Visceral adipose tissue: a relevant inflammatory compartment in obesity-related asthma?

Türk, Y.; Witte, J.A.; Huisstede, A. van; Melgert, B.N.; Schadewijk, A. van; Taube, C.; ... ; Braunstahl, G.J.

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RESEARCH LETTER

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To the Editor,

Asthma is a chronic inflammatory disorder, often characterized by type 2 inflammation, present in more than 80% of asthma patients.[1] In patients without type 2 inflammation (i.e. T2-low asthma), a more neutrophilic inflammatory pattern might be observed in the airways,[2] but, airway inflammation can be absent, particularly patients with obesity.[3] This discrepancy challenges the traditional concept of asthma as a localized chronic inflammatory condition, prompting investigations into possible extra-pulmonary sources of inflammation contributing to asthma in this particular subgroup.

One such candidate is visceral adipose tissue (VAT), which could serve as an extra-pulmonary inflammatory source, which could be particularly relevant in obesity-related asthma.[4] Although this idea seems promising, studies investigating VAT inflammation's direct impact on airway hyperresponsiveness, reversibility and small airway function in obesity-related asthma have been scarce and inconclusive.[5,6] We therefore conducted a study to investigate the potential role of VAT inflammation in obesity-related asthma, with a specific focus on the association between macrophages in VAT and lung function in patients undergoing bariatric surgery.

Our investigation utilized data and materials from a cross-sectional trial investigating the effect of bariatric surgery on asthma control, lung function and systemic inflammation in patients with class III obesity, both with and without asthma. Results of this trial, including bronchial biopsies, have been published before.[7–9] The study participants were adults aged 18–50 with a BMI of 35 kg/m^2 or higher, and asthma diagnosis was in accordance with the GINA guidelines. Exclusion criteria encompassed a smoking history of more than 10 pack-years, current smoking exceeding 10 cigarettes per day, oral corticosteroid use, recent asthma exacerbation within the past 4 weeks, inability to perform pulmonary function tests or the presence of other pulmonary diseases.

Prior to bariatric surgery, pulmonary function tests (spirometry, exhaled Nitric Oxide (FeNO), diffusion capacity and Methacholine provocation test) were performed. Additionally, we assessed asthma symptoms using the asthma control questionnaire (ACQ) and mini Asthma Quality of Life questionnaire (AQLQ).

During the bariatric surgery, we collected VAT samples, which were fixed in formalin and processed for immunohistochemistry (IHC). We specifically identified mast cells, macrophages and 'crown-like structures' (CLS) in the VAT samples using the markers $CD68^+$, $CD11c^+$ and $CD206^+$. Furthermore, we used quantitative RT-PCR to measure mRNA expression levels of leptin, adiponectin and IL-6 in VAT, using the relative standard curve method for analysis.

Out of the 86 patients included in the study, 79 participants (31 with asthma and 48 without asthma) provided sufficient VAT tissue for analysis. Comparing the two groups, patients with asthma exhibited a lower FEV_1 (85.6% vs. 97.0%, $p < .001$), PD20 (0.37 vs. 1.80 mg, $p < .001$) and lower AQLQ scores (5.80 vs. 6.57, $p < .005$). Additionally, patients with asthma had higher ACQ scores (1.14 vs. 0.29, $p < .001$) and serum triglyceride levels (1.18 vs. 0.88×10^9/L, $p = .014$). Baseline eosinophil counts were comparable (0.1 vs. 0.1×10^3 cells/μL, $p = .256$).

Regarding VAT inflammatory patterns, we found no significant differences in the number and size of adipocytes, mast cells or macrophages between patients with and without asthma (Figure 1). Additionally, we did not find any significant associations between VAT inflammation markers and bronchial hyperresponsiveness, FEV_1 or ACQ. Interestingly, solitary macrophages in VAT expressed the M2 marker CD206, while the M1 marker CD11c was primarily observed in macrophages within 'CLS'. However, comparing the area of CLS or the CLS/M2 ratio between the two groups revealed no significant differences. Similarly, mRNA expression levels of leptin, adiponectin and IL-6 in VAT did not differ significantly between patients with and without asthma nor between those with controlled and uncontrolled asthma.

Although no inflammatory differences were found in our study, abdominal circumference had a significant impact on FEV_1 and ACQ, suggesting an important role of the mechanical effects of obesity on asthma symptoms. We have encountered this before in patients with class III obesity and asthma that underwent bariatric surgery.[7] At baseline, BMI and abdominal circumference correlated with small airway function (R5–R20) and small airway impairment was larger in patients with asthma compared to patients without asthma. After surgery, patients lost a significant portion of excess BMI, which was accompanied by a significant improvement in small airway function, both in patients with and without asthma. This improvement in small airway function was not seen in patients with asthma without bariatric surgery (i.e. without excess weight loss). Furthermore, a significant portion of patients with asthma no longer needed inhaler therapy after bariatric surgery. The improvement in asthma control after the loss of excess BMI is likely not attributable to reduced

Y. Türk and J.A. Witte shared first authorship.

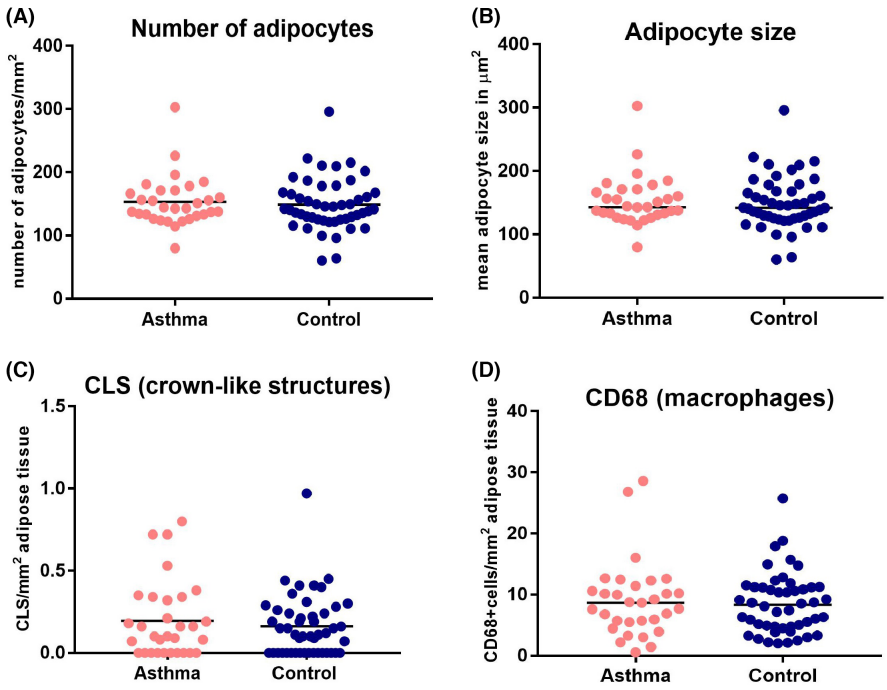

FIGURE 1 Number of (A) fat cells, (B) size of fat cells, (C) number of CLS in adipose tissue of patients with obesity and asthma and controls without asthma and (D) macrophages (CD68+). Horizontal bar represents the median values.

systemic inflammation, as most inflammatory patterns in peripheral blood (e.g. IL-6, IL-8, TNF-α, GM-CSF) and submucosal biopsies (eosinophils, neutrophils, B cells, macrophages, CD4+ T cells and CD8+ T cells) were similar between study groups at all visits.[7,9] Consequently, we propose that the improved asthma control following bariatric surgery can be attributed to a reduction in mechanical pressure resulting from a decrease in abdominal circumference, rather than a reduction in inflammation.

In conclusion, mechanical effects of abdominal fat may have more influence on asthma symptoms than VAT-associated inflammatory processes, emphasizing the importance of weight loss in the treatment of obesity-related asthma. However, new studies are needed, combining IHC with, for example, flow cytometry and gene expression analyses to unravel the intricate interaction between obesity and asthma.

Key Messages

- Adipocyte, macrophage and crown-like structure counts are comparable in obese VAT of patients with/without asthma.
- Abdominal circumference rather than macrophage-associated inflammation in VAT had a significant effect on asthma outcomes.

AUTHOR CONTRIBUTIONS

Y. Türk was involved in the design of the study, performed the immunohistochemistry, analysed and interpreted the data and wrote the first version of the manuscript. J. A. Witte has written the manuscript and processed the feedback from other authors. A. van Huisstede was involved in the inclusion of subjects, collection of blood samples and fat tissue. She had created the initial database. B. N. Melgert contributed to the study by optimizing the double-staining procedure for identification of different macrophage subsets and she trained Y. T. and A. S. to perform the immunohistochemistry in our own lab. She has read the manuscript and has contributed mainly to the Discussion section. A. van Schadewijk performed the immunohistochemistry (with Y. T.) and quantitative RT-PCR. She was a contributor to writing the Method section. C. Taube was involved in the design of the study. He has read the manuscript and revised it. P. S. Hiemstra was involved in the design of the study and he was responsible for the procedure of analysis in the laboratory. He was also involved in the analysis and interpretation of the data. J. H. Kappen has interpreted the data, read the manuscript and revised it. G. J. Braunstahl was involved in the design of the study, the inclusion of participants and the collection of materials and interpretation of the data. He contributed to the manuscript by reading and revising it. All authors have read and approved the letter.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data sets during and/or analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Written informed consent was obtained from all subjects and the local ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam) approved the study protocol (Netherlands Trial Register 3204).

CONSENT FOR PUBLICATION

Not applicable.

Y. Türk[1]
J. A. Witte[1]
A. van Huisstede[2]
B. N. Melgert[3,4]
A. van Schadewijk[5]
C. Taube[5,6]
P. S. Hiemstra[5]
J. H. Kappen[1,7]
G. J. Braunstahl[1,8]

[1]*Department of Pulmonology, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands*
[2]*Department of Pulmonology, NorthWest Clinics, Alkmaar, The Netherlands*
[3]*Department of Pharmacokinetics, Toxicology and Targeting, Groningen Research Institute for Pharmacy, University of Groningen, Groningen, The Netherlands*
[4]*GRIAC Research Institute, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands*
[5]*Department of Pulmonology, Leiden University Medical Centre, Leiden, The Netherlands*
[6]*Department of Pulmonary Medicine, University Hospital Essen—Ruhrlandklinik, Essen, Germany*
[7]*Allergy and Clinical Immunology, Immunomodulation and Tolerance Group, Inflammation Repair and Development, Imperial College, National Heart and Lung Institute, London, UK*
[8]*Department of Pulmonary Disease, Erasmus MC, Rotterdam, The Netherlands*

Correspondence
J. A. Witte, Department of Pulmonology, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM Rotterdam, The Netherlands.
Email: a.witte2@franciscus.nl

ORCID

J. A. Witte https://orcid.org/0000-0002-9037-1002
A. van Huisstede https://orcid.org/0000-0002-3066-492X
B. N. Melgert https://orcid.org/0000-0001-7091-907X

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