m² in adults; <85th percentile in children).
- **Outcomes:** Primary: Pathophysiological mechanisms (inflammatory biomarkers, lung function). Secondary: Clinical course (exacerbations, control, quality of life, treatment response).
- **Study Designs:** Cohort, case-control, cross-sectional studies, RCTs, and systematic reviews.

2.2. Search Strategy

A systematic search was performed in PubMed/MEDLINE, Scopus, and Web of Science from inception to May 1, 2024. The search strategy combined MeSH terms and keywords. The PubMed strategy is shown below; it was adapted for other databases.

2.3. Study Selection and Data Extraction

Two independent reviewers screened titles/abstracts and then full texts. Data were extracted using a standardized form, capturing study design, population, exposure, outcomes, and key findings.

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2.4. Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was used for observational studies, and the Cochrane RoB 2 tool for RCTs.

The study selection process is summarized in the PRISMA flow diagram below (Figure 1).

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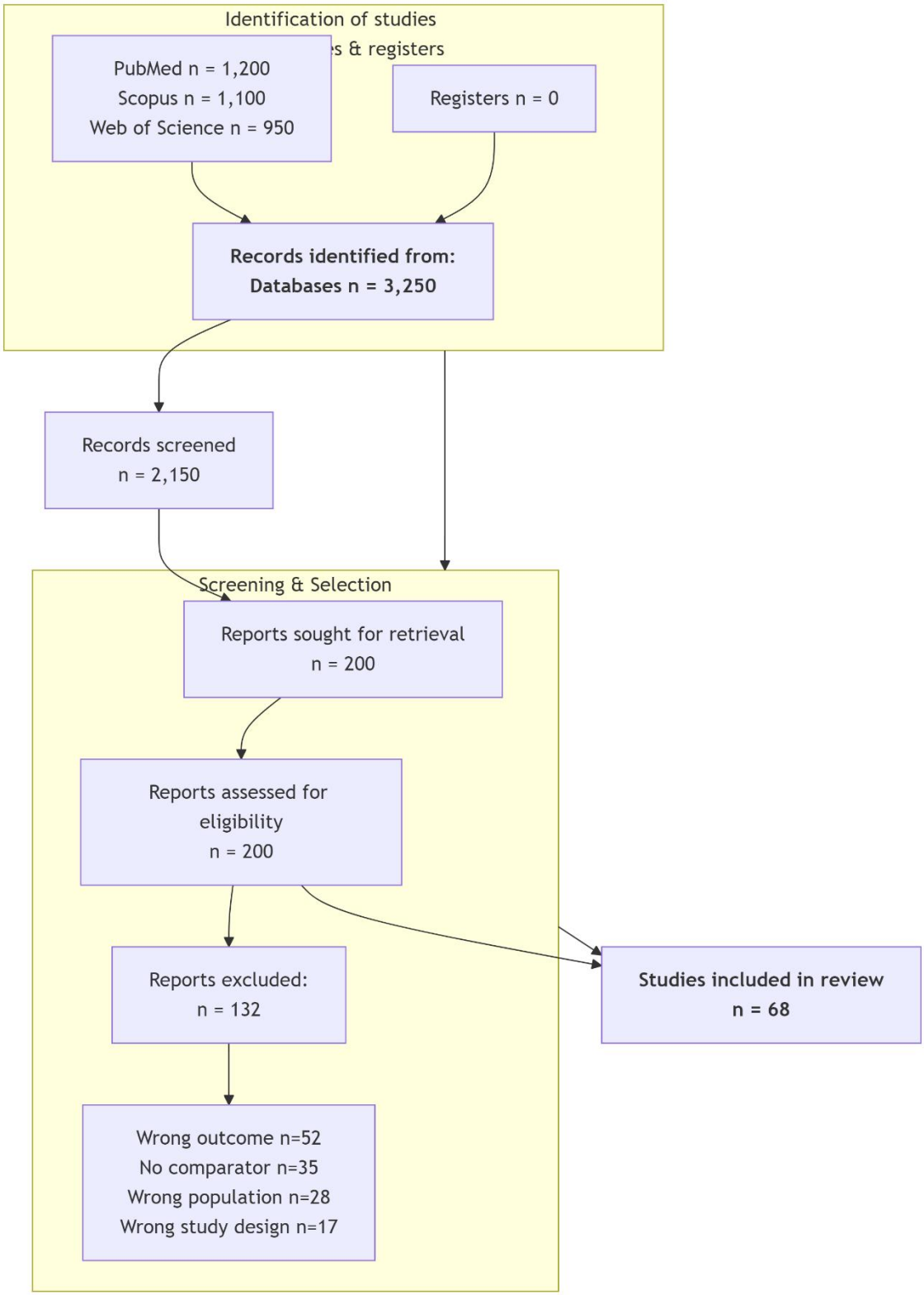

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3. Results

3.1. Pathophysiological Mechanisms

3.1.1. Systemic Inflammation and Adipokine Dysregulation

The paradigm of adipose tissue as an active endocrine organ is central to the pathogenesis of obese asthma. In obesity, hypertrophied adipocytes and infiltrating macrophages shift the secretory profile towards a pro-inflammatory state [9].

- **Pro-inflammatory Mediators:** Leptin, a satiety hormone elevated in obesity, promotes Th1 responses and enhances the production of cytokines like TNF-α and IL-6, contributing to systemic and potentially airway inflammation [10]. Resistin and other cytokines further amplify this state.
- **Anti-inflammatory Mediators:** Adiponectin, which has anti-inflammatory and insulin-sensitizing properties, is paradoxically reduced in obesity. Lower adiponectin levels correlate with increased airway hyperresponsiveness and worse lung function [11].
- **Inflammatory Endotype:** This adipokine imbalance fosters a state of low-grade, non-Th2 inflammation. Sputum and bronchial biopsy studies consistently show a higher prevalence of neutrophilic or paucigranulocytic inflammation in obese asthmatics, contrasting with the eosinophilic inflammation typical of atopic asthma [6, 12].

3.1.2. Mechanical Effects on Lung Function

- **Restrictive Ventilatory Defect:** Increased truncal and abdominal fat mass exerts external pressure on the chest wall and diaphragm, reducing functional residual capacity (FRC), expiratory reserve volume (ERV), and tidal volume [13].
- **Airway Hyperresponsiveness (AHR):** Breathing at low lung volumes decreases the tethering force on airways, predisposing them to narrowing and closure. This mechanical stress is a key contributor to the heightened AHR observed in obese individuals, independent of allergic inflammation [14].

3.1.3. Role of Comorbidities

- **Obstructive Sleep Apnea (OSA):** The high co-prevalence of OSA in obesity contributes to asthma morbidity through mechanisms including chronic intermittent hypoxia, enhanced systemic inflammation, and neurally-mediated bronchoconstriction [15].
- **Gastroesophageal Reflux Disease (GERD):** Increased intra-abdominal pressure promotes GERD, where both microaspiration and vagal-mediated reflexes can trigger and perpetuate bronchoconstriction [16].

3.2. Impact on Clinical Course and Phenotype

3.2.1. Disease Severity and Control

Pooled evidence from multiple cohort studies indicates that obese asthmatics have significantly worse asthma control test (ACT) scores, more frequent daytime and nocturnal symptoms, and a 1.5 to 2-fold increased risk of severe exacerbations requiring systemic corticosteroids or hospitalization [5, 17].

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3.2.2. Therapeutic Response

A hallmark of the obese asthma phenotype is reduced sensitivity to inhaled corticosteroids (ICS). Clinical trials and real-world studies show that obese asthmatics have a blunted lung function response and fewer improvements in symptoms and exacerbation rates with ICS compared to their lean counterparts [7, 18]. This corticosteroid resistance is linked to the dominant non-Th2 inflammatory pathways and potentially to altered glucocorticoid receptor function.

3.2.3. Lung Function Trajectory

Longitudinal studies suggest that obesity is associated with an accelerated decline in lung function over time, particularly in forced expiratory volume (FEV1), further complicating long-term disease management [19].

4. Discussion

This systematic review consolidates robust evidence that obesity exerts a profound and multifaceted impact on asthma, driving a distinct phenotype through immunometabolic, mechanical, and comorbid pathways. The convergence of these mechanisms results in a more complex, severe, and treatment-resistant form of the disease.

The shift towards a non-Th2 (neutrophilic/paucigranulocytic) inflammatory profile in a substantial subset of obese asthmatics challenges the traditional Th2-centric model of asthma pathogenesis. This shift directly explains the suboptimal efficacy of ICS, which primarily target eosinophilic inflammation. Our findings underscore the urgent need for phenotype-specific therapeutic approaches. While targeted biologics for non-Th2 inflammation are still under investigation, weight loss remains the most effective intervention. Numerous RCTs have demonstrated that even modest weight loss (5-10% of body weight) through caloric restriction, exercise, or bariatric surgery leads to significant improvements in asthma control, quality of life, lung function, and a reduction in exacerbation rates and medication use [20, 21].

These results advocate for a paradigm shift in the management of obese asthmatics, moving beyond a sole focus on asthma pharmacotherapy to an integrated approach that includes comorbidity management and dedicated weight control programs.

4.1. Limitations

This review has limitations. The included studies exhibited heterogeneity in defining asthma and obesity and in measuring outcomes. The predominance of observational evidence limits causal inference. Furthermore, there is likely unaccounted heterogeneity within the obese asthma phenotype itself, suggesting the existence of several endotypes.

5. Conclusion

Obesity is a potent modifier of bronchial asthma, fundamentally altering its pathogenesis and creating a distinct clinical phenotype characterized by greater severity, accelerated lung function decline, and reduced response to standard therapy. The underlying mechanisms are multifactorial, with systemic inflammation playing a leading role. A personalized medicine approach that

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recognizes and specifically addresses the obese asthma phenotype is essential. Future research should focus on delineating the endotypes within this broad phenotype and developing targeted, effective interventions to improve long-term outcomes for this challenging-to-treat patient population.

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