Review

From Metabolically Healthy to Unhealthy Obesity Through Low-Grade Inflammation

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From Metabolically Healthy to Unhealthy Obesity Through Low-Grade Inflammation

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Abstract

Of the many clinical phenotypes of obesity the most prevalent are metabolically "healthy" (MHO) and metabolically "unhealthy" obesity (MUO), the latter being associated with a range of comorbidities, including type 2 diabetes mellitus (T2DM). The underlying causes of different obesity phenotypes and the mechanisms of conversion of one phenotype into another, have yet to be fully elucidated. However, increasing evidence suggests the key role of low-grade metabolic inflammation (metaflammation) in pathogenesis of obesity and metabolic dysfunction. This review compares numerous pro-inflammatory mediators observed in MHO and MUO to identify the role of metaflammation in obesity phenotype. A mechanistic model is proposed for the progression from MHO to MUO with the exacerbation of metaflammation and dysfunction of insulin-sensitive organs. MUO is characterized by the excess of visceral adiposity, both local and systemic insulin resistance (IR). Obesity is accompanied by a shift in the immune profile from anti-inflammatory to pro-inflammatory, with its worsening in MUO. However no clinically significant parameter has been identified among soluble factors or leukocyte subtypes in the blood as a predictor of MHO to MUO conversion. Structural and functional changes in adipose tissue are not resolved immediately following bariatric interventions. The persistence of «metabolic memory» in the form of epigenetic modifications in macrophages of adipose tissue and the emergence of large numbers of CD4+ and CD8+ effector memory T cells with senescent phenotype, may predispose to weight regain and T2DM relapse post-surgery. The review discusses mechanisms underlying metabolic memory and potential reversibility of metabolic disturbances after bariatric surgery.

Keywords: metabolically healthy obesity; morbid obesity; type 2 diabetes mellitus (T2DM); low-grade inflammation; bariatric surgery; metabolic memory

1. Introduction

In recent decades, the global prevalence of obesity has been steadily increasing, contributing to diminished quality of life and reduced life expectancy along with increased disability due to its comorbidities - type 2 diabetes mellitus (T2DM), cardiovascular disease, cancer, etc. At the same time, it has been demonstrated that not all obese individuals develop metabolic and cardiovascular disorders. This resulted in specifying two obesity phenotypes: metabolically "healthy" obesity (MHO) and metabolically "unhealthy" obesity (MUO). Some researchers additionally identified specific obesity categories, such as "metabolically unhealthy non-obese" (MUNO) individuals, who have normal body mass index (BMI) but excessive visceral adiposity, insulin resistance (IR), and impaired glucose metabolism, as well as "sarcopenic obesity", characterised predominantly by muscle mass loss [1]. This review concerns two fundamentally distinct phenotypes of obesity: MHO and MUO.

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The concept for obesity characterized by different severity arose a long time ago and has been reconsidered from different perspectives. In early 2025, the International Commission of The Lancet Diabetes & Endocrinology proposed distinguishing "preclinical" obesity, not accompanied by organ dysfunction, from "clinical" obesity complicated by a spectrum of associated diseases, including metabolic disorders [2]. This raises several questions: why do some individuals with abnormal BMI not suffer from metabolic disorders, while others develop T2DM, over time? What factors contribute to the conversion from "metabolic health" to its impairment? Is the progression from MHO to MUO inevitable and merely a matter of time? [3–5] What metabolic, immunological, and hormonal changes accompany this transition? Is it possible to revert to a "metabolically healthy" state after weight loss and T2DM remission following bariatric surgery? Does this depend on the patient's current metabolic, immunological, and hormonal profile? Is it influenced by the duration of obesity?

It is estimated that MHO progresses to MUO in approximately 60% of cases over a 10-year period [6]. Ler et al. observed a transition from MHO to MUO in 56% of cases in a 27-year follow-up [5]. The authors also reported cases of conversion of MUO to MHO. However, the accompanying clinical and immunological changes during such transitions are not discussed in the study. At the same time, several comprehensive reviews have compared MHO and MUO highlighting factors contributing to obesity phenotype and shift of MHO towards MUO. The main reasons for the change in the obesity phenotype include lifestyle, genetic factors [7,8] the predominance of visceral adipose tissue (VAT) [9], structural alterations and inflammation in VAT [8,10,11] accompanied by increased pro-inflammatory factors and inflammatory circulating cells [12–14]. Blüher et al. in their review analyzed several biological factors contributing to the MUO and its transition from MHO [15]. Other reviews have focused on the pathogenesis of different obesity phenotypes in animal models [16], as well as on surgical and therapeutic approaches to MUO treatment [17,18] The review by Duque et al. is notable for the analysis of inflammatory biomarkers patterns (neutrophil-to-lymphocyte ratio, levels of soluble urokinase plasminogen activator receptor (suPAR), or gut and adipose tissue (AT) hormones) for the prevention of cardiovascular disease in patients with MHO [19].

In the present review, we define MHO and MUO phenotypes and analyse the role of various factors in the development of these two obesity types. Given that obesity is accompanied by low-grade metabolic inflammation (or metaflammation), we examine MHO and MUO from its perspective comparing both types of obesity by multiple inflammation-associated parameters. Upon analysing a number of clinical, biochemical, and hormonal parameters, and comparing amount, frequency, and functional activity of various immune cell subsets in the circulation and in AT, we have identified distinct inflammatory patterns accompanying MHO and MUO and highlighted primary and secondary inflammatory mediators. A mechanistic model for obesity as a disease that develops with the intensification of metaflammation and gradual transition from MHO to MUO is proposed. A pattern of key parameters critical to the conversion of MHO to MUO has been identified. Additionally, the issue of metabolic restoration after bariatric surgery (BS) is discussed.

Comprehensive and systematic literature search was performed through PubMed, Scopus and Google Scholar resources. The keywords used to extract studies comprise metabolically healthy and unhealthy obesity, morbid obesity, type 2 diabetes mellitus, low-grade inflammation, bariatric surgery, metabolic memory, with each specific factor (e.g. IL-6, MCP-1, neutrophils, regulatory T and B cells, etc) mentioned to clarify its role in MHO and MUO. . The search limits were defined as 'the beginning of a given database through 31 December 2025' (publication date) between 2000–2025.

2. Differences in Metabolic Status. The Role of General Factors Including Sex, Duration of Obesity, Fat Distribution, and Lifestyle in the Formation of Obesity Phenotypes

A recent meta-analysis of 12 cohort and 7 interventional studies demonstrated that MHO makes up 35% among individuals with obesity with significant regional variation [20]. MHO is more frequently observed in women than in men [21], and there is a tendency for MUO conversion in older people, supporting the role of obesity duration in metabolic complications [22]. The higher prevalence

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of obesity-related comorbidities in postmenopausal compared to premenopausal women [23] suggests that declining sex hormone levels may also play a significant role. Sufficient physical activity can reduce the risk of T2DM and cardiovascular diseases [8][24] . In a large BMI-stratified cohort, Stefan N and colleagues [25] associated excessive hepatic and abdominal fat accumulation with MUO, whereas subcutaneous and predominantly lower extremities fat accumulation were associated with MHO. The protective role of subcutaneous fat has also been reported by other authors [26].

It is commonly hypothesized that excess caloric intake is initially compensated by preferential expansion of subcutaneous adipose tissue (SAT), with increased adipogenesis and angiogenesis, and adipocyte hypertrophy. Subcutaneous fat acts as a "buffer" for fatty acids and triglycerides; however, this buffering capacity and the ability of SAT to expand are limited. Once this threshold is reached, excess fat begins to accumulate in ectopic tissues and visceral depots. It is possible that individual "threshold capacities" of subcutaneous fat buffering determine the development of metabolic syndrome. For this reason, some patients develop metabolic disturbances at lower body mass and BMI values compared to those with MHO [27].

Visceral and ectopic (hepatic and skeletal muscle) fat distribution is a factor influencing metabolic health, possibly to a greater extent than overall fat mass [15] [28]. Visceral obesity and ectopic fat depots initiate a pathological cascade that promotes low-grade metabolic inflammation, which initially manifests in AT and gradually becomes systemic [29]. The degree of metaflammation and the profile of pro-inflammatory mediators appear to differ between MHO and MUO [30–32] MUO is characterized by higher levels of systemic inflammation compared to MHO, with significantly increased circulating pro-inflammatory factors, including cytokines and adipokines (IL-6, TNF-α, leptin, resistin, visfatin, MCP-1, PAI-1) [13] [32–37] as well as greater activation of pro-inflammatory immune cells and their infiltration into adipose depots (M1 macrophages, CD8+ T cells, CD4+ Th1 cells, neutrophils, B cells) [13] [32,33]. Elevated levels of CRP (2–10 mg/L), leptin (53.07 ± 34.56 ng/mL in MUO versus 36.27 ± 24.02 ng/mL in MHO), and HOMA-IR (3.56 in MUO versus 1.37 in MHO) observed in MUO are considered indicators of systemic metabolic inflammation [19]. Individuals with MHO also exhibit signs of metaflammation, but to a lesser degree than those with MUO [32], likely due to lower visceral fat accumulation [37].

Although AT plays a key role in the metabolic disturbances in obesity, significant changes also occur in the liver and skeletal muscle. Notably, the degree of fat accumulation in hepatocytes may even determine the obesity phenotype [38]. A number of studies report that high levels of circulating lysophosphatidylcholines, produced by the liver, can be used to distinguish between MUO and MHO [39]. Visceral fat adipocytes can release large amounts of free fatty acids (FFAs) that reach the liver via the portal vein, leading to hepatic IR and dyslipidemia [17]. Accordingly, reduction of visceral fat volume and attenuation of metaflammation in MUO are associated with improved liver function and reduced IR [40]. Moreover, excessive hepatic fat results in metabolic-associated fatty liver disease (MAFLD) and hepatic IR, one of the key triggers in T2DM development [41]. It has been shown that individuals with MHO have a twofold increased risk of MAFLD, while those with MUO have a 3.5-fold increased risk compared to healthy non-obese individuals [42]. Skeletal muscle in MUO is also characterized by increased intramuscular fat deposition (myosteatosis), impaired fatty acid oxidation, mitochondrial dysfunction, and oxidative stress, leading to local muscle inflammation and reduced insulin sensitivity [43]. Thus, the inflammatory process in obesity involves AT, liver, and muscles, creating a vicious cycle of metabolic disturbances and promoting the MHO to MUO conversion (Figure 1).

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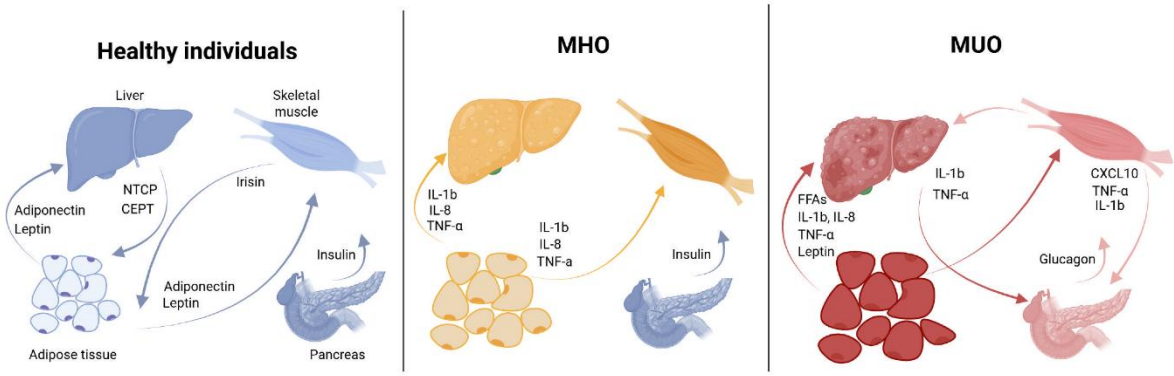

Figure 1. Obesity progression as a conversion from MHO to MUO with intensification of low-grade inflammation. The state of health is based upon balanced interactions between insulin-sensitive organs (AT, pancreas, liver, skeletal muscle) that regulate carbohydrate and lipid metabolism, as well as by an appropriate adaptive response to transient increases in nutrients. Key roles in the regulation of carbohydrate and lipid metabolism are played by AT hormones (leptin, adiponectin), pancreatic hormones (insulin, glucagon), myokines (irisin), and lipid metabolism mediators (CETP—cholesteryl ester transfer protein, NTCP—sodium-taurocholate cotransporting polypeptide). **MHO** is specified by nascent inflammation, initially triggered by AT dysfunction and the impaired regulation between insulin-sensitive organs. AT actively secretes pro-inflammatory factors (TNF-α, IL-8, IL-6, IL-1β), laying a pavement to systemic inflammation. **MUO** is characterized with a significant systemic inflammation, development of systemic insulin resistance (IR) and profound metabolic changes. Excess in TNF-α leads to impaired glucose and lipid metabolism in AT along with hepatic inflammation, fibrosis, and IR, inducing the disturbances of glycogenolysis and gluconeogenesis. IL-6 and IL-1β contribute to the progression of metabolic-associated steatohepatitis and hepatocyte necrosis. Fatty acids, released from AT, accumulate in the liver and in muscle tissue, leading to MAFLD and myosteatosis. Ectopic fat deposition in muscle impairs normal muscle function and fatty acid oxidation, leading to mitochondrial dysfunction, oxidative stress, and inflammation, thereby reducing insulin sensitivity in skeletal muscles. Under systemic inflammation normal pancreatic function is disrupted, with excess fat deposition and immune cell infiltration in pancreatic tissue, resulting in impaired beta cells insulin secretion and increased glucagon secretion by alpha cells. Created in https://BioRender.com.

Metabolic disturbances at MUO comprise IR with impaired carbohydrate metabolism in the form of prediabetes or T2DM, and as a consequence, predictably higher levels of glycaemia and glycated hemoglobin compared to patients with MHO (Tables 1 and S1) [44,45]. In addition, patients with T2DM have a higher prevalence of concomitant dyslipidemia than those without carbohydrate metabolism disorders [46]. In T2DM, dyslipidemia is characterized by low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglyceride levels, and a moderate increase in low-density lipoprotein cholesterol (LDL-C). The pathogenesis of dyslipidemia in T2DM involves increased production of very low-density lipoproteins (VLDL) in the liver, which in turn leads to elevated triglyceride levels [47]. In association with dyslipidemia accompanying MUO, patients with T2DM develop atherosclerotic vascular disease much more frequently compared to those without T2DM. Hyperglycemia leads to increased glycation and oxidation of LDL, with their deposition in the subendothelial space, oxidative stress, increased formation of advanced glycation end products (AGEs) with activation of the intracellular NF-kB signaling pathway, reduced nitric oxide (NO) production, and increased angiotensin II levels, as well as recruitment of monocytes/macrophages into the subendothelial space and their release of pro-inflammatory cytokines. This results in endothelial dysfunction and inflammation, enhanced formation of atherosclerotic plaques [48]. Some clinical, metabolic and AT differences between the MHO and MUO are summarized in Tables 1 and S1:

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Table 1. General characteristics of MHO and MUO.

MHO	MUO
Younger age [8]	Older age [8]
Normal blood pressure, moderate prevalence of atherosclerotic cardiovascular diseases and other associated conditions [8]	Arterial hypertension, high prevalence of atherosclerotic cardiovascular diseases [8]
Elevated levels of cell adhesion molecules (sICAM-1), E-selectin, P-selectin [49], initial endothelial changes [50]	Significantly increased levels of cell adhesion molecules [49], increased levels of AGEs, endothelial dysfunction [50]
Close to normal lipid profile [8], maintenance of relative balance between lipolysis and lipogenesis [7]	Dyslipidemia [8], enhanced lipolysis and release of FFAs [7]
Maintenance of relative insulin sensitivity	Insulin resistance, hyperglycemia, T2DM [8]
Preservation of main liver functions [8]	Metabolic- associated fatty liver disease (MAFLD)[8]
Predominant subcutaneous fat deposition, fat on lower extremities, gluteal region, thighs [8]	Excessive fat deposition in the liver or visceral depot [8]
Maintenance of normal muscle function [43]	Myosteatosis, muscle tissue inflammation, oxidative stress [43]
Less prominent metaflammation than in MUO (increased levels of CRP, IL-6, TNF-α), but more profound than in healthy individuals [13] Higher levels of anti-inflammatory cytokines compared to MUO (adiponectin, IL-10) [51,52]	Distinct elevation of metaflammation markers (IL-6, IL-8, TNF-α, MCP-1, CRP, leptin, resistin, PAI1) [13] [32,33]
Less prominent increase in circulating leukocytes, neutrophils, monocytes than in MUO; balance of Th1/Th2, Th17/Tregs ratios; relatively preserved pool of Tregs and Bregs [14] [53–55]	Significant increase in circulating leukocytes, neutrophils, monocytes, B-cells, CD4+ T cells; increased Th1/Th2 and Th17/Tregs ratios; decreased proportion of Tregs and Bregs [14][53–55]
Preservation of adequate adipogenesis, with hyperplasia predominating over adipocytes hypertrophy; hypoxia and adipocyte apoptosis, AT fibrosis are less prominent than in MUO [56,57] Adipocyte sizes are smaller than in MUO [58]	Significant pathological changes in AT: adipocyte hypertrophy, impaired angiogenesis, hypoxia, adipocyte apoptosis, AT fibrosis [56,57]
Pro-inflammatory cell infiltration in AT is more pronounced than in healthy individuals but less than in MUO; higher number of anti-inflammatory cells compared to MUO [58,59]	Increased secretion of pro-inflammatory cytokines in AT, marked inflammatory cell infiltration in AT [32,33] [59]

3. The Role of Low-Grade Inflammation in the Development of Obesity

Although the association between obesity and inflammation was established back in the 1990s by Gökhan S. Hotamisligil et al. [29], the exact mechanisms of their mutual influence and the subsequent aggravation are still an issue. Obesity-associated metaflammation is chronic, does not resolve within normal timeframes, and causes constant recruitment of immune cells to AT [60], involving metabolic tissues into the pathological process and leading to their dysfunction [61].

Based on the observations and clinical data mentioned above it can be noted that individuals with MHO exhibit moderate systemic and AT inflammation (ATI), which allows them to maintain

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metabolic health. In contrast, in MUO inflammation reaches higher intensity, resulting in the development of a range of metabolic disorders. In this regard, several authors have put forward the hypothesis that MHO represents an intermediate phenotype between metabolically healthy non-obese individuals and MUO (Fig 1) [3,4] [15] [32]. Notably, AT dysfunction is one of the key elements in the development of systemic chronic inflammation and metabolic disturbances. Normally, AT serves as an energy reservoir in the form of triglycerides and functions as an endocrine organ, releasing hormones and bioactive substances (adipokines) that regulate numerous physiological processes related to energy balance, glucose metabolism, and immunity [62]. Cytokines produced by adipocytes and immune cells in AT may exhibit both pro-inflammatory and anti-inflammatory properties, thereby increasing or reducing the level of IR.

The initial stage of AT metaflammation remains an issue; however, it is believed that adipocyte hypertrophy and hypoxia in VAT contribute to the increased expression of proteins like TLRs, NF-kB, HIF1α, associated with inflammation. Interestingly, with age, the AT volume increases primarily due to adipocyte hypertrophy rather than hyperplasia [63]. It is precisely hypertrophied adipocytes that are more prone to activating endoplasmic reticulum (ER) and mitochondrial stress responses, promoting the initiation of a chronic pro-inflammatory state in AT [64]. ATI is accompanied by adipocyte apoptosis, the release of chemotactic mediators, and leukocyte inflammatory infiltration of the fat. Profound changes occur in the composition of resident and migrating immune cells.

In healthy AT anti-inflammatory immune cells predominate, including M2 macrophages, invariant NKT (iNKT) cells, group 2 innate lymphoid cells (ILC2), eosinophils, regulatory T cells, and type 2 helper T lymphocytes. In individuals without excess weight and metabolic syndrome adipocytes predominantly secrete anti-inflammatory cytokines such as adiponectin, transforming growth factor beta (TGF-β), IL-10, IL-4, IL-5, IL-13, neuregulin 4, IL-1 receptor antagonist (IL-1Ra), and apelin. Thereby they maintain the homeostasis of healthy AT and prevent the accumulation and activation of pro-inflammatory immune cells [33] [65,66].In response to altered metabolism and AT stress the levels of FFAs, palmitic acid, and ceramides increase, along with neutrophils recruitment to AT [67]. Persistently maintained local inflammation leads not only to the accumulation of immune cells but also to the shift in their profile: pro-inflammatory cells begin to predominate - the proportion of mast cells, B cells, NK cells, type 1 helper T lymphocytes, cytotoxic CD8+ T cells, ILC1, and macrophages polarizing towards the M1 phenotype in the presence of NK cells increases. An increase in the level of circulating gut antigens can also contribute to the initiation and development of ATI. In individuals with obesity, and especially with MUO, AT predominantly secretes pro-inflammatory cytokines (Table 2) together with obesogenic adipokines. including leptin, visfatin, chemerin, vaspin, resistin, angiotensin II, and plasminogen activator inhibitor-1 [68]. Conversely, levels of anti-inflammatory IL-4, IL-5, IL-10, IL-13, adiponectin, and omentin are reduced in MUO [15] [62].

Table 2. Pro-inflammatory factors in the peripheral blood of healthy individuals and patients with MHO and MUO.

Parameters	Healthy Individuals	MHO	MUO	References
Free fatty acids, mmol/L, mean±SD	0.22 ± 0.21	0.49 ± 0.19 (* for MHO and healthy)	0.55 ± 0.27, (* for MUO and healthy; MUO and MHO)	[49]
AGEs, AU, mean±SD	1.81 ± 0.22	1.86 ± 0.51	2.44 ± 0.67, (** for MUO and healthy; MUO and MHO)	[69]
CRP, mg/L, mean±SD	3.0 ± 5.2	5.7 ± 6.7	6.0 ± 6.5, (** for all groups.)	[12]
IL-6, pg/mL, mean±SD	1.3 ± 1.1	1.8 ± 1.1	1.9 ± 1.3, (** for all groups)	[12]

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TNF-α, pg/mL, mean (95% CI)	10.70 (9.76–11.64)	11.41 (9.85–12.96)	11.43 (8.73–14.14)	[51]
IFN-γ, pg/mL, mean±SEM	402.4 ± 14.3	446.1 ± 17.8	434.6 ± 20.3, NS for all groups	[70]
IL-8, pg/mL, mean (95% CI)	26.17 (24.48–27.87)	27.84 (24.37–31.30)	28.42 (23.94–32.89)	[51]
IL-1β, pg/mL, mean (95% CI)	10.09 (8.48–11.70)	10.30 (8.79–11.81)	10.11 (7.79–12.44)	[51]
IL-17a, pg/mL, median [IQR]	–	≈ 150 [50–300]	≈ 450 [200–1000] (**)	[71]
IL-21, pg/mL, median [IQR]	–	≈ 5 [2.5–15]	≈ 15 [7.5–30] (#)	[71]
IL-10, pg/mL, mean (95% CI)	10.01 (8.90–11.12)	10.41 (9.11–11.71)	10.10 (8.02–12.18)	[51]
C3, mg/dL, mean±SEM	126.66 ± 20.88	140.45 ± 21.06	148.2 ± 23.98, (*** for all groups)	[72] [73]
PAI-1, ng/mL, mean±SEM	24.58 ± 10.73	24.79 ± 9.75	30.53 ± 12.34, (*** for MHO vs MUO and for MHO vs healthy)	[72] [73]
MCP-1, pg/mL, mean±SD	324.7 ± 221.7	359.9 ± 210.1	346.1 ± 213.9, NS for all groups	[74]
Leptin, pg/mL, mean±SD	12 ± 12	43 ± 12, (* MHO vs healthy)	41 ± 9, (* MUO vs healthy)	[49]
Adiponectin, μg/mL, mean±SD	12.1 ± 7.2	3.1 ± 1.5, (* MHO vs healthy)	2.7 ± 1.9, (* MUO vs healthy and MHO)	[49]
Vaspin, ng/mL, mean±SD	–	2.07 ± 3.2	2.14 ± 2.2, NS	[75]
Resistin, ng/mL, mean±SEM	5.56 ± 3.90	5.63 ± 2.71	6.09 ± 2.74, (## for MUO vs MHO and for MHO vs healthy)	[72]
Visfatin, ng/mL (Me [IQR])	14,961.90 [12,397.98–20,576.90]	14,809.15 [13,715.20–19,280.44]	15,319.60 [12,696.9–17,003.08, NS for all groups.	[76]
Adipsin, mg/L (Me [IQR])	1.37 [0.92–1.96]	0.98 [0.81–1.24]	1.03 [0.85–1.51], # for all groups.	[76]
Fetuin-a, μg/mL, mean±SD	–	327 ± 74	377 ± 59, (##)	[75]
Chemerin, ng/mL, mean±SD	–	194 ± 33	236 ± 35, (**)	[75]
Myeloperoxidase of neutrophils, ng/mL, mean±SD	17.3 ± 5.5	27.1 ± 10.8 (**)	–	[77]
CD66b expression (MFI, arbitrary units, mean±SD)	129.7 ± 9.2	177.3 ± 43.7 (**)	–	[77]

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Retinol-binding protein-4, μg/mL, mean±SD	–	42.7 ± 23	88.6 ± 32, (**)	[75]
sICAM-1, ng/mL, mean±SD	267.8 ± 73.4	273.1 ± 78.6, (NS for MHO vs healthy)	298.7 ± 86.2, (** for MUO vs healthy)	[12]
sE-selectin, ng/mL, mean±SD	51.2 ± 23.2	56.0 ± 22.9, (NS for MHO vs healthy)	64.0 ± 29.9, (** MUO vs healthy)	[12]
Fibrinogen, mg/dL (Me [IQR])	248.00 [220.00–297.00]	256.00 [234.00–278.50]	303.00 [260.25–334.00], (* for all groups)	[76]
Calprotectin, ng/mL, mean±SD	65.1 ± 23.1	115.5 ± 43.5 (**)	–	[77]

Abundant pro-inflammatory mediators and the increasing number of migrating pro-inflammatory immune cells within AT contribute to its further dysfunction and damage. This leads to the emergence of additional so-called second order pro-inflammatory molecules, most of which are associated with damage-associated molecular patterns (DAMPs) and are frequently observed in MUO—such as succinate [78], N-formyl peptides [79], AGEs, cholesterol crystals, islet amyloid peptide [80], and reactive oxygen species (ROS). Monocytes / macrophages, key mediators of inflammation, are capable of recognizing more than 1,000 DAMP patterns [81]. Patients with MUO exhibit more pronounced infiltration of AT by macrophages and other immune cells, as well as a higher density of crown-like structures [82]—apoptotic adipocytes surrounded by macrophages, which serve as markers of ATI and dysfunction [83]. Prolonged stimulation by obesogenic antigens leads to the appearance of memory cells in inflamed tissues and alters their epigenetic profile. Senescent cells, particularly among T cells, emerge, producing a distinctive pro-inflammatory profile, known as the senescence-associated secretory phenotype (SASP). This includes IL-6, IL-1β, MCP-1, PAI-1, IL-8, insulin-like growth factor binding protein 3 (IGFBP3), high-mobility group protein B1 (HMGB1), and ROS. Several of these mediators are also associated with MUO—HMGB1 [84], IGFBP3 [85], and PAI-1 [72]. Subsequent AT dysfunction including destabilization of angiogenesis, remodeling impairment and adipogenesis attenuation ultimately lead to both local and systemic IR [63] [86].

Pro-inflammatory adipokines modulate IR of adipocytes either directly, by affecting the insulin signaling pathway, or indirectly, through stimulation of other inflammatory pathways. The phosphorylation of serine residues in the insulin receptor substrate (IRS) molecule by various adipokines, either directly or via inflammatory pathways including the c-Jun N-terminal kinase (JNK) pathway and the NF-κB pathway, impairs signal transduction from the insulin receptor, leading to local IR [62]. A possible mechanism underlying the development of inflammation and AT dysfunction during the conversion of MHO into MUO is illustrated in Figure 2.

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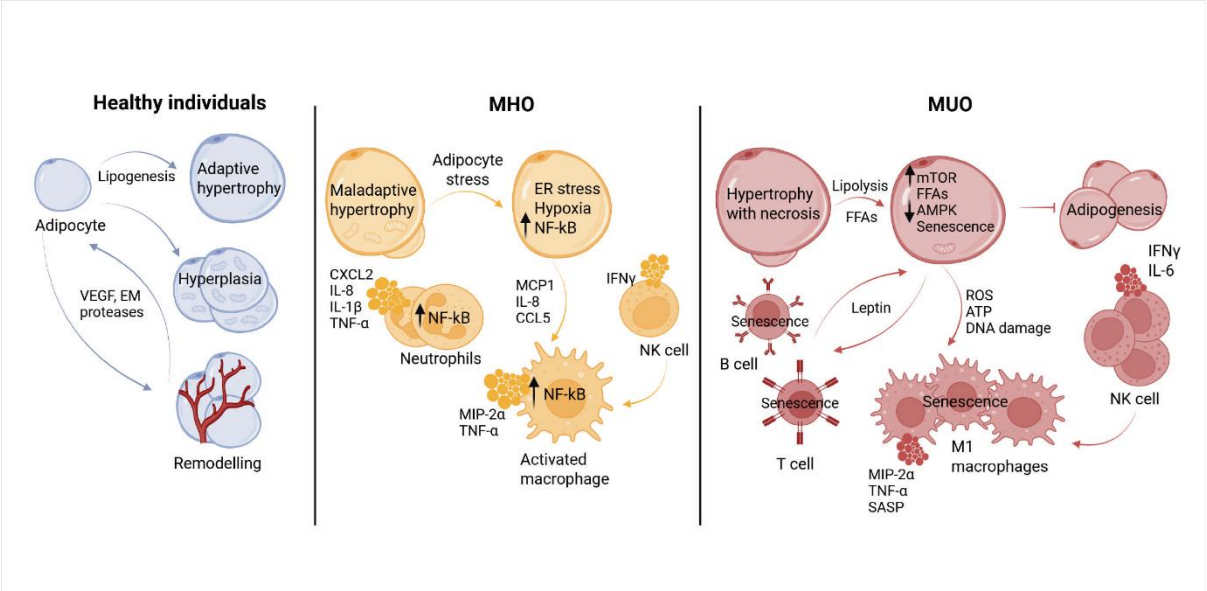

Figure 2. The model of inflammation progression in AT during the conversion from MHO to MUO. Normally, short-term nutrient excess elicits a physiologically adaptive response, aimed at removing lipid overload and excessive glucose from the bloodstream to maintain metabolic homeostasis. This involves moderate adipocyte hypertrophy, preadipocyte differentiation, and AT remodeling. The **MHO** stage is characterized by the activation of the NF-κB pathway in hypertrophic adipocytes due to hypoxia and endoplasmic reticulum stress, leading to the secretion of pro-inflammatory mediators (IL-6, IL-8, CCL5, PAI-1), which attract neutrophils and other blood leukocytes to AT. The immune cell profile shifts from anti-inflammatory to pro-inflammatory Th1/M1 type. Leptin, which increases with the progression of obesity, stimulates lipolysis and activates its own receptors on immune cells, promoting their activation and metabolic reprogramming. Expression of MHC II and production of co-stimulatory molecules in adipocytes further activate T cells. The increased concentration of FFAs due to lipolysis, in turn, reactivates macrophages, neutrophils, and adipocytes. The **MUO** stage is typified by an exacerbation of inflammation, as well as functional and structural changes in tissues. In response to DNA damage, mitochondrial dysfunction and ROS generation, AT secretes additional immunostimulatory mediators associated with further tissue damage (multiple DAMPs, stress proteins, HMGB1, DNA, mitochondrial components). Cells with a senescent phenotype (macrophages, endothelial cells, preadipocytes and mature adipocytes, T cells) increasingly accumulate in AT. Abbreviations: VEGF – vascular endothelial growth factor; ECM – extracellular matrix; FFAs – free fatty acids; ER – endoplasmic reticulum; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; MCP-1 – monocyte chemoattractant protein 1; CCL5 – chemokine (CC motif) ligand 5; PAI-1 – plasminogen activator inhibitor-1; HMGB1 – high-mobility group protein B1; ROS – reactive oxygen species; MHC II – major histocompatibility complex class II; mTOR – mechanistic target of rapamycin; AMPK – AMP-activated protein kinase; ATP – adenosine triphosphate; IL – interleukin; DAMPs – danger associated molecular patterns. Created in https://BioRender.com.

Thereafter, dysfunctional AT plays a primary and central role in the initiation and progression of subsequent systemic inflammation. Pro-inflammatory mediators released by AT into the circulation enhance hematopoiesis (both lymphopoiesis and myelopoiesis), attracting increasing numbers of various leukocyte types into the bloodstream and into adipose and other tissues, thereby promoting a wider spread inflammation [87]. Patients with MHO exhibit an intermediate phenotype, characterized by a balance between pro- and anti-inflammatory mediators [52]. Metaflammation accompanying obesity begins to spread beyond AT developing in other organs (liver, muscles, pancreas) involving not only recruited and activated immune cells but also myokines (in muscles) and hepatokines (in the liver). Visceral fat releases a large amount of pro-inflammatory cytokines and FFAs in MUO. The release of FFAs into the bloodstream causes hepatocyte injury and stimulates the synthesis of pro-inflammatory cytokines. IL-17 promotes cytokine production by adipocytes and macrophages, contributing to the development of MAFLD, including steatohepatitis, impaired liver

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function, and hepatocyte death. As in AT, macrophages accumulating in the liver in obesity are characterized by an M1 phenotype. Excessive triglyceride accumulation and hepatic inflammation are accompanied by increasing hepatic IR [88].

Recent studies also demonstrate the presence of obesity-related inflammation in the central nervous system and gastrointestinal tract [89]. It is important to note that prolonged exposure to pro-inflammatory stimulation underlying obesity and metaflammation induces epigenetic changes and functional exhaustion of cells. This functional exhaustion exacerbates the severity of inflammation in all metabolically active tissues and leads to dysfunction of both mature and progenitor cells [90].

4. Differences in the Levels of Circulating Pro-Inflammatory Factors Between Metabolic Healthy and Unhealthy Obesity

Progression from MHO to MUO is accompanied by increasing level of circulating pro-inflammatory factors (IL-6, IL-8, IL-17, IL-21, IFN-γ, TNF-α, MCP-1, CRP, FFAs, advanced glycation end- products (AGEs), cell adhesion molecules, leptin, chemerin, resistin, etc.) together with a reduction in the level of anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13) and adipokines (adiponectin, omentin) (Table 2). In MUO, insulin-resistant AT is characterized by a predominance of lipolysis, leading to elevated FFAs plasma level, which is associated with IR and beta-cell dysfunction [91,92]. Consequently, T2DM is often accompanied by increased plasma FFAs [93,94].

In recent years, AGEs and their role in the pathogenesis of chronic inflammation and metabolic complications in obesity have been actively studied. Advanced glycation end-products constitute a non-homogenous, chemically diverse group of compounds formed either endogenously, especially in the context of pre-existing metabolic disorders, or exogenously, particularly with sugar-sweetened beverages/foods, through smoking, etc. Metabolic syndrome, including obesity, hyperlipidemia, and hyperglycemia, can be accompanied by enhanced AGEs production via the non-enzymatic Maillard reaction between reducing sugars (glucose, fructose, galactose, ribose, or deoxyribose) and various molecules (proteins, lipoproteins, lipids, or DNA). Upon binding to their receptors (RAGE), various AGE products can induce inflammation, IR, T2DM, and diabetic complications [95].

A distinct role in endothelial dysfunction and in the development of micro- and macrovascular complications in MUO with T2DM is attributed to cell adhesion molecules. These molecules are upregulated under conditions of chronic hyperglycemia and oxidative stress and facilitate the transmigration of leukocytes into tissues, promoting chronic inflammation, endothelial dysfunction, and micro- and macrovascular complications in T2DM. The main cell adhesion molecules involved in the development of microvascular complications are vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectins (E-selectin, L-selectin, and P-selectin). Research data indicate that levels of cell adhesion molecules are elevated in patients with T2DM [96].

Thus, the changes observed in MUO are characterized by chronic hyperglycemia, pronounced dyslipidemia, proatherogenic status, endothelial dysfunction, enhanced formation of AGEs and elevation of lipolytic activity accompanied by the release of FFAs.

5. Differences in the Number and Activity of Circulating Leukocytes and Their Subpopulations

Inflammation is mediated through the activities of numerous immunocompetent cells, whose coordinated action is crucial for its resolution. Since the cytokines and various inflammatory mediators described above are produced predominantly by immune cells circulating in the blood and infiltrating AT and other tissues, a more detailed characteristics of these cells and an assessment of their role in maintaining systemic inflammation is warranted.

Circulating **leukocytes** represent a heterogeneous group of cells that participate not only in the defence against foreign agents but also in the elimination of aberrantly functioning cells (due to stress or tumor transformation), and their degradation products. As a component of the immune system and the primary source of immune cells infiltrating AT during obesity, blood leukocytes and their

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subpopulations could potentially serve as biomarkers of subclinical inflammation and predictors of morbid obesity [54][97]. Indeed, there are studies that report a trend towards an increase in the total leukocyte counts in obesity and metabolic disorders [98–100]. However, the absolute count of all leukocytes or their major subsets (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and their main subtypes—T, B, and NK lymphocytes) lacks clinical significance to reveal patients with the risk of conversion from MHO to MUO [97]. The range of leukocyte counts, both total and for their individual subpopulations, often falls within normal reference interval, and is characterized by high variability with overlapping values between comparison groups. This complicates the determination of clinically meaningful cut-off values (Table 3). The clinical utility of circulating leukocytes counts (and their major subtypes) is limited, likely because most studies are cross-sectional and do not assess this parameter dynamically. In contrast, longitudinal studies indicate that a baseline leukocyte count of 6.5–6.9 × 10^9 cells/L may serve as an independent predictor of diabetes development, even in non-obese patients [54] [98] [101].

Table 3. Circulating immune cells in healthy Individuals, MHO, and MUO.

Cell Type	Healthy Individuals	MHO	MUO	References
Leukocytes, ×10^3/mm^3, mean±SD	8107 ± 2022	7877 ± 1993 – non-progressors	8555 ± 1780, progressors, (** for MUO vs MHO)	[14]
	6060 ± 1940	6040 ± 1660	6580 ± 2130, (** for all gr.)	[100]
	6750 ± 1800		7270 ± 2010, (**)	[54]
			>6910 – independent risk factor for T2DM	[101]
Monocytes, ×10^3/mm^3, mean±SD	440 ± 250	478 ± 235	352 ± 290, (* for MHO vs MUO)	[14]
	520 ± 160		560 ± 220, (**)	[54]
CD11b+ activated monocytes, rMFI (arbitrary units, mean ± SE)	11.2 ± 2.0		42.6 ± 9.4, (# for MUO+MHO vs healthy)	[53]
Neutrophils, ×10^3/mm^3, mean±SD	4977 ± 1760	4900 ± 1727 – non-progressors	5110 ± 1655, progressors, (NS for MHO and MUO)	[14]
		4000 ± 1440	4350 ± 1580, (**)	[54]
Neutrophil/Lymphocyte ratio, median (min, max)	1.21 (0.52, 2.09)	1.33 (0.53, 2.23) (#)		[102]
Neutrophil/Lymphocyte ratio, mean±SD	1.82 ± 1.02	3.67 ± 0.95 (** for MHO+MUO vs healthy)		[103]
Eosinophils, ×10^3/mm^3, mean±SD	196 ± 157	189 ± 155 – non-progressors	225 ± 204 – progressors, (NS MHO and MUO)	[14]
Basophils, ×10^3/mm^3, mean±SD	40 ± 52	47 ± 6 – non-progressors	47 ± 13 – progressors, (NS	[14]

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			for MHO and MUO)	
Lymphocytes, ×10³/mm³, mean±SD	2441 ± 78	2373 ± 696 – non-progressors	2576 ± 813 – progressors, (NS for MHO and MUO)	[14]
NK cells, ×10³/mm³, Me [IQR]	100 [80–150]	140 [100–190], (metabolic status not specified), #		[104]
NK cells, % of lymphocytes, mean ± SEM	12.3 (SEM not specified) (# for healthy versus MHO+MUO group)	11.7 ± 0.9	6.5 ± 3.1, (*** for MUO and MHO)	[105]
NK cells, % of lymphocytes, mean (range)	16.6 (7.6–28.6)		7.6 (2.2–19.0), * (but with BMI > 40 kg/m²)	[106]
Natural killer T cells (CD3+, CD56+; % of PBMCs), mean ± SEM	3.9 ± 0.9	3.8 ± 1.1, NS (metabolic status not specified)		[107]
B cells, ×10³/mm³, mean±SD	260 ± 140		310 ± 170, (** for healthy vs MUO)	[108]
Transitional CD19+CD27+CD38^{high} B cells, % of mononuclear cells, mean ± SD	2.4 ± 0.6	0.7 ± 0.2, (# (metabolic status not specified)		[109]
CD19+CD24^{high}CD38^{high}IL-10+ Bregs, % of mononuclear cells, mean±SD	6.0 ± 0.9	3.9 ± 1.4, NS (metabolic status not specified)		[109]
CD8 cells, % of lymphocytes, mean (SE)	19.9 (SE not specified), (* for healthy vs MHO+MUO)	13.4 (SE <1.1)	9.3 (SE < 1.4), (# for MHO and MUO)	[105]
Th1/Th2 ratio, mean±SE	1.0 ± 0.2		2.3 ± 0.5 (# for MHO+MUO vs healthy)	[53]
Th1 % of CD4+ lymphocytes, mean±SE	~ 2.4 ± 0.8		~ 4.7 ± 1.4 (NS for MHO+MUO vs healthy)	[53]
Th2 % of CD4+ lymphocytes, mean ± SE	~ 4.0 ± 1.3	~ 2.0 ± 0.4 (NS for MHO+MUO vs healthy)		[53]
Th17 % of CD3+CD4+ lymphocytes, median [Q1; Q3]	0.041 [0.023; 0.099]	0.097 [0.044; 0.289], (# metabolic status not specified)	–	[110]
Treg % of CD4+ lymphocytes, Me [IQR]	1.2 [0.67–2.01]	0.73 [0.32–1.11] (# for MHO+MUO vs healthy)		[55]

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CD4+FOXP3^{high}CD45RA- % of CD4+ lymphocytes, mean±SEM	~ 1.3 ± 0.14	~ 0.9 ± 0.07, (# metabolic status not specified)	[111]

In a large cohort (24,897 individuals from the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort), divided into five groups by white blood cell count and followed for an average of 7.5 years, a direct correlation was found between new cases of T2DM and the baseline leukocyte count, independent of other factors (age, heredity, physical activity, and even obesity (BMI). Adjusting for obesity significantly reduced the predictive power of the total leukocyte count in the model but still retained it as a significant factor [101]. Patients with obesity and elevated white blood cell count (>6.5 × 10^9 cells/L) are at higher risk of developing T2DM [98]. Another study also found that an elevated baseline leukocyte count correlated with the development of T2DM and insulin action worsening [14].

Monocytes play an important role in the pathogenesis of obesity, which is often associated with an increase in their number in the circulation [97][112,113]. Moreover, after the discovery of monocyte and macrophage infiltration into AT of mice and humans circulating monocytes attract considerable attention [114,115]. Monocytes are known to play a key role in the pathogenesis of atherosclerosis, a complication of obesity [116,117]. Activation of myelopoiesis, and monopoiesis in particular, has been reported in animals and humans on a high-calorie diet [118,119]. However, data on changes in the number of circulating monocytes in different obesity phenotypes are conflicting. Higher blood monocyte levels (on average 13–18% higher) have been recorded in overweight and obese individuals compared to those without excess weight, and correlated with higher BMI values and metabolic syndrome [97] [112,113] [120]. Nevertheless, other studies have not found such a correlation [121,122]. No consistent patterns of change in the number of classical CD14+CD16- monocytes, which constitute the majority of monocytes and reflect changes in their total population, were found either [97] [121]. On the other hand, a higher frequency of circulating CD16+ monocytes in obesity and their correlation with BMI and waist circumference have been reported [112] [120]. Notably, correlations have been observed between systemic inflammation (the number of CD16+ monocytes) and inflammation in SAT (the number of CD68+ macrophages) [123], as well as between an increase in circulating non-classical monocytes (CD14+CD16++) and lipid accumulation in VAT macrophages [124] in obese patients compared to healthy controls. However, it is unlikely that specific circulating monocyte subpopulations could be direct precursors to specific macrophage subpopulations in inflamed AT [97] [124]. It is possible that activation status of monocytes more accurately captures the alterations associated with metabolic dysregulation in obesity. Indeed, increased expression of the integrin molecule CD11b is observed in obesity, and it correlates with IR, Table 3 [53].

Neutrophils are the most abundant group of blood leukocytes. They play a crucial role in the early stages of inflammatory responses and represent the primary line of defence during inflammation. As cells with cytotoxic functions, they are the first to migrate to the site of inflammation, preceding the arrival of monocytes/macrophages, dendritic cells, and various types of lymphocytes [67]. Neutrophils exert their effector functions through (i) oxidative burst and release of lytic enzymes (myeloperoxidase and elastase); (ii) phagocytosis and production of pro-inflammatory cytokines; and (iii) formation of neutrophil extracellular traps (NETs), thereby eliminating the source of inflammation and subsequently undergoing apoptosis. Notably, obesity-associated inflammation is also accompanied by an increase in circulating neutrophils [97] [125]. A correlation is reported between neutrophil levels and waist circumference as well as BMI. Overweight patients with neutrophilia demonstrated elevated CRP levels [99]. In the large PREDIMED study, higher baseline neutrophil levels or an increase in neutrophil count over more than 3.5 years of follow-up were independently associated with an approximately 30% increased risk of developing MUO among individuals aged 55 years and older without cardiovascular disease [113]. In addition, neutrophils in MUO are characterized by an activated phenotype, with elevated levels of myeloperoxidase and calprotectin and increased expression of CD66b, a marker of neutrophil degranulation [77].

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The neutrophil-to-lymphocyte ratio (NLR), a well-known marker of systemic inflammation, may serve as an early indicator and predictor of clinical complications in T2DM, such as nephropathy, retinopathy and macular oedema, ketoacidosis, and diabetic foot syndrome [126]. Moreover, an elevated NLR can reveal ongoing subclinical inflammation in MHO [102,127], while a high NLR is a statistically robust and independent predictor of T2DM in MUO [103].

Eosinophils, known for their role in regulating allergic reactions and responses to parasitic infections, can infiltrate specific tissues where they play an additional role in regulating local immunity and/or tissue remodeling and repair [128]. The protective role attributed to eosinophils in obesity appears to be played by AT eosinophils rather than circulating eosinophils [129]. Data on changes and the function of circulating eosinophils are scarce and contradictory. Some studies have reported increased absolute and relative eosinophil counts, an association between obesity and eosinophilia, and a positive correlation between eosinophil count, BMI, and metabolic syndrome [130]. Other studies have not found changes in eosinophil levels [131]. One study notes an overall positive correlation between eosinophil count and BMI, but after eosinophils exceed 200 cells/μL, this correlation becomes negative [132].

Although **T lymphocytes** are not critical drivers of metaflammation, they can significantly modulate it [133]. Various T cell subpopulations release cytokines, sustaining inflammation in both MHO and MUO. Moreover, T cells, both in the periphery and locally in AT, may indicate changes in metabolic status from prediabetes to T2DM [134]. Some studies have found that the total number of T cells increased by 15–50% in individuals with obesity compared to those without excess weight [135], and this increase was associated with specific components of metabolic syndrome (higher triglyceride levels, lower HDL cholesterol) [108].

Analysis of lymphocyte subpopulations is sometimes contradictory. Regarding **CD4+ T cells**, most researchers report elevated levels in both MUO [135] and MHO [136] compared to non-obese individuals. CD4+ T cells are coordinators of the immune response. Depending on the antigen, dose and duration of stimulation, on the co-stimulatory chemokines/cytokines in the microenvironment, and on interactions with other cells, CD4+ T lymphocytes differentiate into several main subtypes (Th1, Th2, Th9, Th17, Th22, follicular T cells, and various subsets of FoxP3+ regulatory T (Treg) lymphocytes), directing the immune response according to distinct cytokine secretion profiles [137]. Th1 lymphocytes produce IFN-γ and IL-2, with their differentiation driven by IL-12 [138]. Th2 lymphocytes are associated with the humoral immune response and secrete anti-inflammatory cytokines IL-4, IL-5, IL-9, and IL-13, stimulating the activation of eosinophils and M2 macrophages [139]. Th17 cells are characterized by secretion of IL-17, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF), whereas regulatory T cells produce IL-10 and TGF-β.

Several studies demonstrate that the number of Th1 cells in peripheral blood do not differ between individuals with obesity and those without [135]. However, other authors report that the percentage of Th1 cells does increase in patients with obesity and correlates with the degree of IR [53]. Interestingly, the number of circulating Th2 cells, which have an anti-inflammatory profile, also increases in individuals with pathological obesity and correlates with BMI [135]. Nevertheless, the Th1/Th2 ratio remains higher in MUO compared to MHO and non-obese individuals [53]. In individuals with obesity and T2DM, elevated levels of circulating Th1 and Th17 lymphocytes positively correlate with the IR, leptin and insulin levels, and negatively with HDL cholesterol [140]. In addition to changes in the number of Th subtypes and their ratios, Th cell functional activity is enhanced. This is manifested by increased cytokine production and a shift towards a pro-inflammatory profile, even in MHO [13] [133] [107]. Increased Th1 and Th2 cytokines in obesity are often a marker of prediabetes [134]. The production of pro-inflammatory cytokines by CD4+ T cells is higher in MUO compared to MHO [71]. MHO is characterized by the presence of Th2 cytokines IL-10, IL-13, and IL-4. In contrast, MUO with T2DM is characterized not only by Th1 cytokines IL-2 and IL-12p70, but also by Th17 cytokines IL-17A, IL-17F, IL-21, IL-22, MIP3α/CCL20, and GM-CSF, the majority of which are produced by Th17 cells [71]. In obesity, Th17 cells make a particular contribution to

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inflammation and hyperglycemia. IL-17 may play an important role in recruiting neutrophils and macrophages.

Obesity, as a chronic inflammatory disease, is closely linked to immunosenescence [141]. In the study by Sbierski-Kind et al., MHO with an insulin-sensitive phenotype was associated with a higher proportion of naïve CD4+ and CD8+ T cells, while MUO with an insulin-resistant phenotype positively correlated with the frequency of CD45RA-CD27-CD28- effector and CD57+ senescent CD8+ memory T cells [142]. Increased levels of senescent CD4+ and CD8+ T cells with the CD45RA+CCR7- and CD45RA+CD28-CD27-CCR7-KLRG1^{high} phenotype have also been observed in T2DM [143,144].

Regulatory FoxP3+ T cells **(Tregs)** are a subset of T helper cells whose unique role is to maintain immune tolerance and suppress the activation, proliferation, and effector responses of innate and adaptive immune cells. In contrast to Th1, Th17, Th2, and Th9 (effector) cells, which promote systemic and local inflammation in AT during obesity, Tregs counteract the development of inflammation [134]. Patients with obesity show an inverse correlation between BMI and the proportion of circulating Tregs [145]. It has been reported that the percentage of circulating Treg cells among total CD4+ T cells is lower in individuals with obesity compared to those without excess weight [55], being lower in MUO than in MHO. According to some studies, the percentage of Tregs may be an indicator of metabolic health: a lower number of Treg cells is associated with higher leptin and HbA1c levels, i.e., with MUO [55].

FoxP3+ Tregs represent a highly heterogeneous group of cells. Primarily, they are categorized into two main groups based on their origin: natural Tregs (nTregs) that develop in the thymus, and induced Tregs (iTregs), which arise in the periphery under the special microenvironment [146]. Naïve CD4+ T cells can differentiate into FoxP3+ iTregs, particularly in the presence of TGF-β and low-dose antigenic stimulation. Interestingly, under certain conditions, many differentiated Th cells demonstrate a high degree of plasticity, changing their phenotype and function. The conversion of Tregs into Th1-like cells has been described; these cells co-express the transcription factors FoxP3 and Tbet and secrete IFNγ. The emergence of such Th1-like Tregs has been observed in some autoimmune diseases, including type 1 diabetes [147]. Furthermore, the plasticity between Tregs and Th17 cells is also well recognized and characterized by reciprocal relationships. Under certain conditions, in the presence of IL-1β or under the influence of microbial stimulation of TLR2 or epigenetic modifications, FoxP3+ Treg cells can differentiate into Th17-like Tregs expressing IL-17 [148]. The balance between pro-inflammatory Th17 and anti-inflammatory Tregs is critical for maintaining immune homeostasis, as it determines whether the immune response develops towards immunosuppression or inflammation. Numerous endogenous microenvironmental factors, including cytokines and metabolic factors, regulate the differentiation of Th17 and Tregs arising from naïve CD4+ T cells [149].Thus, TGF-β, which is important for the differentiation of both Th17 and Tregs, in the presence of pro-inflammatory cytokines (IL-6, IL-1β), directs the differentiation of iTregs towards Th17 lineage. Cell activation accompanied by metabolic reprogramming can also influence differentiation. Chronic excess of glucose and lipids directly impacts the activation of Th17 and Tregs, modulating the activity of energy sensors, influencing cellular metabolism. Specifically, Th17 cell function depends on glycolysis, fatty acid synthesis (FAS), and glutaminolysis, whereas Tregs rely on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) [149]. Activation of the mammalian target of rapamycin (mTOR), a key regulator of cellular metabolism, is necessary for the differentiation of effector T cells, particularly Th17. mTOR is activated in response to PI3K/Akt pathway activation following the activation of naïve T cells after TCR stimulation and the receipt of a co-stimulatory signal. mTOR stimulates hypoxia inducible factor 1α (HIF1α), which regulates the transcription of many glycolytic enzymes. HIF1α is required for Th17 T cell differentiation and inhibits Tregs [150]. Inhibition of mTOR by rapamycin shifts Th cell differentiation towards Tregs. A high-calorie diet promotes differentiation of the Th17 phenotype via activation of FAS *de novo*, mediated by acetyl-CoA carboxylase 1 (ACC1). This leads to increased expression of IL-17A, IL-23R, leukotriene B4 receptor (LTB4R), and CCR6. AMPK, an energy deficiency sensor activated by an increased AMP/ATP ratio, inhibits mTOR activity and promotes FoxP3-induced OXPHOS and FAO, enabling

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cells to produce ATP and generate energy. AMPK is particularly active in Tregs, and its activation leads to the differentiation of naïve T cells into Tregs rather than Th17, enhancing FAO. Notably, metformin, an indirect activator of AMPK, suppresses T cell proliferation and inhibits Th17 differentiation, thereby promoting Tregs [151]. Thus, the balance between pro-inflammatory Th17 and anti-inflammatory Tregs may play a critical role in the development of obesity and the transition from MHO to MUO.

The data on **cytotoxic CD8+ T cells are** contradictory, but most studies report a decrease in the absolute and/or relative content of CD8+ T cells in obesity, especially in MUO [97] [105]. But among CD8+ T cells an increase in the number of effector memory CD8+ T cells was observed in children with MUO [152].

B cells also contribute to the development of metabolic dysfunction. Through their ability to (1) produce antibodies, (2) present antigens and regulate T cell responses, and (3) secrete cytokines, B cells can control obesity-associated inflammation by modulating cytokine production by T cells [153]. Improvement of metabolic disease following B cell depletion in animal models suggests that B cells may play a pathogenic role [154]. According to research data, the number of B lymphocytes in the blood is increased in individuals with obesity compared to those with normal weight [97]. Moreover, MHO may be associated with elevated levels of circulating B lymphocytes. An increased proportion of circulating B cells (above 14.95%) was found to be an independent predictor and correlated with the risk of developing T2DM [155].

Obesity is also accompanied by changes in the B cell subpopulations. Normally, B cells consist of naïve IgD+CD27- B cells, memory B cells with switched (IgD-CD27+) and unswitched (IgD+CD27+) antibody classes, and a small proportion of double-negative IgD-CD27- (DN) B cells. In obesity, the proportion of switched IgD-CD27+ memory B cells decreases, while the frequency of DN B cells increases. These DN B cells, also known as late memory B cells, rendered as an inflammatory B cell subpopulation [156]. Notably, circulating B cells isolated from individuals with obesity secrete elevated levels of IgG reactive to self-protein lysates from SAT [157]. These B cells, which secrete antibodies against self-antigens, are characterized by CD95+CD21-CD11c+ phenotype and expression of the transcription factor T-bet [158]. Furthermore, the balance of pro- and anti-inflammatory B cell subpopulations in individuals with obesity is shifted towards a reduction in anti-inflammatory regulatory CD19+CD24^{high}CD38^{high} B cells (Bregs), which secrete IL-10 (in both MUO and MHO) [109,159]. Obesity is also associated with a decrease in the peripheral transitional CD19+CD27+CD38^{high} B cells [109], among which IL-10-secreting and CD1d-expressing Bregs may constitute a significant fraction. B cells isolated from the blood of individuals with obesity secrete IL-6 and TNF-α more actively, and IL-10 less actively, after in vitro stimulation [158].

The pro- and anti-inflammatory subpopulation balance of B cells may be regulated by an individual's metabolic status - in particular, through interaction with leptin. Leptin, which is present in excess in obesity and for which B cells express receptors (long isoform of leptin receptor-Ob-Rb), activates mTORC1 and initiates protein synthesis, ribosome biogenesis, and inhibits autophagy. Activation of this pathway in immune cells is generally associated with pro-inflammatory function [160].

Chronic obesity-associated inflammation leads to an imbalance in the structure of all lymphocytes, including B lymphocytes and results in a weaker immune response to infections, vaccination, or tumors. Normally, B cell response develops through early extrafollicular activity, subsequent induction of a response in germinal centers (GC), and culminates in final production of high-affinity and long-lived antibodies, and the formation of memory B cells. In obesity, B cell activation occurs mainly extrafollicularly, reducing the availability of precursors for GC induction. This not only enhances the production of autoantibodies by IgD-CD27- DN B cells but also leads to a reduction in GC-derived plasma cells and memory cells capable of producing high-affinity neutralizing antibodies [159]. As a consequence, this provokes a severe course of infectious disease in MUO due to the uncontrolled extrafollicular activity and formation of low-affinity antibodies with reduced neutralizing activity and a narrow range of epitopes against foreign antigens. Additionally

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it is exacerbated by a reduced proportion of Bregs and IL-10-secreting transitional B cells, concomitant with the expansion of IL-6- and TNF-α-producing B cells.

NK cells attract particular attention in obesity studies due to their involvement in the innate immune response to infections and malignancies, the incidence of which increases with the severity of obesity and its morbid phenotype [161]. In addition, NK cells are an important link between obesity-associated metabolic stress and inflammation in VAT [162]. The previous studies demonstrate a complex and contradictory picture regarding changes in circulating NK cells and their functional activity in obesity, with the prevailing concept of a reduction in NK cell count in MUO and no changes in MHO [97][105] [106]. According to Lydia A. Lynch et al., patients with obesity often have fewer circulating NK cells compared to healthy individuals without excess weight. When comparing MHO and MUO, the latter had almost 50% fewer circulating CD56+ NK cells [105]. At the same time, in children with obesity and hepatic steatosis, the absolute number of circulating NK cells was 66% higher compared to children with obesity without steatosis [97]. A number of studies report no differences between healthy and overweight individuals [161][163,164]. Among the general NK cell population, some researchers demonstrate a decrease in $CD56^{dim}CD16^{bright}$ and an increase in $CD56^{bright}CD16^{dim/neg}$ NK cell subpopulations in obesity [107]. This could be caused by the activation of NK cells by obesity-associated metabolic products and conversion of the $CD56^{dim}CD16^{bright}$ subpopulation to the $CD56^{bright}CD16^{dim/neg}$ phenotype [161]. Metabolic changes in obesity also affect the functional properties of NK cells, but the data are conflicting. Both increased activation (increased expression of CD69, NKp46 [165]) and decreased activation of NK cells (reduced proportion of CD69, NKp46, and NKG2D-positive cells [107][165]) have been reported in obesity. There are frequent reports on reduced secretion of granzyme B, perforin and macrophage inflammatory protein (MIP)-1β by NK cells from obese people during interaction with tumor cells lines *in vitro* [165]. This could be one of the reasons for the increased risk of tumor formation in obesity. Interestingly, a specific population of NK cells expressing IL-6 receptors (IL-6Ra) and Csf1r (colony stimulating factor 1 receptor) has been described in humans and mice. This subset accompanies metaflammation and IR. IL-6/STAT3-dependent formation of this NK cell subset correlates with MUO [163].

Based on the data presented above, stratification of patients with different obesity phenotypes according to altered profiles of circulating leukocytes is not yet standardized in clinical practice. Threshold values for various leukocyte subpopulations to predict MUO and T2DM have not been fully established. At the same time, in MUO-associated inflammation, there is a general trend towards increased total numbers of leukocytes, lymphocytes, neutrophils, monocytes, B lymphocytes (particularly IgD-CD27- DN B cells, or late memory B cells), CD4+ T lymphocytes, as well as Th1 and Th17 lymphocytes. The ratio of pro- to anti-inflammatory cells may play a significant role—MUO is often accompanied by an increased neutrophil/lymphocyte ratio (NLR), as well as Th1/Th2 and Th17/Treg ratio. In addition, MUO positively correlates with the frequency of senescent CD4+ and CD8+ T cells with the CD45RA+CCR7- and CD45RA+CD28-CD27-CCR7-$KLRG1^{high}$ phenotype, and CD45RA-CD27-CD28- effector and CD57+ senescent CD8+ memory T cells, which secrete pro-inflammatory cytokines. MUO is also associated with the emergence of a specific population of IL-6+/STAT3+ NK cells and an increase in $CD56^{bright}CD16^{dim/neg}$ NK cells. At the same time, the transition from MHO to MUO is marked by a decrease in the number of Tc-cytotoxic, Treg-regulatory, regulatory $CD19+CD24^{high}CD38^{high}$ B cells (Bregs), $CD19+CD27+CD38^{high}$ B cells, as well as switched IgD-CD27+ memory B cells and $CD56^{dim}CD16^{bright}$ NK cells.

6. Cellular Differences in the Adipose Tissue Associated with Between Metabolic Healthy and Unhealthy Obesity

Numerous studies have demonstrated that obesity-associated changes in immune cell balance occur not only in circulation, but also in AT. It is well established that obesity triggers a more complex and intense inflammatory response in VAT than in SAT, and it is precisely the cellular changes in visceral fat that are more strongly associated with MUO [166].

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Neutrophils. As the first cells to infiltrate AT, neutrophils play a key role in the early stages of obesity and its associated inflammation [67]. Normally, when migrating into healthy AT in response to an inflammatory stimulus, neutrophils do not remain there for long. Macrophages that arrive in their place, and polarizing towards the anti-inflammatory M2 phenotype, clear away apoptotic neutrophils and damaged tissue via the process of repair and tissue remodeling. Any disruption of this tightly coordinated response and failure to resolve inflammation within a short time window leads to chronic inflammation, contributing not only to secondary tissue damage but also to immune exhaustion and aging, as observed in metabolic disorders [167]. However, animal models have shown that in diet-induced obesity, neutrophils persist in AT for extended periods (over 90 days) [168]. Typically, neutrophils are recruited by several chemotactic factors released by AT in obesity, primarily IL-8, secreted by inflamed adipocytes; recruited neutrophils, in turn, release C–X–C motif chemokine ligand 2 (CXCL2), another important neutrophil chemoattractant [67]. Lipids released from dying adipocytes also attract neutrophils and macrophages [169]. The latter, by releasing MIP-2α (macrophage inflammatory protein 2 alpha) further attract neutrophils. FFAs released by stressed adipocytes during lipolysis attract and activate neutrophils, stimulating them to produce IL-1β and TNF-α via NF-kB pathway, which in turn activates other adipocytes and immune cells, promoting local inflammation of AT. IL-1β can activate macrophages in various organs. Moreover, IL-1β together with TNF-α in the pancreas can de-differentiate β-cells, reducing the expression of the transcription factor FOXO1, which regulates β-cell differentiation [67]. Neutrophil elastase disrupts energy expenditure regulation in AT and promotes IR [170]. In hyperglycemia and obesity, neutrophils are activated and release NETs via NADPH oxidase (Nox) activation. There is a causal link between persistent NET formation and MUO in the form of diabetic nephropathy, a complication of T2DM [171]. Increased neutrophil numbers further stimulate excessive macrophage AT infiltration, thereby contributing to IR [140]. In MUO, neutrophils are activated both in circulation and in AT [172], whereas weight loss after BS leads to a reduction in their numbers in both subcutaneous and visceral AT.

Eosinophils. They are present in healthy AT in significant numbers, residing alongside adipocytes and other tissue-resident leukocytes. The stromal-vascular fraction of VAT normally contains ≈5% eosinophils [173]. The recruitment of eosinophils into AT depends on the level of eotaxin CCL11, produced by mesenchymal stem cells and adipocytes in AT [174]. The effect of eosinophils on glucose homeostasis and energy expenditure in AT depends on intercellular interactions within AT. Under physiological conditions, eosinophils, as the main source of local IL-4 in AT, promote the differentiation of preadipocytes into “beige” adipocytes expressing uncoupling protein 1 (UCP-1). This stimulates thermogenesis and increases energy expenditure, thereby restraining obesity [129]. Eosinophil activity in AT is regulated by the transcriptional repressor Krüppel-like factor 3 (KLF3), which controls meteorin-like hormone (METRNL) and IL-33, both of which regulate thermogenesis [175]. Eosinophils produce a range of Th2 cytokines, including IL-4, IL-10, IL-13, and TGF-β. Animal studies have shown that eosinophils play a positive role in inducing M2 macrophages and Th2 cells, and suppress inflammation indirectly via IL-4 and IL-13 [176]. In mouse models, a baseline defect or low number of eosinophils in AT was associated with impaired glucose tolerance, reduced insulin sensitivity, altered adipocyte maturation, increased inflammation in AT, and increased AT mass [177,178]. Caloric restriction in obese mice led to an increase in eosinophil numbers in AT [179].

Currently, scientific debates are ongoing regarding the role of eosinophils in human obesity induced by a high-calorie diet. Research data indicate that the accumulation of eosinophils in AT may support metabolic health [174]. Obesity-induced metaflammation is associated with a reduction in eosinophil numbers, contributing to pathological expansion of AT and increased IR risk [180]. It can be hypothesized that during the transition from MHO to MUO, eosinophil numbers rapidly decline, and impairment of their protective functions further exacerbates the development of chronic inflammation and associated metabolic disturbances.

At the same time, some studies have shown controversial results. Moussa K et al. found that SAT eosinophil content was doubled in patients with metabolic syndrome compared to the control

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group (p=0.005) [181]. This may be explained by several factors. In particular, changes in subcutaneous fat, which is inherently less metabolically active than visceral fat, may develop more slowly and be less pronounced during the progression of obesity and T2DM compared to the visceral depot. Furthermore, it cannot be ruled out that at the early stages of MHO to MUO conversion, compensatory mechanisms may be observed, such as a temporary increase in eosinophil numbers followed by a steady decline. In any case, a limited number of studies, and the existing contradictions regarding the role of AT eosinophils in obesity and T2DM require further investigation.

Mast cells. These cells, primarily associated with inflammatory reactions observed in allergies, are found in various AT types. Their precursors are also found in abundance in AT, where, after maturing into mast cells, they interact with adipocytes and participate in immune cell recruitment [182]. Normally, mast cells promote adipocyte differentiation and ensure adequate AT vascularization [183].

Mast cells contain a rich repertoire of pro-inflammatory mediators, including cytokines, chemokines, biogenic amines, proteases (tryptase, chymase), leukotrienes, prostaglandins, etc, and can contribute to AT inflammation [184]. Studies in animal models and humans have shown that, in obesity, the number of mast cells increases in both SAT and VAT [184,185], indicating their potential in metabolic dysregulation. Leptin, which is elevated in obesity, stimulates their activation, degranulation, and cytokine synthesis [186]. Deactivation of mast cells leads to weight loss [187]. In AT, mast cells interact with CD8+ T cells and secrete TNF-α, IL-8, and oncostatin [188]. They can also interact with dendritic cells, CD4+ T cells, and Tregs [187] [189]. Mast cells promote lipid uptake by macrophages and therefore the formation of foam cells [190]. Their number, particularly in SAT, positively correlates with waist circumference, glucose, triglyceride levels, HOMA-IR, leptin, IL-1β, IL-6, and activation of p38 MAPK and NF-kB signaling pathways in circulating monocytes, indicating an important role for these cells in the pathogenesis of obesity-associated metabolic syndrome. At the same time, there are some contradictory data regarding mast cells in AT. For example, according to Lopez-Perez et al. 2021, patients with MHO had significantly higher numbers of mast cells in AT than patients with MUO [183]. García-Rubio et al. 2018 showed that after BS, the number of mast cells increased tenfold in VAT and fourfold in SAT [172][191].

Macrophages. These innate immune cells exhibit high plasticity and easily change their phenotype depending on the microenvironment. Two polar phenotypes, so-called M1 and M2 macrophages, that differ fundamentally in their functions, are known [191,192]. M2 macrophages posess anti-inflammatory potential, characterized by the production of interleukins IL-4, IL-5, IL-10, and IL-13, whereas M1 macrophages are considered pro-inflammatory and produce TNF-α, IL-6, IL-1β, IL-12, and IL-23. The composition and ratio of tissue macrophage types depend on the activating microenvironment stimuli. Accordingly, unsaturated fats and carbohydrates with a low glycemic index promote macrophage polarization towards the M2 phenotype, while saturated fats and simple carbohydrates favour the M1 phenotype [193]. In obesity, the balance between M1 and M2 macrophages undergoes changes. Increased body mass and IR are associated with a shift towards the pro-inflammatory M1 phenotype, along with enhanced migration of monocytes into AT [62] [140]. Recruitment of circulating monocytes into AT, which becomes the primary site of inflammation in obesity, is initiated by chemokines (e.g., MCP-1 produced by adipocytes under obesity-associated hypoxia), cytokines secreted by other immune cells (IFNγ from Th1 and CD8+ T cells, NK cells), extracellular vesicles from apoptotic adipocytes and neutrophils, and numerous DAMPs generated by uncleared apoptotic cells. Nucleic acids, ATP, mitochondrial DNA, cytochrome c, TFAM (mitochondrial transcription factor), and other nuclear and cytosolic proteins can serve as DAMPs. Secretion of various DAMPs can lead to the production of LTB4, which also attracts monocytes, and participates in a positive feedback amplification loop that sustains chronic inflammation, as seen in diabetes [194]. M1 macrophages are also an important source of ROS and nitric oxide, which can contribute to inflammation and fibrosis in AT. In contrast, resident macrophages in healthy AT are considered metabolically “favourable,” maintaining homeostasis by clearing dead adipocytes and participating in adipogenesis and thermogenesis [195].

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It is now recognized that there is a continuum of macrophage subtypes between the M1 and M2 phenotypes. In obesity, both SAT and VAT contain macrophages with a mixed phenotype, so-called metabolically activated macrophages (MMe), which are associated not only with pro-inflammatory function but also with activation of lipid metabolism and expression of ATP binding cassette subfamily A member 1 (ABCA1), CD36 (fatty acid translocase, involved in fatty acid uptake), and perilipin 2, which regulates lipid droplet formation [196]. High concentrations of glucose, insulin, and palmitates contribute to the polarization towards the MMe phenotype [195,196]. Resident macrophages in unhealthy human AT may have mixed M1/M2 polarization, as they can express M2 markers (CD206 and CD163) while still producing inflammatory cytokines [197]. Another group, CD9+ macrophages, can accumulate lipids and participate in the removal of dead adipocytes via lysosomal exocytosis, which makes them similar to MMe, but they also resemble classical M1/M2 macrophages due to expression of CD206 and CD11b [198]. CD9+ macrophages may also express the lipid receptor Trem2, which can be activated in response to lysophosphatidylcholine or phosphatidylserine from apoptotic cells [199]. Notably, Trem2+ macrophages prevent adipocyte hypertrophy, inflammation, and metabolic dysfunction [200], which suggests the activation of the reparative function of Trem2+ macrophages in AT in response to inflammation.

Macrophages phagocytosing fragments of dead adipocytes, may initiate the adaptive immune response through antigen capture and presentation to lymphocytes. Notably, due to epigenetic and metabolic changes, macrophages have features of immunological memory, a trait once thought to be unique only to adaptive T and B cells [201,202]. The altered state of macrophages persists and maintains their activation in AT even after weight loss [203]. Toll-like receptor ligands (LPS and IFN-γ) and saturated FFAs (stearic acid) found in abundance in obesity alter macrophage metabolism [204,205].

Macrophages can influence the transition from MHO to MUO. CD95+ macrophages and miR-155 deficiency can correlate with this transition [206]. Additional physiological factors determining the conversion of MHO into MUO include differences in the distribution of M1/M2 macrophage subtypes and differential gene expression in SAT. MHO is characterized by an increased number of M2 macrophages in SAT and is associated with higher expression of genes related to lipid synthesis and transport (fatty acid binding protein 7 or FABP7), whereas MUO is associated with increased expression of transcripts responsible for inflammatory processes (MCP-1) in AT [207]. The MHO phenotype is also associated with lower activation of the NLPR3 inflammasome and reduced caspase-1 activity in VAT macrophages [38]. Thus, patients with MHO have a less intense inflammatory profile in AT compared to those with MUO.

Lymphocytes. CD4+ T helper cells and their subpopulations. Obesity is associated with the accumulation of cytotoxic CD8+ T lymphocytes and CD4+ T helper cells in AT. It is interesting that according to some reports, activated CD4+ T cells accumulate AT prior to the infiltration by inflammatory macrophages [208,209]. However, other studies demonstrate that it is macrophages and adipocytes in VAT, acting as antigen-presenting cells (APC), that induce the proliferation and differentiation of CD4+ T cells into an inflammatory phenotype. Activation of CD4+ T cells occurs via the cognition by their TCR of an antigen presented by the major histocompatibility complex class II (MHC II) on APC [210]. Although the key antigens that drive the activation of CD4+ and/or CD8+ T cells remain unclear [133]. In addition, various adipokines (leptin, resistin, TNF-α, and IL-6) regulate the differentiation and function of T lymphocytes. IL-6 promotes the expansion of Th17 cells, which are critical for sustaining inflammation in AT.

The total number of CD4+ T cells and IL-17 production in AT are positively associated with obesity and IR, indicating the development of inflammation. The increase in Th17 cells in AT correlates with HbA1c and glucose levels. The numbers of pro-inflammatory Th1, Th17, and Th22 cells are elevated in both SAT and VAT in patients with MUO compared to those with MHO, whereas anti-inflammatory Th2 and Treg cells help maintain normal AT homeostasis in non-obese individuals and those with MHO [140]. A higher number of Th2 cells in both VAT and SAT is inversely associated with systemic inflammation and IR in humans [33] [211]. Individuals with MUO also exhibit a high proportion of memory CD4+ T cells (CD45RA−CCR7+CD62L+) in AT [212]. Additionally, exhausted

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CD4+ T cells populations have been described, and their numbers may also increase with the progression of obesity [213,214].

Upon accumulating in AT, T cells alter their phenotype and metabolism, switching to anaerobic glycolysis. Adipokines, cytokines, and lipids from VAT contribute to the formation of new T cell phenotypes, which drives the subsequent progression of inflammation and obesity. Obesity-induced changes in the phenotype of CD4+ T cells lead to dysfunction of the adaptive immune system and persist even after weight loss. This complicates the treatment of obesity-associated metabolic conditions. Obesity facilitates chronic stimulation of CD4+ T cells within AT, resulting in their exhaustion and functional impairment, and manifesting by the expression of inhibitory receptors (PD-1 and CD153) and a distinct transcriptional state [214]. In addition to exhaustion, obesity also accelerates the aging of CD4+ T cells [215]. Aged CD4+ T cells actively secrete osteopontin, which enhances inflammation in VAT [216].

Tregs possessing distinct properties in different depots of AT participate in the regulation of local inflammation and metabolism. Normally, MHC II-mediated antigen presentation determines the development of Tregs in VAT. It is presumed that macrophages and dendritic cells are the main MHCII+ APCs responsible for delivering signals to TCR of Tregs in visceral fat [217]. Obesity-induced inflammation in AT is accompanied by an imbalance between local pro-inflammatory T cells and Tregs, disruption in metabolism and the impairment in inflammation resolution. As obesity progresses, the number of Tregs in VAT decreases and inversely correlates with BMI and IR. At the same time the Th17/Treg ratio increases. Importantly, obesity increases MHCII expression in adipocytes, and in experiments involving TCR ligation by MHCII expressed on adipocytes, a reduction in Treg numbers in VAT was observed in obese mice [218]. Similar to findings in mice, visceral fat Tregs in humans play a protective function in obesity and are involved in maintaining glucose levels. However, as obesity develops, adipocytes express higher levels of leptin, which correlates with MHC II expression on adipocytes, and this restrains Treg accumulation in VAT. Interestingly, in individuals with MHO, Foxp3 expression in both SAT and VAT was increased [219].

Cytotoxic CD8+ lymphocytes. Similar to Th1 lymphocytes, CD8+ T lymphocytes demonstrate increased number in AT of obese individuals, contributing to the recruitment of macrophages [220] and enhancing IL-6 and TNF-α expression by adipocytes [62]. CD8+/CD4+ ratio is also increased in obesity. A comparative study found no significant differences in the relative proportions of CD8+ T cells between MHO and MUO groups; however, the absolute number of CD8+ cytotoxic T cells was higher in individuals with MUO [212].

Obesity promotes the formation of pathological CD8+ T cells, whose activation occur in response to endogenous AT antigens presented by MHC class I, or exogenous antigens derived from food or released by the gut microbiome [221,222]. Adipocytes can activate CD8+ T cells in individuals with obesity. The infiltrating CD8+ T cells have a restricted TCR-Vβ repertoire, which narrows the range of recognized antigenic epitopes but enhances the specificity of binding to antigens within the inflamed AT [222]. Antigen-specific activated cytotoxic CD8+ T cells, accumulating in VAT, can potentially secrete large amounts of IFNγ, recruit monocytes/macrophages, and destroy hypertrophied adipocytes. Notably, obesity may promote lipid uptake by activated cytotoxic CD8+ cells, shifting their metabolism from glycolysis towards fatty acid oxidation [223].

The role of CD8+ T lymphocytes in AT inflammation is not fully understood. It has been shown that CD8+ T lymphocytes are heterogeneous and include two subpopulations: Tc1 cells characterized by hyperproduction of IFNγ, IL-12, and IL-18, and Tc2 cells which produce anti-inflammatory cytokines IL-4 and IL-5, and. It is possible that leptin can shift the differentiation of CD8+ cytotoxic T cells towards the Tc1 phenotype and, via the STAT3-dependent signaling pathway, enhance PD-1 expression, leading to cytotoxic T cell exhaustion [223].

B lymphocytes. In healthy AT B cells maintain homeostasis by supporting an anti-inflammatory microenvironment, primarily through the secretion of IL-10 and IgM [159]. Obesity is accompanied by the trafficking of B cells into VAT, their accumulation, and a shift in their subpopulation balance and functional activity towards a pro-inflammatory state. By modulating T cell responses and producing

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pathogenic antibodies under altered obese microenvironment, B cells contribute to metaflammation and further metabolic dysfunction of AT, including the development of IR.

As obesity progresses, the composition of B cell subpopulations changes. The frequency of pro-inflammatory IgD-CD27- DN B cells, which secrete pathogenic autoantibodies and increase in the periphery during obesity, also rises in AT. Conversely, the proportion of CD20+CD27+CD43+ B cells and IgM antibodies, which inhibit the development of inflammation and IR, decreases in both SAT and VAT during obesity and metabolic syndrome [224]. The proportion of Bregs, which maintain the homeostasis of healthy AT and exert anti-inflammatory effects through IL-10 secretion, is also reduced in obesity compared to healthy AT [159]. Normally, IL-10 produced by B cells promotes polarization of macrophages towards the M2 phenotype. In humans, obesity has been shown to be associated with a reduction in CD27+CD38^{high} memory B cells, as well as in IL-10-secreting Bregs [109].

Numerous mechanisms have been proposed to explain the pathogenic involvement of B cells in AT dysfunction. Adoptive transfer of B2 cells into the VAT of mice promoted the development of metabolic disturbances, as these cells likely produce pro-inflammatory cytokines and contribute to IR through the secretion of LTB4 [225], as well as by activating macrophages and suppressing Tregs [33]. In obesity, B cells, acting as antigen-presenting cells, can present antigens to T cells (Th1 and CD8+ Tc), thereby enhancing IFNγ production and promoting macrophage polarization towards the M1 phenotype. B cells also undergo phenotypic changes, switching antibody classes and beginning to produce IgG (including IgG2c), which enhances TNFα secretion by macrophages [226]. Additionally, B cells secrete chemokines (such as IL-8), which attract new immune cells into AT, forming a positive feedback loop that sustains inflammation. Furthermore, T-bet+ B cells, able to secrete CXCL10, which can induce pancreatic β-cell dysfunction, also found in obese AT [227,228].

Natural Killer Cells. Like other cells of the innate immune system, NK cells play an important role in the early stages of inflammation development in AT. Moreover, they play a role of «sensors» of AT metabolic stress [229]. Accumulation of NK cells in VAT is observed in humans with obesity [104]. In addition, mice models support that a reduction in NK cell numbers in fat is associated with improved insulin sensitivity and a decrease in total macrophage numbers [230]. IL-12 and IL-15, which appear in AT at the onset of obesity, lead to local accumulation of NK cells, primarily through proliferation rather than recruitment from the circulation. Analysing NK cell subsets, there is a notable increase specifically in the CD56^{bright}CD16- NK cell population in AT during obesity. By producing excessive amounts of IFNγ and TNF-α in AT [231], these cells promote polarization of macrophages towards the M1 phenotype and the development of IR [162] [230]. In mice on a high-fat diet, the number of NK cells in VAT increases 3- to 5-fold, and stressed adipocytes show increased expression of the ligand for NKp46, one of the activating receptors of NK cells, thereby stimulating NK cells to produce IFNγ [162]. Mice deficient in NK and NKp46 developed obesity on a high-fat diet but did not develop IR, highlighting the critical role of NK cells in metaflammation and the development of MUO. Thus, despite many stress factors contributing to the macrophage accumulation and inflammation in AT, the surpassing of a certain threshold of NKp46 ligand expression on adipocytes may be the key point at which NK cells provide the immunological "license" for macrophages to switch to the pro-inflammatory M1 phenotype and subsequently drive IR [232].

Innate Lymphoid Cells (ILCs). Being tissue-resident lymphocytes, ILCs comprise a heterogeneous group of lymphoid lineage cells with lack antigen-specific B or T cell receptors. ILCs include NK cells and helper ILCs of three subtypes (ILC1, ILC2, ILC3). Obesity and metabolic syndrome are associated with the accumulation of ILC1 in SAT and VAT, accompanied by excess IFNγ and M1 polarization of macrophages [233]. In contrast, ILC2 are more commonly found in AT in the absence of obesity and inflammation, where they help maintain eosinophil and M2 macrophage activity; their numbers decrease in obesity and metabolic syndrome [234].

Comparing the AT cellular composition under different metabolic statuses is a complex task, as most available data have been obtained from mouse models, with analysis of various visceral fat depots (epididymal, perigonadal fat, etc.), whereas data on human AT are quite limited and mainly

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pertain to subcutaneous fat, partly due to technical limitations in obtaining tissue samples. These circumstances may explain some of the contradictions in current findings regarding the dynamics of AT cellular composition in MHO and MUO. The differences in adipose tissue immune cells between healthy adipose tissue, MHO and MUO are summarized in Table 4.

Table 4. Adipose tissue immune cells in healthy adipose tissue, MHO and MUO.

Cell type	Healthy	MHO	MNO	References
Neutrophils, % of SVF in mice with obesity in epididymal fat	~0.1	up to 1.5, (#)	In mice with active *ELANE* gene (neutrophil elastase), tissue sensitivity to insulin was worse (20% suppression of gluconeogenesis in the liver compared to 60% in NE knockout mice, #)	[168]
Neutrophils, % of all immune cells in AT of mice	~ 1.0	10–20-fold increase in the number of neutrophils in visceral AT of mice		[67] [235]
Macrophages, F4/80+ cells, % of immune cells in AT of mice, mean ± SD	12 ± 2 in SAT and VAT	41 ± 4 (##, in SAT and VAT)		[114]
Macrophages, % of immune cells in human AT	~ 10–15 in SAT (?)	Up to 40–60 in SAT (?), metabolic status not specified		[236]
Macrophages, % of the total number of adipocytes in humans, mean ± SEM		4.1±1.2 in SAT and 6.3±1.7 in VAT	9.1±1.9 in SAT (# for MUO and MHO) 14.6±4.1 in VAT, (NS for MUO and MHO)	[185]
Eosinophils, % of SVF, mean ± SEM / x10³ cells per 1g of VAT in mice, mean ± SEM	~6.4±0.9 % or ~ 25±5 x10³ cells per 1g	~1.1±0.3% (*) or 11.6±4 x10³ cells per 1g (#)		[177]
			In humans, an increase in HOMA-IR index by 1.030 was accompanied by 1% decrease in eosinophils in SAT (##)	[237]
Mast cells, x10⁵ cells/mm² in human AT, mean ± SEM	~ 1.6 ± 0.45 x10⁵ cells/mm² of mast cells expressing chymase in VAT	~ 0.5 ± 0.23 x10⁵ cells/mm² of mast cells expressing chymase in VAT, NS	The number of two mast cell phenotypes (expressing chymase and tryptase) was significantly	[185]

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			increased (max 10 ± 5.9 x10^5cells/mm^2) in both fat depots (# for MUO vs MHO)	
Mast cells, % Astra Blue positive / expressing tryptase in human SAT, median (IQR)		~ 20 (10–20.5) (Astra Blue positive); ~ 40 (10–50) (expressing tryptase)	~ 50 (40–60)*** (Astra Blue positive), ~ 60 (40–80) (expressing tryptase)*	[184]
NK cells, cells*10^3 in VAT of mice, mean ± SEM	~ 3.1 ± 0.7 * 10^3	~ 6.8 ± 1.6 * 10^3 (#)		[162]
NK cells in human VAT, % of live cells, Me [IQR]	2.7 [1.64–4.09]	~3.79 [2.66–6.02], (# for MHO+MUO versus healthy)		[104]
CD8+ lymphocytes, % of TCRαβ+ cells in epididymal fat of mice, mean ± SEM	5±1.1	16±1.1 (#)		[238]
CD8+ lymphocytes, n x 10^5/g in mouse VAT, mean ± SEM		~0.5±0.05 x 10^5/g		[220]
CD8+ lymphocytes, % of total T cells in human VAT, mean ± SD		38.4 ± 6.8		[211]
CD8+ lymphocytes, % of CD3+ cells in human VAT, mean ± SEM	~ 40±2.5	~ 45±2.5, NS		[212]
Th1 lymphocytes, % of CD4+ cells or n cells g^{-1}*10^3 in mice, mean ± SEM	41.3 % or ~ 20.0±4.0 cells·g^{-1}*10^3 in VAT; 14,9 % or 10±0.5 cells g-1*10^3 in SAT	50.3 % or ~ 60±14 cells·g^{-1}*10^3 in VAT, (#); 32.4 % or 38±2.0 cells g-1*10^3 in SAT, (#)		[239]
Th1 lymphocytes (CD4+ IFN-γ), % of CD4+ cells in human SAT, mean ± SD	57 ± 24	66 ± 22	68 ± 13, NS for all groups.	[240]
Th2 lymphocytes (GATA3+ cells), % of CD4+ cells or n cells·g^{-1}*10^3 in VAT of mice, mean ± SEM	33.7% or 14.9±0.5 cells·g^{-1}*10^3	15.3 % (#) or 19±4.5 cells·g^{-1}*10^3, NS		[239]
Th2 lymphocytes (CD4+ IL-13), % of CD4+ cells in human SAT, mean ± SD	13.0 ± 9.7	14.1 ± 10.2	13.0 ± 9.7, NS for all groups	[240]

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Th17, % of CD4+ cells or n cells·g^{-1}*10^3 in mice, mean ± SEM	1.97% or 1.1 ± 0.5 cells·g^{-1}10^3 in VAT; and 2.1 % or 1.2 ± 0.06 cells·g^{-1}10^3 in SAT	0.58% or 0.8 ± 0.125 cells·g^{-1}10^3 in VAT, NS; and 2.93% or 2.8 ± 0.1 cells·g^{-1}10^3 in SAT (#)		[239]
Th17 (CD4+ IL-17), % of CD4+ cells in human SAT, Me [Q1; Q3]	~1.2 [0.5; 4.0]	~1.8 [0.5; 5.0]	~14 [2.8; 17], (# for MUO versus MHO and healthy)	[240]
Th22 (CD4+ IL-22), % of CD4+ cells in human SAT, Me [Q1; Q3]	~2 [0,5; 11]	~4 [1,2; 6,8]	~11 [4.5; 18], (# for MUO versus MHO and healthy)	[240]
Treg lymphocytes, % of CD4+ cells or n cells·g^{-1}*10^3 in VAT of mice, mean ± SEM	29.0% or 13.6±1.4 cells·g^{-1}*10^3	7.9% (#); or 10.5±0.2 cells·g^{-1}*10^3, NS		[239]
Treg lymphocytes, % of CD4+ T cells in human AT, mean ± SEM	19±3.6 in VAT; 24±4.5 in SAT	3.5±4.3 in VAT and 7±2.9 in SAT, (*** for MHO + MUO vs healthy)		[241]
B lymphocytes in VAT of mice, % of SVF	~10	~20 (#)		[225]
B lymphocytes, % of CD45+ cells in SVF in gonadal adipose tissue of mice, mean ± SD	~2 ± 1	~5.5 ± 3.5 (*)		[242]
B lymphocytes, estimated relative number of cells in human VAT			The relative number of B cells was higher in MUO compared to MHO (***)	[243]
CD19+CD27+CD38^{high} memory B cells, cells/mm^3 in human SAT, mean ± SD	2.8 ± 1.7	0.3 ± 0.2 (#), metabolic status not specified)		[109]
Innate lymphoid cells (ILCs type 1), cells mg^{-1} in human omentum, mean ± SD	5 ± 3	15 ± 3	23 ± 3 (** for all groups)	[233]

Thus, it can be concluded that AT dysfunction, with its structural remodeling, pro-inflammatory cellular infiltration, and production of a wide range of pro-inflammatory cytokines observed in obesity and metabolic syndrome, leads to the loss of normal insulin sensitivity in AT and the subsequent development of prediabetes/T2DM. The transition from MHO to MUO is accompanied by an increase in the numbers of neutrophils, macrophages (M1), mast cells, B cells (IgD-CD27- DN, T-bet+), pro-inflammatory Th1, Th17, Th22, CD8+ T cells (with an increased Tc1/Tc2 ratio), as well as memory CD4+ T cells with the CD45RA-CCR7+CD62L+ phenotype and exhausted CD4+ cells, CD56^{bright}CD16- NK cells, and ILC1, along with a simultaneous decrease in M2 macrophages, eosinophils, Tregs, Th2, Bregs, CD20+CD27+CD43+ B cells, CD19-CD27+CD38^{high} memory B cells.

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7. Reversibility of Metaflammation Following T2DM Remission After Bariatric Surgery. Metabolic Memory

The advent of BS marked a turning point in the treatment of obesity and T2DM, as it appeared not only highly effective in fighting against excess weight but also introduced the concept of diabetes remission. T2DM remission is defined as achieving an HbA1c level of ≤6.5% for at least three months in the absence of glucose-lowering therapy. Due to its potential to achieve T2DM remission, BS has also recognized as "metabolic" surgery.

BS can be divided into two main groups based on surgical technique: restrictive procedures, which primarily limit food intake (gastric banding, intragastric balloon, sleeve gastrectomy), and combined procedures, which incorporate both restrictive and malabsorptive components (Roux-en-Y gastric bypass, one-anastomosis gastric bypass/mini gastric bypass (OAGB-MGB), biliopancreatic diversion with SADI and Duodenal Switch modifications). Currently, the most performed procedures are sleeve gastrectomy (SG), gastric bypass (GB), and biliopancreatic diversion (BPD). Weight loss after BS is often assessed as EWL (excess weight loss percentage). According to a systematic review by L.Fischer et al., EWL for SG averages 56.1%, for GB 68.3% [244], and according to P.E. O'Brien et al., EWL for BPD reaches 74.1% or more [245], making BPD the most effective intervention for both weight loss and T2DM remission.

It has been shown that during the first year after BS, both SAT and VAT decrease in volume [246], with a reduction in the size of subcutaneous [247] and visceral adipocytes [248,249]. Human studies have shown that the size of subcutaneous adipocytes decreases after BS, resembling those in non-obese individuals [57] [250]. Data on changes in the size and number of visceral adipocytes after BS are limited due to rare postoperative VAT sample collection.

After BS, most patients experience not only rapid weight loss but also marked improvements in lipid and glucose metabolism. This raises the important questions: does BS lead to a resolution of the pathological inflammatory characteristic of MUO in patients with T2DM? Is it possible to discuss the reversibility of MUO and its conversion to MHO or to a completely "healthy" phenotype? Indeed, according to several studies, BS can shift the adipokine balance towards an anti-inflammatory profile [251] and even reverse AT dysfunction and inflammation, regardless of EWL after BS [252]. Recent research shows that, in the long term, circulating adiponectin levels increase significantly (by about 12%), while leptin levels decrease (by about 45%) after BS [253] [254]. Similar results have been shown for reduction in other pro-inflammatory cytokines and adipokines (TNF-α, resistin) [254–256] and increase in anti-inflammatory adipokines (omentin) [257], collectively indicating a regression of inflammatory changes in AT after BS, highlighting the modulatory effect of BS on adipose tissue inflammation and structure. BS affects the systemic inflammatory status of patients by increasing the level of anti-inflammatory cells producing IL-10, including B lymphocytes, while reducing pro-inflammatory cells producing IL-6, as shown three months after GB [258]. Twelve months after SG, a shift from a pro-inflammatory to an anti-inflammatory pattern was also observed, accompanied by a decrease in CD4+ effector memory T cells (CD45RO+CD27-) and an increase in circulating Tregs, although not reaching levels seen in healthy individuals [253]. At the same time, some studies demonstrate that despite significant weight loss and improved metabolic status after BS, the altered pro-inflammatory cytokine profile persists in patients with obesity and T2DM (patients with T2DM after surgery had elevated levels of IFN-β, IL-27, IL-1α, IL-2, regenerating islet-derived protein 3A, visfatin, and osteopontin [259], serum amyloid A, and MCP-1 [260]).

Numerous studies report a reduction of inflammation in both SAT and VAT after weight loss resulting from BS [57] [140] [172] [261,262]. In the study by V.A. Palomäki et al., the dynamics of SAT macrophage infiltration was examined before and 12 months after BS (60 patients with morbid obesity, 62 controls). The number and density of "crown-like structures" formed by macrophages around apoptotic adipocytes decreased from 4.1 to 1.1 per 1000 adipocytes after surgery [261]. Furthermore, several studies have demonstrated that there was also a shift towards a predominance of anti-inflammatory macrophages in both SAT and VAT after BS [140] [262]. Weight loss after BS in humans was also accompanied by a reduction in neutrophil numbers in both fat depots, whereas no

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significant changes in T cell levels were observed [172]. An interesting finding was that after BS, the number of mast cells increased in both SAT and VAT, as did the number of adipocyte progenitor cells, which was associated with a favourable immunophenotypic profile of AT [172].

At the same time, several studies have found no positive changes in AT after weight loss due to BS [263–265]. Despite marked metabolic improvements observed with weight loss, persistent inflammatory changes in visceral fat may remain both in humans after BS and mice under caloric restriction [266,267], characterized by continued pro-inflammatory macrophage polarization and no change in Treg cell numbers [264,265] [268]. D.K. Hagman et al. showed that over 12 months of follow-up after BS in humans CRP levels decreased, while adiponectin levels increased. However, not only was there no regression of inflammation in SAT, but on the contrary, the number of neutrophils increased by 15-20 times, without significant changes in the amount of other leukocyte subsets [263]. Thus, several studies support the hypothesis of "metabolic memory" following weight loss [269,270]. Indeed, given the gradual development of inflammation in obesity, many researchers anticipated a resolution of inflammation after weight loss [133]. Unexpectedly, however, inflammation may persist following weight loss, both in the periphery and in AT. The activity of CD4+ and CD8+ T cells producing type 1 and type 17 cytokines is maintained, driven by macrophages that remain in AT. Thus, despite the restoration of carbohydrate metabolism, improved insulin sensitivity, and reduced level in cholesterol and triglycerides, AT maintains a metabolic memory by preserving the microenvironment established earlier during obesity. Indeed, BS cannot instantaneously alter the structure of AT, as the cellular composition cannot be renewed immediately.

Close relationship between immunity and metabolism, as well as the phenomenon of worsening metabolic health (characterized by reduced glucose tolerance and insulin sensitivity) during multiple weight cycling episodes suggest a hypothesis that metabolic changes may lead to the formation of immunological memory, which is retained by the immune system [215] [271].The immune system is indeed capable of retaining memory of all antigens it has encountered. Information regarding metabolic status may be "memorized" by both adaptive immune cells (long-lived memory T cells) and trained cells of innate immunity. For instance, macrophages possess long-term memory for specific antigens and respond with greater intensity upon re-exposure to a previously encountered obesogenic stimulus. Epigenetic (such as histone modifications, DNA methylation) and metabolic changes in macrophages (e.g., glycolysis) determine the immune memory responses of macrophages [201,202]. Immune memory responses during weight loss can enhance the inflammatory response and maintain macrophages in an activated state, thereby promoting weight regain [203]. Notably, unlike adaptive immunity, macrophages are less selective; they may respond to the secondary stimulus not precisely matched the primary one or even be of a different nature, not associated with obesity but, for example, with hypertension [272].

Among adaptive immune cells, CD4+ and CD8+ effector memory T cells (Tem) in AT have been identified as critical in forming obesogenic memory, which contributes to weight regain during weight fluctuations. A specific role of Th1 and Th17 cells growing in number during weight regain after weight loss has been noted [133]. The presence of CD4+ and CD8+ Tem cells in AT, as well as a reduced T-cell receptor repertoire, supports the existence of obesogenic antigens that stimulate T cells and maintain the memory cell pool [152]. Although macrophages, dendritic cells, B cells, and adipocytes are potentially capable of presenting antigen to T cells in AT, it currently remains unclear what type of antigen-presenting cell is involved and what specific antigen participate in T-cell activation in obesity [271]. Prolonged stimulation of T-cell receptors by antigen, as observed in chronic inflammation in obesity, may lead to the emergence of both functionally exhausted and senescent immune cells, which differ in both phenotype and functional characteristics [273]. A key distinguishing feature of senescent cells, as opposed to exhausted cells, is their increased capacity to produce suppressive and pro-inflammatory cytokines (TGF-β, IL-10, as well as TNF-α, IL-8, IL-6, IL-2, IFN-γ), contributing to the unique senescence-associated secretory phenotype (SASP) associated with T2DM [141]. Notably, senescent CD4+ and CD8+ T cells with the CD45RA+CD28-CD27-CCR7-KLRG1^{high} phenotype are elevated in T2DM [143,144]. The accumulation of senescent cells negatively

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affects the immune system. Furthermore, in addition to immune cells, the persistence of transcriptional and functional memory of obesity has also been reported in adipocytes and endothelial cells [274].

Thus, an individual patient's "immunological content" is formed, which does not disappear following BS: upon encountering an old stimulus, cells retaining memory of the obesogenic antigen respond with an intense inflammatory reaction. Moreover, the recurrence of T2DM after BS may also be explained by the patient's obesogenic memory. Previously, predictors of T2DM relapse after BS included indicators of a more severe prior course of T2D: longer disease duration, higher HbA1c levels, lower C-peptide and insulin levels, and a greater number of glucose-lowering medications. The return of diabetes was also associated with a more severe and prolonged course of T2DM prior to BS and "exhaustion" of pancreatic reserves. Currently, it is hypothesized that a more severe course of T2DM before BS is accompanied by more pronounced and persistent inflammation of AT, which does not resolve after BS, thereby predisposing to T2DM relapse.

8. Conclusions

Numerous studies confirm that obesity may manifest by different phenotypes. Obesity is often accompanied by a range of comorbidities and manifests as MUO, underpinned by a state of chronic metaflammation. Apparently, MHO represents a transitional form towards the MUO phenotype, although some studies report possible conversion from MUO to MHO [5]. Clinically, the MUO phenotype is characterized by visceral fat accumulation, ectopic fat deposition in other organs, and impaired adipogenesis in AT. High hepatic fat content and elevated levels of circulating lysophosphatidylcholines produced by the liver may be used to stratify patients with MUO and MHO [39]. Excessive fat accumulation and inflammation in the liver may serve as one of the triggers for the development of T2DM. MUO is also accompanied by both systemic and local (in AT, liver, and pancreas) IR. The differential diagnosis of patients with different obesity phenotypes based on blood leukocyte subpopulations has not yet been introduced into clinical practice, as most studies have been cross-sectional, without longitudinal analysis. Further research is required, considering all relevant factors and a unified criterion for defining MHO and MUO. Moreover, different studies have included patients with varying degrees of MUO severity: for example, individuals with BMI 30–35 and HbA1c up to 8.0%, versus those with BMI >40 and HbA1c >8.0–10% may have different levels of inflammation. This may also explain the inconsistency and heterogeneity of the results across studies. Nevertheless, in MUO-associated inflammation, a general trend is observed towards increased numbers of circulating leukocytes, neutrophils, monocytes, B lymphocytes, CD4+ T cells, elevated NLR, Th1/Th2 and Th17/Treg ratios, reduced proportions of Tregs and Bregs, and increased proportions of senescent CD4+ and CD8+ T cells secreting pro-inflammatory cytokines. At the level of soluble blood factors, MUO is characterized by increased levels of pro-inflammatory mediators (CRP, IL-6, IL-8, MCP-1, TNF-α) and a concomitant decrease in anti-inflammatory factors (IL-4, IL-5, IL-10, IL-13). Transition to MUO is accompanied by a gradual increase in levels of cell adhesion molecules (VCAM-1, ICAM-1, E-, L-, and P-selectins). Elevated leptin and HOMA-IR may also be considered as markers of systemic metabolic inflammation. The transition to MUO is also accompanied by more intense AT cellular infiltration, with predominance of neutrophils, M1 macrophages, mast cells, B cells, pro-inflammatory Th1, Th17, CD8+ T cells, as well as CD4+ memory T cells, NK cells, and ILC1, together with a decrease in M2 macrophages, eosinophils, Tregs, Th2, Bregs, and ILC2.

The potential for reversibility of inflammatory changes and metabolic impairments after weight loss achieved through low-calorie diets, increased physical activity, or BS has attracted significant interest among researchers, especially with the advancement of bariatric interventions for obesity and the introduction of the concept of T2DM remission. However, there still remain many controversies. Some studies report the persistence of a pro-inflammatory background both systemically and in AT, which creates a predisposition for weight regain and T2DM relapse, supporting the hypothesis of "metabolic memory." Identification of critical parameters, their

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threshold values and correlations with other indicators that may have prognostic significance for T2DM relapse is an important clinical issue. Unraveling the mechanisms underlying "metabolic memory" will help identify the potential targets for obesity and T2DM treatment.

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Abbreviations

AGEs - Advanced glycation end products
AT- adipose tissue
ATI- adipose tissue inflammation
AMPK – AMP-activated protein kinase
ATP – adenosine triphosphate
ABCA1- ATP binding cassette subfamily A member 1
ACC1- acetyl-CoA carboxylase 1
BMI- body mass index
BPD- biliopancreatic diversion
BS- bariatric surgery
CXCL- C–X–C motif chemokine ligand
CRP- C-reactive protein
CCL – chemokine (CC motif) ligand
CCR6- C-C chemokine receptor type 6
Csf1r- colony stimulating factor 1 receptor
DAMPs - danger associated molecular patterns
DNA- deoxyribonucleic acid
EWL- excess weight loss
ECM – extracellular matrix
ER – endoplasmic reticulum
FABP7- fatty acid binding protein 7
FFAs - free fatty acids
FAS- fatty acid synthesis
FAO- fatty acid oxidation
GC - germinal center
HMGB1 – high-mobility group protein B1
HIF1a- hypoxia inducible factor 1α
ILC- innate lymphoid cell
IR- insulin resistance
IRS- insulin receptor substrate
IL – interleukin
iCAM- intercellular adhesion molecule
IFN- interferon
IGFBP3- insulin-like growth factor binding protein 3

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JNK- c-Jun N-terminal kinase
LTB4R- leukotriene B4 receptor
MSCs- mesenchymal stem cells
METRNL- meteorin-like hormone
MHO - metabolically "healthy" obesity
MUO - metabolically "unhealthy" obesity
MIP- macrophage inflammatory protein
MAFLD - metabolic-associated fatty liver disease Начало формы
MCP-1 – monocyte chemoattractant protein 1
MHC – major histocompatibility complex
mTOR – mechanistic target of rapamycin kinase
NLPR3- NLR family pyrin domain containing 3
NF-kB - nuclear factor kappa-light-chain-enhancer of activated B cells
NLR- neutrophil to lymphocyte ratio
NO- nitric oxide
NETs- neutrophil extracellular traps
OXPHOS- oxidative phosphorylation
OAGB- one anastomosis gastric bypass
PAI-1 – plasminogen activator inhibitor-1
RAGE- receptor for advanced glycation end products
ROS – reactive oxygen species
RYGB- Ry- gastric bypass
SAT-subcutaneous adipose tissue
SASP- senescence-associated secretory phenotype
SG- sleeve gastrectomy
SADI- single anastomosis duodeno-Ileal bypass
T2DM- type 2 diabetes mellitus
TNF-a- tumor necrosis factor-a
TGF- transforming growth factor
TLR- toll likereceptor
TCR- T cell receptor
TFAM - mitochondrial transcription factor
UPR- unfolded protein response
UCP-1- uncoupling protein 1
VAT- visceral adipose tissue
VEGF – vascular endothelial growth factor
vCAM- vascular cell adhesion molecule

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