Immunological substrates of depressive symptoms in patients with severe obesity: An exploratory study

In this pilot study, we explored the immune phenotype of patients with severe obesity and comorbid depressive symptoms compared to non-depressed patients with obesity and normal-weight controls. Immune cell subsets were analysed by flow cytometry and depressive symptoms assessed using the Patient Health Questionnaire (PHQ-9). Cell frequencies were correlated with depressive symptom scores and waist-to-hip ratio (WHR). Patients with obesity and comorbid depression showed significantly lower numbers of circulating cytotoxic natural killer cells, dendritic cells and CD8+ effector memory T cells, compared to normal-weight controls. Regulatory T cells and CD4+ central memory T cells were increased compared to non-depressed patients with obesity and compared to normal-weight controls, respectively. Frequencies of cytotoxic natural killer cells and CD4+ central memory T cells significantly correlated with PHQ-9 scores, but not with WHR. Reduced numbers of dendritic cells were observed in both patient groups with obesity and correlated with PHQ-9 scores and WHR. These findings provide evidence for an altered immune composition in comorbid obesity and depression, supporting a pathobiological overlap between the two disorders.

**KEYWORDS**

depression, immunophenotyping, inflammation, obesity

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**1 | INTRODUCTION**

Major depressive disorder (MDD) is a common psychiatric disorder with a life-time prevalence of approximately 20%. MDD is associated with increased mortality, and causes substantial burden of disease. Importantly, MDD is frequently associated with medical comorbidities, including metabolic disorders such as type 2 diabetes and metabolic syndrome. In particular, a strong bidirectional epidemiological link has been established between obesity and MDD, with both conditions increasing the risk of developing the other by approximately 50%. Intriguingly, a recent analysis revealed that the link between depression and obesity may drive the association with numerous other medical comorbidities of...
MDD. Furthermore, this may extend to sub-clinical levels as a metabolomics study in MDD patients detected significant dyslipidaemia, characterised by increased very low-density lipoprotein (VLDL) and triglycerides as well as reduced high-density lipoprotein (HDL). These findings were independent of sex, age or body mass index (BMI), suggesting that they may be early manifestations of metabolic dysfunction in MDD.

Emerging evidence supports the notion that comorbid obesity and depression may—at least in part—be due to converging biological pathways. For example, work in animal models has shown that obesity induces accumulation of senescent glial cells, which, in turn, directly drive the occurrence of anxiety/depression-like behaviour. Clearance of these pro-inflammatory cells rescued the behavioural phenotype. Similarly, inflammatory mechanisms have been implicated in comorbid depression and obesity in humans, as genetic risk factors overlap between these disorders. This association was particularly obvious in patients with “atypical depression”—characterised by hyperphagia/weight gain, hypersomnia and fatigue—who were also more likely to carry genetic variants implicated in higher BMI and increased levels of C-reactive protein (CRP) and leptin.

Indeed, chronic, low-grade inflammation has been described in both obesity and MDD with increased levels of peripheral markers such as CRP and cytokines, including interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α). The “immuno-metabolic” model of depression thus describes how a chronic pro-inflammatory state might induce symptoms like fatigue, changes in appetite/weight, hypersomnia/hyposomnia and depressed mood. Adipose tissue also directly influences the function of the immune system through production of pro-inflammatory cytokines. Of note, changes in frequencies of circulating lymphocytes, monocytes and natural killer cells have been described in both obesity and MDD.

Taken together, these findings support the idea that obesity-induced immune dysfunction might be one pathophysiological mechanism that is shared by obesity and MDD. Studying immune alterations in patients with severe obesity and comorbid depression could provide further insights into the potential role of the immune system in linking these two disorders.

2 | MATERIAL AND METHODS

2.1 | Participants

Three groups of participants were included in this study: lean healthy controls, participants with severe obesity and patients with severe obesity and comorbid depressive symptoms. The study was approved by the local ethics committee (Charité Universitätsmedizin Berlin, Campus Mitte, EA1/063/16). The study was conducted in accordance with the ethical standards concerning clinical studies involving human participants as stated in the Declaration of Helsinki. Written consent was provided by all participants prior to enrolment.

Healthy controls were recruited via online advertisements and bulletins and were free of relevant medical disorders (hypertension, insulin resistance or diabetes, hypothyroidism or coronary heart disease), or psychiatric illnesses, as assessed by taking their detailed medical history, weight and blood pressure measurements, and standard laboratory diagnostics (including count of leukocytes and quantification of haemoglobin, cholesterol, triglycerides, HDL, LDL and HbA1c).

Participants with obesity were recruited from the Department of Psychosomatic Medicine (Charité), at the beginning of a 6-month multimodal (psychosocial, nutritional and exercise) outpatient treatment programme specifically designed for patients with severe obesity.

2.2 | Clinical examination and questionnaires

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9) and caseness defined by a score of ≥10. The Generalized Anxiety Disorder 7-item (GAD-7) scale was used to assess the level of anxiety. Clinical parameters (blood pressure, height, weight, waist and hip circumference) were measured by trained medical staff.

2.3 | Blood collection and isolation of peripheral mononuclear blood cells

Whole blood was collected in heparinized tubes (BD, Germany), diluted in phosphate-buffered saline (PBS, 1:1; Gibco, Thermofisher Scientific, Germany) and layered on top of density medium (Biocoll, Merck, Germany) + 0.5 M EDTA (Promega, Germany)). PBMCs were collected from the interphase and after two washing steps with PBS, cells were aliquoted in RPMI 1640 + GlutaMax medium (Gibco, Thermofisher Scientific, USA) containing 25% foetal calf serum (FCS; Merck, Germany) and 10% dimethyl sulfoxide (DMSO; AppliChem, USA) at 1 × 10⁷ cells/mL. Aliquots were stored in a freezing container filled with isopropyl alcohol (Mr. Frosty, Merck, Germany) at −80°C for 24 hours and then transferred to liquid nitrogen for long-term storage.

2.4 | Flow cytometry

Immunophenotyping of cryopreserved PBMC samples was performed by flow cytometry. Four antibody panels were established and applied for identification of several T cell subsets (including regulatory T cells, CD4+ and CD8+ naive/memory T cells), B cells, natural killer cells (NK), monocyte subsets (classical, non-classical and intermediate) and dendritic cells (DCs). A detailed description of all antibody panels is presented in Table S1. Experiments were carried out on a FACSCanto II flow cytometer (BD, Germany). Instrument set-up and compensation were performed prior to the experiments using the same protocol. Antibody staining mixes were freshly prepared in staining buffer (PBS (Sigma Aldrich, USA), +0.5% bovine serum albumin (Miltenyi Biotec, Germany) + 0.5 M EDTA (Promega, Germany)).

Two vials of cryopreserved PBMCs were thawed per donor. After removal from liquid nitrogen, PBMC vials were transferred to a 37°C water bath for 1 to 2 minutes. Cells were then slowly transferred
into a 12 mL centrifuge tube containing 10 mL pre-warmed RPMI 1640 + Glutamax medium (Gibco, Thermofisher Scientific, USA) + 10% FCS. Cells were centrifuged at 250xg for 6 minutes at room temperature (RT) and re-suspended in media. The samples were filtered using cell strainer 70 μm filters (Sarstedt, Germany) to obtain single-cell suspensions, washed three times with PBS (4°C) and then evenly distributed to four 5 mL flow cytometry tubes. Following a centrifugation step, PBMCs were incubated with 50 μL of a live/dead (L/D) marker in PBS. For the naive/memory T cell panel, CCR7 APC antibody was also added to the cell suspension. After a 15 minutes incubation time, antibody premixes were added to the respective tubes and incubated for an additional 15 minutes. Following incubation, 1 mL of staining buffer was added to each tube and samples were centrifuged at 350xg for 5 minutes. PBMCs were re-suspended in FACS buffer and tubes were kept on ice until measurement.

The gating strategies for the identification of PBMC sub-populations are depicted in Figures S1 and S2.

### Analysis and statistics

Analysis of flow cytometry data was carried out using FlowJo software version 10.1 (Treestar Inc., USA). PBMC sub-population frequencies were expressed as percentages among a suitable reference population. Due to varying sample quality, we only included cell populations of samples with at least 100 events in the respective parent gate. This explains diverging sample sizes for analyses of different cell populations. Sample sizes for each analysis are listed in the figure legends.

Statistical analyses were computed in GraphPad Prism Version 7 software (GraphPad Software Inc., USA). For this exploratory study, we employed a stepwise statistical approach: First, for each immune cell subset analysed, we performed an omnibus Kruskal-Wallis test, with adjusted pairwise post hoc comparisons (Dunn’s multiple comparison test) in case of an overall effect in the omnibus test. Finally, for those markers that showed robust group differences in the post hoc test, we also ran correlation analyses (Spearman’s correlation) to explore the strength of association with psychiatric (GAD-7 scores, PHQ-9 total scores and individual item scores, the latter are reported both without and with adjustments for multiple testing using Holm’s correction) and metabolic (WHR, systolic and diastolic blood pressure) variables of interest. For display purposes, we show the Spearman rank correlation data as scatter plots of raw data.

### RESULTS

#### 3.1  |  Patient characteristics

Clinical and demographic characteristics of healthy controls (HCs), patients with obesity (Ob) and patients with obesity and comorbid depression (Ob + D) are shown in Table 1. Age and sex distributions were similar across groups. The two cohorts of people with severe obesity did not differ in BMI or waist circumference. PHQ-9 scores in the depressed group indicated moderate to severe depression. As expected, patients with obesity and comorbid depressive symptoms also reported higher scores on the GAD-7 scale.

#### 3.2  |  CD4⁺ and CD8⁺ T cell subsets

Overall, significant differences were observed regarding the frequency of CD4⁺ central memory T cells (TCM) (KW P = .018) (Figure 1A). The post hoc test was significant for the comparison between Ob + D and HC. Frequencies of circulating CD4⁺ TCM were significantly correlated with depression severity (r = 0.3711, P = .0087), but not WHR measurements, GAD-7 scores or blood pressure measurements (Figure 1B). Furthermore, as an explorative post hoc analysis, the following PHQ item scores were significantly correlated with CD4⁺ TCM frequencies: Loss of interest and/or pleasure (PHQ 9_1, r = 0.2986, P = .0415), difficulty sleeping (PHQ_3, r = 0.2909, P = .0473), changes in appetite (PHQ_5, r = 0.3471, P = .0168) and difficulty concentrating (PHQ_7, r = 0.3687, P = .0108) (Figure 1C). However, no associations exceeded the threshold for significance after adjusting for multiple testing. No significant differences in population frequencies of naive, effector memory or effector memory CD4⁺ T cells re-expressing CD45RA were detected (Figure S4).

The frequency of circulating regulatory T cells (Treg, defined as CD4⁺CD25⁺CD127⁻ cells) was significantly different across groups. (KW P = .023). Specifically, frequencies were increased in patients with obesity and comorbid depressive symptoms (Ob + D) when compared to non-depressed patients with obesity (Ob) (Figure S3A). No group differences in relative frequencies of naive and memory Treg sub-populations were detected (Figure S3B). The expression of the inhibitory marker PD-1 on Treg was significantly increased in patients with obesity compared to HCs (Figure S3C). However, numbers of regulatory T cells did not correlate with PHQ-9 scores or WHR.

In the CD8⁺ T cell compartment, significant reductions of effector memory T cells (CD8⁺ TEM) were observed in Ob compared to HC (KW P = .03) (Figure S5C). The amount of circulating CD8⁺ TEM did not correlate with PHQ-9 scores or WHR. No changes in relative frequencies of naive CD8⁺ T cells (Figure S5A), CD8⁺ central memory (Figure S5B) or CD8⁺ effector memory T cells re-expressing CD45RA (Figure S5D) were detected.

#### 3.3  |  Natural killer cell subsets

The relative frequency of circulating cytotoxic natural killer cells (NKc) showed significant group differences (KW P = .006, Figure 2A), with post hoc test confirming lower levels in Ob + D compared to HC. Neither frequency of total natural killer cells (NK) nor regulatory NK cells (NKreg) differed between groups (Figure 2A). Frequencies of NKc were inversely correlated with PHQ-9 scores (r = –0.3862, P = .01, Spearman's test), but not significantly associated with WHR (Figure 2B). The exploratory post hoc analysis showed a significant correlation of the following PHQ item scores with relative NKc
3.4 Dendritic cells, monocyte and B cells

Frequencies of dendritic cells (DCs) showed significant group differences (KW \( P = .001 \), Figure 3A), driven by lower levels in both Ob and Ob + D compared to HC. Frequencies of circulating DCs inversely correlated with both depression severity (\( r = -0.4167, P = .0016 \), Spearman's test) and WHR (\( r = -0.4022, P = .0026 \)) (Figure 3B). In addition, we found significant correlations of the following PHQ item scores: low energy level (PHQ_4, \( r = -0.3622, P = .0066 \)), changes in appetite (PHQ_5, \( r = -0.3485, P = .0091 \)), negative self-perception (PHQ_6, \( r = -0.3154, P = .019 \)), difficulty concentrating (PHQ_7, \( r = -0.2912, P = .031 \)) and psychomotor symptoms (PHQ_8, \( r = -0.3478, P = .0093 \)) (Figure 3C). Again, none of the PHQ item correlations remained significant after correcting for multiple comparisons. No significant group differences concerning the relative frequencies of classical, intermediate or non-classical monocytes (Figure S6A) or B cells (Figure S6B) were found.

4 DISCUSSION

In this exploratory study, we observed alterations in several innate and adaptive immune cell subsets between HCs, patients with obesity and patients with obesity and comorbid depression. Our most robust
findings included lower frequencies of NKc and higher levels of CD4 TCM cells in patients with comorbid obesity and depressive symptoms when compared to lean HCs. These findings also showed a significant bivariate association with depression severity but not WHR. This indicates potentially depression-specific immune dysregulations in patients with severe obesity.

In addition, numbers of dendritic cells were significantly reduced in patients with obesity as well as patients with obesity and comorbid depression compared to HCs. Importantly, the number of dendritic cells correlated with both WHR and PHQ scores. Our results thus suggest that dendritic cell frequency may be an immunological correlate that is shared between obesity and depression.
Decreased function\textsuperscript{33-35} and lower numbers of NK cells\textsuperscript{24,34,36,37} in MDD have long been reported in the literature, although not all studies have found this.\textsuperscript{26} Gene expression analyses of PBMCs obtained from depressed patients revealed significant down-regulation of genes contributing to NK cell activation.\textsuperscript{38} The findings of our study—lower numbers of circulating NKc in patients with obesity and comorbid depression—are in line with most previous findings in MDD. In obesity, dysregulation of NK cells also has pathophysiological implications.\textsuperscript{39} Since reduced frequency of NKc significantly correlated with depression severity, but not waist-to-hip ratio, this might indicate some specificity of this association with depression, at least in comorbid patient cohorts like ours.

The role of dendritic cells in MDD is less clear. We observed significantly reduced numbers of DCs in patients with obesity as well as in patients with obesity and comorbid depression compared to HCs. Furthermore, the amount of circulating DCs correlated with both depression severity and WHR in the total sample. One study examining patients with Alzheimer’s disease found that reduced numbers of circulating dendritic cells were significantly associated with depression severity.\textsuperscript{40} A study in patients suffering from bipolar disorder also identified impaired function of DCs, which was improved upon in vitro treatment with lithium.\textsuperscript{41} Reduced numbers of dendritic cells and their functional impairment have previously been reported in patients with severe obesity,\textsuperscript{42} which is also in accordance with our findings. Given that number of dendritic cells correlated with both PHQ scores and WHR, altered dendritic cell number and function might be involved in a shared pathophysiological mechanism of obesity and MDD.

In our study, we defined dendritic cells as CD20\textsuperscript{−}/CD14\textsuperscript{−}/CD56\textsuperscript{−}/HLA-DR\textsuperscript{+} of the CD3\textsuperscript{−} non-T cell population.\textsuperscript{43} This identification strategy has obvious limitations, since we did not stain for markers specific for dendritic cells such as CD11c and CD123, which also allow for the differentiation of myeloid and plasmacytoid DCs.\textsuperscript{43,44} In spite of these shortcomings, we believe that our findings could serve to encourage further research on dendritic cells in MDD and obesity, as altered phenotypes of other cells belonging to the myeloid lineage have been described in both MDD\textsuperscript{23} and obesity.\textsuperscript{20,22}

We detected increased frequencies of CD4\textsuperscript{+} central memory T cells in patients with obesity and comorbid depression compared to HC, which also correlated with depression severity (but not WHR). While there are, to this date, not many studies that have specifically investigated the role of memory T cells in MDD,\textsuperscript{24} there is a body of evidence that suggests a role of altered T cell phenotypes in MDD.\textsuperscript{23,33,36,37} One possible explanation for the higher numbers of CD4\textsuperscript{+} central memory T cells could be the increased vulnerability to infection in patients with depression.\textsuperscript{45} A significant association of depression and herpes simplex-1 infection, among others, has been confirmed in a meta-analysis.\textsuperscript{46} Higher numbers of CD4\textsuperscript{+} TCM could be caused by more frequent and/or persistent infections in MDD patients compared to the general population, especially in those with comorbid obesity, given that obesity itself poses a risk factor for increased susceptibility to viral infection.\textsuperscript{42}

Concerning correlations with individual PHQ items, in the case of dendritic cells, their abundance was correlated with appetite changes and fatigue (defined as “low energy level”), two symptom domains that are considered central to the atypical/“immuno-metabolic” depression profile.\textsuperscript{1,12} Concerning CD4\textsuperscript{+} TCM, significant correlations were observed in the domains of appetite changes and changes in sleeping patterns, also associated with this subtype of depression. In contrast, the PHQ sub-items, which were significantly correlated with the abundance of NKc, could be cautiously interpreted to be more reminiscent of a melancholic depression subtype.\textsuperscript{1} However, following adjustment for multiple testing, none of the correlations with PHQ sub-items remained below a significance level of 0.05. Since these post hoc analyses were explorative in nature, these results need to be interpreted with great caution and should be followed-up in larger samples.

In our study, we found significantly increased frequencies of regulatory T cells in patients with obesity and comorbid depression.
compared to controls with obesity but not compared to HCs. Previous studies on regulatory T cells in obesity are conflicting: One study reported lower frequencies in individuals with obesity, but another study reported an increase of regulatory T cells. These inconsistencies might be, in part, caused by different marker combinations for identification of regulatory T cells using flow cytometry. Since changes in the abundance of regulatory T cells in the depressed group did not correlate with PHQ-9 scores, our results should be interpreted with caution. Generally speaking, the role of regulatory T cells in MDD and obesity is still being debated, with some studies reporting higher abundance and others reduced numbers.

It should be noted that we did not observe changes in the abundance of monocyte populations. Our findings are thus in contrast with previous reports, where an increase in non-classical and inflammatory monocytes has been reported for both obesity and MDD. Similarly, monocyte-derived microglia-like cells have been shown to be correlated with suicidal ideation in psychiatric patients. The discrepancies between our findings and the current literature could be due to the small sample size investigated in this study and warrant further clarification in the form of well-controlled, large-scale studies. While our study might encourage further research to be focused on the subsets we identified, monocytes and monocyte-derived cells remain important candidates to be investigated for their potential pathophysiological role in mood disorders with and without comorbid obesity.

Several potential limitations of our study need to be considered. First, our sample was comparatively small. Depression was defined by a PHQ-9 score ≥10 and not diagnosed by means of a structured clinical interview conducted by a trained psychiatrist. Our analysis of the immune phenotype was purely descriptive and does not include any functional readouts. We used measures of waist-to-hip ratio instead of BMI for correlation analyses, given the known shortcomings of BMI for assessing risk factors associated with obesity. However, measuring waist and hip circumference can prove difficult in patients with morbid obesity. We refrained from performing correlation analyses of PHQ-9 scores with BMI and waist circumference given their strong bimodal distribution in our sample. Importantly, while some of our findings suggest potential additive associations with obesity and depressive symptoms, our study did not include a group of lean participants with depressive symptoms. Thus, these results should be interpreted with caution.

The cross-sectional nature of our study precludes any interpretations of cause and effect between depressive symptoms and immunological markers. Longitudinal or interventional studies would be needed to better understand the relationship between them. Moreover, additional factors, such as health behaviours (diet, exercise, smoking, etc.) may play a role. For example, a study on patients with coronary heart disease uncovered a direct association of depressive symptoms and poor lifestyle behaviours, including higher BMI and waist-to-hip ratio. Another recent study identified a strong behavioural overlap between obesity and depression.

Obesity affects treatment outcome in MDD, since patients with higher BMI tend to show an unfavourable treatment response to conventional treatment strategies. Therefore, identifying patients with “immuno-metabolic” depression may ultimately help to optimize treatment strategies. In summary, our results indicate a potential role of cytotoxic NK cells, dendritic cells and certain T cell subsets in obesity with comorbid depression. These findings are in line with the notion that the immune system might play a role in the shared pathophysiology between MDD and obesity.

ACKNOWLEDGEMENTS
This research was in part supported by a mentor-based postdoctoral fellowship program from the National MS Society (MB-1707-28359). Open Access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST
Dr. Otte reports personal fees from Allergan, Ferring, Fortbildungskolleg, Limes Klinikgruppe, Lundbeck, MedOnline, Medical Tribune, Neuraxpharm, SAGE Therapeutics and Stillachhaus outside the submitted work and reports research support from the German Research Foundation (DFG), German Ministry of Education and Research (BMBF), the European Commission (Innovative Medicines Initiative) and the Brain & Behavior Foundation (NARSAD). Dr. Gold reports, personal fees from Almirall S.A., grants from Biogen, personal fees from Mylan GmbH, personal fees from Celgene, personal fees from FomF, grants from German Research Foundation (DFG), grants from German Ministry of Education and Research (BMBF), grants from German Ministry of Health (BMG), grants from the National MS Society (NMS), grants from the European Commission (Innovative Medicines Initiative). The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
All data displayed in this publication, including supplementary materials, are available from the corresponding author upon request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Stiglbauer V, Gamradt S, Scherzer M, et al. Immunological substrates of depressive symptoms in patients with severe obesity: An exploratory study. Cell Biochem Funct. 2021;39:423–431. https://doi.org/10.1002/cbf.3608