Obesity is associated with local T-cell abnormalities in adipose tissue. Systemic obesity-related abnormalities in the peripheral blood T-cell compartment are not well defined. In this study, we investigated the peripheral blood T-cell compartment of morbid obese and lean subjects. We determined all major T-cell subpopulations via six-color flow cytometry, including CD4+ and CD8+ T cells, CD4+ T-helper (Th) subpopulations, and natural CD4+CD25+FoxP3+ T-regulatory (Treg) cells. Moreover, molecular analyses to assess thymic output, T-cell proliferation (T-cell receptor excision circle analysis), and T-cell receptor-β (TCRB) repertoire (GeneScan analysis) were performed. In addition, we determined plasma levels of proinflammatory cytokines and cytokines associated with Th subpopulations and T-cell proliferation.

Morbid obese subjects had a selective increase in peripheral blood CD4+ naive, memory, natural CD4+CD25+FoxP3+ Treg, and Th2 T cells, whereas CD8+ T cells were normal. CD4+ and CD8+ T-cell proliferation was increased, whereas the TCRB repertoire was not significantly altered. Plasma levels of cytokines CCL5 and IL-7 were elevated. CD4+ T-cell numbers correlated positively with fasting insulin levels. The peripheral blood T-cell compartment of morbid obese subjects is characterized by increased homeostatic T-cell proliferation to which cytokines IL-7 and CCL5, among others, might contribute. This is associated with increased CD4+ T cells, with skewing toward a Treg- and Th2-dominated phenotype, suggesting a more anti-inflammatory set point.

Obesity is a major cause of preventable death in the Western world (1), and its prevalence is rapidly increasing (2). Type 2 diabetes mellitus and cardiovascular diseases are responsible for the majority of obesity-related morbidity and mortality (2). Obesity is primarily considered to be a metabolic disease. However, in recent years, it has become clear that obesity is also associated with immunological abnormalities (3).

From the 1Department of Immunology, Erasmus University Medical Center, Rotterdam, the Netherlands; the 2Department of Internal Medicine, Reinier de Graaf Group of Hospitals, Delft, the Netherlands; the 3Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands; the 4Department of Internal Medicine, Haga Hospital, The Hague, the Netherlands; the 5Department of Pulmonology, Sint Franciscus Gasthuis, Rotterdam, the Netherlands; the 6Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands; and the 7Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, the Netherlands.

Corresponding author: P. Martin van Hagen, p.m.vanhagen@erasmusmc.nl. Received 29 July 2011 and accepted 25 November 2011.

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These abnormalities probably result from intricate adipose-immune interactions (4) and contribute a great deal to obesity-related morbidity (5).

Immunological abnormalities associated with obesity are often seen as a state of chronic low-grade inflammation. This state of chronic low-grade inflammation is nowadays considered to be crucial in the development of long-term complications of obesity, such as diabetes (6,7) and atherosclerosis (8). The state of chronic low-grade inflammation has long been thought to be primarily due to an accumulation of proinflammatory macrophages within the adipose tissue and the production of proinflammatory cytokines by adipocytes and macrophages, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 (9). However, T-cell accumulation was demonstrated recently in both mouse and human obese adipose tissue (10–12), which even preceded macrophage accumulation (13,14). Therefore, T cells are thought to be important participants in the initiation of adipose tissue inflammation (9). This idea is further supported by the finding that T-cell depletion reduced adipose tissue macrophage accumulation and improved insulin sensitivity in mice fed a high-fat diet (13,15). Altogether, several lines of evidence suggest a direct link between obesity and a deregulated T-cell accumulation within adipose tissue (9).

Given the systemic nature of obesity, it can be anticipated that the peripheral blood T-cell compartment is affected as well. So far, however, only a limited number of studies have investigated the composition of the peripheral blood immune system in obesity. Positive correlations have been reported between BMI and total white blood cell count (16–19) and T-cell numbers in peripheral blood (16–18,20), but conflicting data have been published as well (21). In the peripheral blood T-cell compartment, increased CD4+ and normal CD8+ T-cell numbers have been found (16,17), whereas both subpopulations were found to be decreased in another study (21). To date, however, studies on CD4+ T-cell subpopulations, T-cell proliferation history, and T-cell diversity are lacking.

In this study, we performed a detailed analysis of the peripheral blood T-cell compartment in morbid obese and lean subjects. For this purpose, we determined the absolute counts and relative frequencies of all major T-cell subpopulations via six-color flow cytometry, including CD8+ T cells; CD4+ T cells; the CD4+ T-cell subpopulations T-helper (Th)1, Th2, and Th17 cells; and natural CD4+CD25+FoxP3+ T-regulatory (Treg) cells. These numerical analyses were combined with molecular analyses to assess thymic output, T-cell proliferation (T-cell receptor excision circle [TREC] analysis), and T-cell receptor-β (TCRB) repertoire usage.
PERIPHERAL BLOOD T CELLS AND OBESE SUBJECTS

RESEARCH DESIGN AND METHODS

A total of 13 morbid obese (BMI >40 kg/m2) and 25 lean (BMI <25 kg/m2) healthy control subjects were included in this study. Subjects with overt type 2 diabetes mellitus or liver enzyme test abnormalities were excluded. The presence of concomitant medical illness was excluded by medical history assessment in morbid obese and lean subjects. All subjects gave their written informed consent. The study was approved by the medical ethical committee of Erasmus University Medical Center.

Blood was obtained using vacuumed sodium heparin-containing tubes (Greiner Bio-one, Alphen a/d Rijn, the Netherlands) and further processed within 1 h after collection. Plasma was isolated by centrifugation and frozen for further analyses. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll density separation and viably frozen for further analyses.

Flow cytometry and cell sorting. Total leukocyte count was measured in freshly collected blood using a Coulter Counter (Beckman Coulter B.V., Woerden, the Netherlands). Cell and leukocyte subpopulations were determined by flow cytometry based on CD45 expression and side scatter. For immunophenotyping of T-cell subpopulations, viably frozen PBMCs were used. Antibodies used for flow cytometric analyses and sorting experiments are summarized in Supplementary Table 1. T-cell subpopulations were defined as naive (CD45RA- and CCR7+), central memory (CD45RA- and CCR7-), effector memory (CD45RA+ and CCR7+), and terminally differentiated (CD45RA+ and CCR7-). Natural Treg cells were defined as CD4+CD25+FoxP3+. Intracellular cytokine detection, PBMCs were stimulated with phorbol-12-myristate-13-acetate (PMA; 50 ng/mL, Sigma-Aldrich, St. Louis, MO) and ionomycin (500 ng/mL; Invitrogen Ltd., Paisley, UK) for 4 h in the presence of GolgiStop (BD Biosciences, San Jose, CA). Thereafter, cells were stained for extracellular markers, fixed with 2% paraformaldehyde, and permeabilized with 0.5% saponin, followed by intracellular staining for IFN-γ, IL-4, and IL-17A. Stained cells were measured using a FACS LSRII (BD Biosciences), and data were analyzed with FlowJo software (TreeStar, Ashland, OR). Th1 cells were defined as CD4+IFN-γ+, Th2 cells as CD4+IL-4+, and Th17 cells as CD4+IL-17A+.

To determine sjTREC dilution, DNA was extracted from different T-cell subpopulations using the GeneElute Mammalian Genomic DNA miniprep kit (Sigma-Aldrich). Signal joint TREC (sjTREC) analysis was used to evaluate thymic output and peripheral T-cell proliferation. The sjTREC is a stable genomic DNA, is not duplicated during cell proliferation, it will dilute out during consecutive cell divisions, making it a useful marker to determine proliferation history in αβ T cells (Supplementary Fig. 1A) (23). Because the sjTREC, in contrast to genomic DNA, is not duplicated during cell proliferation, it will dilute out during consecutive cell divisions, making it a useful marker to determine proliferation history in αβ T cells (Supplementary Fig. 1B) (24).

Flow cytometric analyses on isolated PBMCs revealed that NK- and B-cell numbers did not differ between the morbid obese and lean subjects (Fig. 1B). T-cell numbers, however, were significantly (P < 0.01) increased in morbid obese subjects. This was mainly due to a twofold increase in CD4+ T cells (P < 0.01), whereas CD8+ T-cell numbers remained normal (P = 0.35) (Fig. 1C). This resulted in an increased CD4-to-CD8 ratio (morbid obese 2.82 [1.62-6.17] vs. lean 1.54 [1.29-5.23], P = 0.03, data not shown).

Peripheral blood CD4+ T-cell subpopulations that display an anti-inflammatory phenotype are increased in morbid obesity. Next, we performed extensive flow cytometric analyses to determine whether distinct T-cell subpopulations are affected in morbid obese subjects. Within the CD8+ T-cell compartment, cell numbers within the different subpopulations were similar in morbid obese and lean subjects (Fig. 2A). Within the CD4+ T-cell compartment, increased numbers of CD80 (P = 0.04), central memory (P < 0.01), and terminally differentiated (P = 0.03) T cells were found in morbid obese subjects, whereas no differences were found in the effector memory subpopulation between morbid obese and lean subjects (Fig. 2A). Also, absolute counts of natural CD4+CD25+FoxP3+ Treg cells were increased.

RESULTS

Peripheral blood CD4+ T-cell numbers are increased in morbid obesity. An initial general examination of the blood samples did not reveal clear differences in the total leukocyte number or the numbers of distinct leucocyte subpopulations between morbid obese and lean subjects (characteristics of the subjects are summarized in Table 1). However, a trend toward increased lymphocyte numbers was present in morbid obese subjects (Fig. 1A). Detailed flow cytometric analyses on isolated PBMCs revealed that NK- and B-cell numbers did not differ between the morbid obese and lean subjects (Fig. 1B). T-cell numbers, however, were significantly (P < 0.01) increased in morbid obese subjects. This was mainly due to a twofold increase in CD4+ T cells (P < 0.01), whereas CD8+ T-cell numbers remained normal (P = 0.35) (Fig. 1C). This resulted in an increased CD4-to-CD8 ratio (morbid obese 2.82 [1.62-6.17] vs. lean 1.54 [1.29-5.23], P = 0.03, data not shown).

Peripheral blood CD4+ T-cell subpopulations that display an anti-inflammatory phenotype are increased in morbid obesity. Next, we performed extensive flow cytometric analyses to determine whether distinct T-cell subpopulations are affected in morbid obese subjects. Within the CD8+ T-cell compartment, cell numbers within the different subpopulations were similar in morbid obese and lean subjects (Fig. 2A). Within the CD4+ T-cell compartment, increased numbers of CD80 (P = 0.04), central memory (P < 0.01), and terminally differentiated (P = 0.03) T cells were found in morbid obese subjects, whereas no differences were found in the effector memory subpopulation between morbid obese and lean subjects (Fig. 2A). Also, absolute counts of natural CD4+CD25+FoxP3+ Treg cells were increased.

Table 1. Characteristics of morbid obese and lean healthy subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subject</th>
<th>Lean</th>
<th>Morbid obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometric and cytokine analysis</td>
<td>n</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.2 ± 1.4</td>
<td>42.4 ± 6.7</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 ± 9</td>
<td>45 ± 10</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>9/2</td>
<td>8/0</td>
<td></td>
</tr>
<tr>
<td>TREC and GeneScan analysis</td>
<td>n</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.9 ± 1.9</td>
<td>42.1 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 ± 7</td>
<td>48 ± 11</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>12/2</td>
<td>13/0</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD.

**TABLE 1.** Characteristics of morbid obese and lean healthy subjects
(P < 0.01) (Fig. 2B). Effector CD4+ T-cell subpopulations were determined by measuring the intracellular cytokine profile after stimulation with PMA and ionomycin. The numbers of IFN-γ-producing T cells (Th1) and IL-17A-producing T cells (Th17) were similar in morbid obese and lean subjects, whereas the number of IL-4-producing T cells (Th2) was increased in morbid obese subjects (P = 0.03) (Fig. 2B).

Additional correlation analyses demonstrated a significant correlation between BMI and the number of total T cells as well as the numbers of CD4+ T cells, naive CD4+ T cells, terminally differentiated CD4+ T cells, central memory CD4+ T cells, natural CD4+CD25+FoxP3+ Treg cells, and Th2 cells. For age, only a significant correlation was observed with the number of Th2 cells (Supplementary Table 2).

Taken together, these data demonstrate that morbid obesity is associated with increased naive and memory CD4+ T cells and with increased numbers of anti-inflammatory natural CD4+CD25+FoxP3+ Treg cells and Th2 cells.

**Proliferation of CD4+ and CD8+ T cells is increased in morbid obesity.** Several mechanisms, including increased thymic output, increased peripheral proliferation, decreased apoptosis, or altered redistribution, can account for the observed increased CD4+ T-cell numbers found in morbid obese subjects. To distinguish between increased thymic output and increased peripheral proliferation or survival, the sjTREC content in peripheral blood T-cell subpopulations was determined (Supplementary Fig. 1C). A significantly lower sjTREC content, which together with increased cell numbers resembles increased proliferation (Supplementary Fig. 1C), was found in total αβ-T cells (P < 0.01) and CD4+ naive (P = 0.03), CD4+ memory (P = 0.02), and CD8+ naive (P = 0.02) T-cell subpopulations of morbid obese subjects (Fig. 3A). Moreover, a significant negative correlation (P < 0.01) was found between αβ-T cell sjTREC content and BMI (Fig. 3B, left).

A negative correlation between sjTREC content and age has been reported previously (25), but although the morbid obese group was significantly older than the lean control group (morbid obese aged 45 years [28–62] vs. lean aged 31 years [25–51]; P = 0.02), the sjTREC content in αβ-T cells did not correlate significantly with age (Fig. 3B, right), although we cannot exclude that this might be due to the relatively limited number of subjects studied. Moreover, in multiple regression analysis, the BMI was the only variable significantly associated with the TREC content (R = 0.8, R² = 0.58, P = 0.001, P_age = 0.28, P_BMI = 0.002), demonstrating that the decreased sjTREC content in morbid obesity is mainly determined by obesity and not by age.

Overall, the decreased sjTREC content together with the increased T-cell numbers in morbid obese subjects is indicative of increased proliferation within the T-cell compartment of these subjects.

**Increased T-cell proliferation in morbid obesity is not driven by dominant antigens.** Several studies describe a reduced diversity within the TCRB repertoire of T cells isolated from adipose tissue of obese mice, suggesting a local antigen-driven immune response toward the main antigens present within adipose tissue (13,27). We determined TCRB diversity in peripheral blood T-cell subpopulations. We observed a diverse TCRB repertoire in CD4+ and CD8+ naive and memory T cells from both morbid obese and lean subjects (Fig. 4A and B). Minor alterations in
levels of CCL5 (proliferation, survival, and recruitment (29– lean subjects (Fig. 5A), cytokines respectively associated with Th1, Th2, or TNF- 
BMI 41.6 23.6 6 
4 DIABETES diabetes.diabetesjournals.org 
found to a limited extent in the CD4+ memory T cells and the (normally Gaussian distributed) TCRB repertoire were
particular T-cell clones. Instead a rather broad TCR repertoire in morbid obese subjects (Fig. 4A and B). In addition, 
we obtained fat tissue that was removed during surgery from five other morbid obese subjects. No peripheral blood T cells were available from these patients because only adipose tissue and plasma samples were stored. Nevertheless, it gave us an opportunity to investigate the TCR repertoire of adipose tissue T cells. Hence, we performed GeneScan analysis on the T cells present in the adipose tissue. We observed a polyclonal TCR repertoire (Supplementary Fig. 2), indicating that there was no strong skewing toward particular T-cell clones. Instead a rather broad TCR repertoire was present in the adipose tissue T cells.

**T-cell growth factors in plasma are elevated in morbid obesity.** Because obesity is characterized by abnormal production of proinflammatory cytokines (28), we hypothesized that cytokines involved in T-cell proliferation, survival, and recruitment might also be produced in excess in morbid obese subjects. Therefore, we determined a broad panel of cytokines in plasma from morbid obese and lean subjects.

Plasma levels of the proinflammatory cytokines IL-6 and TNF-α did not differ between morbid obese and lean subjects (Fig. 5A). Also, plasma levels of IFN-γ, IL-4, and IL-17A, cytokines respectively associated with Th1, Th2, or Th17 subpopulations, were similar in morbid obese and lean subjects (Fig. 5B).

The cytokines CCL5, IL-2, and IL-7 enhance T-cell proliferation, survival, and recruitment (29–31). Plasma levels of CCL5 ($P < 0.01$) and IL-7 ($P < 0.01$) were significantly elevated in morbid obese subjects (Fig. 5C) and correlated positively with BMI (Supplementary Table 3). IL-2 plasma levels were similar in morbid obese and lean subjects (Fig. 5C).

As expected, IL-7 and CCL5 plasma levels positively correlated with total CD4+ T-cell numbers but not with total CD8+ T-cell numbers (Fig. 5D and E). In the CD4+ T-cell compartment, a positive correlation was found between IL-7 plasma levels and the number of naive CD4+ T cells, terminally differentiated CD4+ T cells, central memory CD4+ T cells, and natural CD4+CD25+FoxP3+ Treg cells; CCL5 plasma levels correlated positively with the number of terminally differentiated CD4+ T cells, central memory CD4+ T cells, and natural CD4+CD25+FoxP3+ Treg cells (Supplementary Table 4).

**Increased CD4+ T-cell numbers correlate with fasting insulin levels in morbid obesity.** Although the morbid obese subjects did not have type 2 diabetes mellitus, we investigated the correlations between the increased CD4+ T-cell numbers and metabolic measures. Fasting glucose and insulin levels were determined in the morbid obese group only (32). A significant correlation was found between fasting insulin levels and CD4+ T-cell numbers (Fig. 6A). Moreover, the glucose-to-insulin ratio was calculated as a measure of insulin sensitivity. This ratio also correlated with CD4+ T-cell numbers (Fig. 6B). Fasting insulin levels and insulin sensitivity did not correlate with CD8+ T-cell numbers (Fig. 6C and D). No significant correlations were found between fasting blood glucose levels and T-cell subpopulations (data not shown).

**DISCUSSION**

This study is the first to comprehensively investigate the peripheral blood T-cell compartment of morbid obese subjects. Our main finding was a selective increase in CD4+ T-cell numbers within the peripheral blood T-cell compartment of morbid obese subjects. Peripheral blood CD8+ T-cell numbers were normal in morbid obese subjects. This latter observation is in contrast with the increased numbers of local effector and memory CD8+ T cells described in adipose tissue of obese subjects (12,13).

In mice, diet-induced obesity results in reduced sjTREC content in splenic CD4+ T cells (33). This is accompanied by a reduction in naive T cells and a more restricted TCRB repertoire, suggesting that in this mouse model, the decrease in sJtREC is mainly the result of reduced thymic output (33). Because ageing also is associated with a reduction in thymic output, resulting in a reduced TREC content and a reduction in naive T-cell numbers, it was suggested that obesity is related to accelerated ageing of the T-cell compartment (33,34).

In our study, we found a decreased sJtREC content in peripheral blood T-cell subpopulations of morbid obese subjects. However, in contrast to observations in ageing studies (35,36), the decreased sJtREC content was accompanied by increased numbers of naive as well as memory CD4+ T cells and only an insignificant skewing of the TCR repertoire. Therefore, despite the limitation of the significant age difference between morbid obese and lean subjects in our study, we conclude from the increased naive T-cell numbers that the decrease in sJtREC content in morbid obese subjects predominantly results from increased proliferation rather than accelerated ageing and decreased thymic output. This notion is further supported by the decreased telomere length observed in leukocytes of obese subjects (37).

The increased proliferation within the peripheral blood T-cell compartment is more likely of homeostatic nature
rather than driven by dominant antigens because the latter would result in increased memory and effector T-cell subpopulations with prominent skewing of the TCRB repertoire, whereas the naïve T-cell compartment would remain unaffected. In our cohort, we do not see such changes in the peripheral blood T-cell compartment. Moreover, in an additional analysis, a rather polyclonal TCR repertoire was observed in adipose tissue T cells of morbid obese subjects. It therefore seems likely that there is no vast change in TCR repertoire in the adipose tissue T cells in our cohort. However, we formally cannot exclude the possibility of some skewing of the TCRB repertoire within adipose tissue T cells.

Several T-cell mitogenic factors, such as adipokines, fatty acids, or bacterial products, can be elevated in plasma of morbid obese subjects (38–40). Also, increased levels of IL-7 and CCL5, cytokines capable of stimulating homeostatic T-cell proliferation, survival, and recruitment (29–31), have been found in adipose tissue of obese mice and men (41–43). We also found highly elevated plasma levels of IL-7 and CCL5 in morbid obese subjects in this study, which positively correlated with peripheral blood CD4+ T-cell numbers. On the basis of these data, we hypothesize that IL-7 and CCL5, as well as the other T-cell mitogenic factors, might contribute to the increased homeostatic CD4+ T-cell proliferation in morbid obese subjects.

Despite the selective increase in CD4+ T-cell numbers in peripheral blood, CD8+ T cells also displayed decreased sgTREC content, indicating that CD8+ T cells also undergo increased homeostatic proliferation due to the increased IL-7 and CCL5 cytokine levels in morbid obese subjects. However, peripheral blood CD8+ T-cell numbers were not increased, suggesting a selective redistribution of CD8+ T cells into adipose tissue, which is in line with the described preferential accumulation of CD8+ T cells in obese adipose tissue (12,13). Also, CCL5 is a more potent chemoattractant for CD4+ T cells than for CD8+ T cells (44), and in obesity, systemic levels of CCL5 are ~100-fold higher than those locally produced within adipose tissue (41). Therefore, the elevated CCL5 plasma levels that we observed may contribute to the selective retention of CD4+ T cells in peripheral blood of morbid obese subjects.

With regard to the increased numbers of peripheral blood CD4+ T cells, we observed that this was accompanied by a selective increase in natural CD4+CD25+FoxP3+ Treg cell numbers. In addition, stimulation of PBMCs with PMA/ionomycin specifically induced a Th2 phenotype within the CD4+ T-cell compartment of morbid obese subjects. This indicates that the numerically elevated peripheral blood CD4+ T-cell compartment of morbid obese subjects is skewed toward a Treg- and Th2-dominated phenotype, suggesting a more anti-inflammatory set point. Despite this clear skewing, plasma levels of cytokines associated with the Th2 phenotype were mostly undetectable in plasma from both morbid obese and lean subjects, as was the case for cytokines associated with the Th1 and Th17 phenotypes.

Natural CD4+CD25+FoxP3+ Treg cells and Th2 cells are capable of polarizing monocytes/macrophages toward an anti-inflammatory M2 phenotype, which is characterized by the production of anti-inflammatory mediators such as IL-10 receptor antagonist, IL-10, and transforming growth factor-β (45,46). We hypothesize that the preferential skewing of the CD4+ T-cell compartment toward a Treg- and Th2-dominated phenotype can be considered as a mechanism to counterregulate the proinflammatory activity that exists systemically and locally within the monocyte/macrophage compartment (47–50) in obesity. The absence of increased IL-6 and TNF-α plasma levels in our cohort of morbid obese subjects supports this notion.

We demonstrated this anti-inflammatory T-cell set point in a morbid obese cohort that was selected on the basis of being nondiabetic and, thus, relatively healthy and free of...
comorbidities (although we are not informed on the atherosclerotic state of our patients). To date, it is unknown whether changes in this set point away from the anti-inflammatory phenotype are associated with the development of obesity-related comorbidities.

Atherosclerosis, which frequently occurs during obesity, is characterized by accumulation of Th1 CD4+ T cells within the plaques (51), whereas CD4+ T-cell depletion reduces the development of atherosclerosis in mice (52). Also, the development of type 2 diabetes mellitus is delayed in mice with diet-induced obesity when T cells are depleted (13,15). In addition, we also demonstrated that CD4+ T-cell numbers positively correlated with fasting insulin levels.

On the basis of these literature data and our own data presented herein, it is thus tempting to speculate that changes away from the Treg- and Th2-dominated phenotype toward a more proinflammatory Th1- or Th17-dominated set point may prove an important indicator, or even mediator, for the development of atherosclerosis or diabetes in morbid obese subjects. Longitudinal studies in morbid obese subjects will be important to further address these issues.

In conclusion, the peripheral blood T-cell compartment of morbid obese subjects is characterized by an increased homeostatic proliferation of both CD4+ and CD8+ T cells to which cytokines such as IL-7 and CCL5 probably contribute. This increased homeostatic proliferation is associated with an increase in peripheral blood CD4+ T-cell numbers, with a skewing toward a Treg- and Th2-dominated phenotype, suggesting an anti-inflammatory set point of the peripheral blood CD4+ T-cell compartment.

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No potential conflicts of interest relevant to this article were reported.

K.v.d.W. researched data and wrote the manuscript. W.A.D. contributed to discussion and wrote, reviewed, and

FIG. 5. Plasma levels of IL-6 and TNF-α (A); Th1 cytokines IL-12p70 and IFN-γ, Th2 cytokines IL-4 and IL-10, and the Th17 cytokine IL-17A (B); and IL-2, IL-7, and CCL5 in morbid obese and lean subjects (C). D: Correlation between IL-7 plasma levels and CD4+ or CD8+ T-cell counts in peripheral blood. E: Correlation between CCL5 plasma levels and CD4+ or CD8+ T-cell numbers in peripheral blood. White dots represent lean subjects (n = 11, BMI 23.2 ± 1.4 kg/m²); gray dots represent morbid obese subjects (n = 8, BMI 42.4 ± 6.7 kg/m²). *P < 0.05.

FIG. 6. Correlation between CD4+ T-cell count in peripheral blood and fasting insulin levels (A) and insulin sensitivity (fasting glucose–to–fasting insulin ratio) (B); Correlation between CD8+ T-cell count in peripheral blood and fasting insulin levels (C) and insulin sensitivity (fasting glucose–to–fasting insulin ratio) (D). Gray dots represent morbid obese subjects (n = 8, BMI 42.4 ± 6.7 kg/m²).
edited the manuscript. B.S. and D.H.S. researched data. A.W.L. researched data, contributed to discussion, and reviewed and edited the manuscript. H.A.D. contributed to discussion and wrote, reviewed, and edited the manuscript. R.M.K., M.O.v.A., and A.v.H. researched data. J.J.M. v.d. and A.-J.v.d.L. contributed to discussion and reviewed and edited the manuscript. F.J.T.S. and P.M.v.H. contributed to discussion and wrote, reviewed, and edited the manuscript. P.M.v.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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