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The Role of Immunometabolic Dysregulation in Obesity-Associated Cardiovascular Risk: A Narrative Review

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Abstract

Background: Obesity is a major global health problem and an established risk factor for cardiovascular disease (CVD). Beyond traditional risk factors, chronic low-grade inflammation and immune-cell metabolic dysfunction may provide a mechanistic link between obesity and vascular disease.

Objective: To synthesise current evidence on adipose tissue inflammation, monocyte and macrophage immunometabolic reprogramming, mitochondrial dysfunction, and the pathways connecting obesity with cardiovascular risk, while identifying emerging therapeutic targets.

Methods: A narrative review was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published from 2000 to July 2026. Original human, animal, and in vitro studies addressing adipose tissue macrophages, immunometabolic reprogramming, inflammatory signalling, metabolic dysfunction, or cardiovascular outcomes were included and synthesised thematically.

Results: Obesity was consistently associated with adipose tissue macrophage recruitment and expansion, particularly through CCR2/CCL2 signalling, together with pro-inflammatory metabolic reprogramming characterised by increased glycolysis, altered fatty-acid oxidation, mitochondrial dysfunction, reactive oxygen species production, and activation of HIF-1α and NF-κB. The resulting release of TNF-α, IL-6, and IL-1β contributes to insulin resistance, endothelial dysfunction, hepatic steatosis, and atherosclerosis. Shared inflammatory and metabolic pathways were identified in obese adipose tissue and atherosclerotic lesions. However, a subgroup of individuals with obesity showed little adipose inflammation and relatively preserved vascular function, indicating that adipose tissue quality may be more informative than adiposity alone. Potential therapeutic targets include CCR2, AMPK, ANT2, SIRT3, mitochondrial reactive oxygen species, and dietary macronutrient composition.

Conclusion: Immunometabolic dysregulation appears to be a central mechanism linking obesity with cardiovascular disease. Strategies that restore immune-cell metabolism, preserve mitochondrial function, and reduce adipose tissue inflammation may complement conventional weight-management approaches, although further longitudinal and clinical studies are required.

Keywords: Adipose tissue macrophages, obesity, insulin resistance, immunometabolism, cardiovascular disease, atherosclerosis, CCR2, AMPK, ANT2, mitochondrial dysfunction, inflammation

Introduction

Obesity represents a major and growing global public health challenge. In 2022, more than one billion people worldwide were living with obesity, including approximately 879 million adults and 159 million children and adolescents [1]. Since 1990 the age-standardised obesity prevalence has doubled among women (from 8.8% to 18.5%) and tripled among men (from 4.8% to 14%). Globally, the number of annual CVD deaths attributable to high BMI (25 kg/m2 or over) more than doubled between 1990 and 2021, reaching 1.9 million in 2021 [2]. Cardiovascular disease remains the leading cause of death globally, accounting for an estimated 19.2 million deaths in 2023 [3].

The relationship between obesity and CVD is complicated and complex, and negative relationships between obesity and traditional risk factors (triglyceride, hypertension, glucose, and lipid parameters) as well as non-traditional risk factors (chronic inflammation, endothelial dysfunction and thrombosis) have been found. Metaflammation," or a chronic low-grade inflammatory state linked to obesity, has revolutionised the concept of obesity's relationship to cardiovascular risk [4].

For many years, adipose tissue has been viewed as an inert energy reserve producing an "inactive" hormone, the hormone leptin, but it is now recognized as an active producer of many another fat hormone (adipokines), cytokines, and chemokine [5]. Macrophages in particular invade adipose tissue and it is associated with hypertrophy, hyperplasia and adipocyte remodelling that is a key part of the process in obesity. All of these changes become chronic and characterized by low-grade inflammation, which has been confirmed as a characteristic of an obese human profile and its associated co-morbidities, such as insulin-resistance (IR), Type 2 Diabetes (T2D) and cardiovascular disease [6].

Obesity markedly affects macrophage cellular metabolism, linking macrophage function to metabolism. Increased glycolytic activity (Warburg effect), decreased oxidative stress, and increased levels of glycolytic intermediates and succinate are characteristic of M1-like macrophages [7]. This metabolic shift is not only a response to activation but is also closely intertwined with its pro-inflammatory phenotype in a cause-and-effect manner, for several possible reasons. Increased glycolysis provides metabolic intermediates for biosynthetic pathways and promotes the rapid production of inflammatory mediators [8]. Succinate stabilizes HIF-1α and reactivates the pro-inflammatory genes under succinate-elevated conditions. Mitochondrial dysfunction includes downregulation of respiratory function and upregulation of mitochondrial reactive oxygen species (mtROS) production leading to activation of inflammatory pathways through activation of the NFκB and NLRP3 Inflammasome [9].

This is because there are a number of surprising key metabolic regulators for macrophage polarization and function. One of these, called AMP-activated protein kinase (AMPK), has been considered a master energy sensor that turns on fatty acid burning and switches off inflammatory pathways. AMPK activity is already negatively affected in obesity causing an increase in lipid levels and inflammation in macrophages [10]. Adenine nucleotide translocase 2 (ANT2) has been identified as a new mitochondrial regulator of pro-inflammatory macrophage activation, regulating the opening of the mitochondrial permeability transition pore (mtPTP) and production of mtROS induced by free fatty acids. Not only are these metabolic changes immediate responses to activation, but they are also permanent metabolic adjustments that can maintain inflammation in obesity and promote trained immunity [11].

Recent progress in identifying the role of immunometabolic dysregulation in obesity, however, has not yet been synthesized into a more complete picture of the molecular mechanisms by which linkages between adipose inflammation and atherosclerosis might contribute to cardiovascular risk, where shared pathogenic pathways exist. In this narrative review, we consolidate the latest information on the immunometabolic dysregulation induced by ATscc in obesity-associated cardiovascular risk and present potential therapeutic routes for the emerging global problem of obesity-associated metabolic and cardiovascular diseases.

Methodology

A literature review was carried out to evaluate the association between immunometabolic dysfunction and obesity-related cardiovascular disease. The medical subject headings (MeSH) were combined with the corresponding keywords for the different studies in the four electronic databases including PubMed, Scopus, Web of science, and Google Scholar and those published from 2000 to July 2026 on the databases were screened. Included studies were original human, animal and in vitro reports of biology of ATMs, immunometabolic reprogramming, inflammatory signalling, metabolic dysfunction or cardiovascular outcomes. Any published studies in English were acceptable, regardless of the date. Conference abstracts, reviews, systematic reviews, meta-analyses, case reports and editorials, opinion articles, letters, studies not reporting any methodological aspects, and studies not involving immune cells other than macrophages, or not relevant to obesity, insulin resistance, and/or cardiovascular disease were excluded.

The selection of studies was systematic to ensure transparency and rigour. These publications were also screened by hand, with a reference list of other relevant reviews and studies added to the search. The data were compiled in a standard format, including study design, study population, experimental models, molecular mechanisms investigated, immune and metabolic outcomes, cardiovascular findings, biomarkers, therapeutic targets, main results, relevance and translation, and study limitations. Data movement was performed by two independent reviewers, who reached consensus in the event of conflicts.

Studies were organised into a thematic narrative approach, grouped under general headings that encompass adipose tissue macrophage accumulation/polarisation, mechanisms of macrophage recruitment, immunometabolic reprogramming, impact on systemic metabolism and cardiovascular systems, impaired signalling pathways, and therapeutic opportunities. Data was analysed for identifying consensus and conflicting findings, gaps in knowledge and new mechanisms and therapeutic targets. In total, 15 themes were summarised across five focus areas: (1) Identification of Mechanical Pathways; (2) Relationships between Mechanical Pathways and Metabolic Phenotypes; (3) Temporal and dose-response relationships; (4) Therapeutic Targets and Interventions; (5) Mechanisms by which Adipose Damage and Inflammation links to cardiovascular disease. The extraction and synthesis of the data were performed without specialised software for data management or analysis. This is a narrative review, and no primary data were collected from human or animal participants; hence, no ethical approval is required. All studies within this scope of review adhered to ethical standards for research involving human subjects, with informed consent and appropriate institutional review board approval, and to standards for animal welfare in animal studies. The authors state that there are no conflicts of interest to disclose.

Review

The characteristics of the included studies have been presented in Table 1.

Table 1: Major Key findings and Clinical Relevance of the Studies Synthesizing Evidence.

Author (Year)	Study Design	Key Mechanism	Major Findings	Clinical Relevance
Weisberg et al. (2003)[12]	Human & animal experimental	Adipose tissue macrophage (ATM) infiltration	Obesity increased ATMs to ~40–50% of adipose stromal cells, with elevated levels of TNF-α, IL-6, and MCP-1.	Established ATMs as central mediators of obesity-induced inflammation and insulin resistance.
Weisberg et al. (2006)[13]	Mouse knockout study	CCR2/CCL2-mediated macrophage recruitment	CCR2 deficiency reduced macrophage infiltration, hepatic steatosis, and inflammation and improved insulin sensitivity.	Identified CCR2 as a therapeutic target to reduce metabolic and cardiovascular complications.
Galic et al. (2011)[14]	Mouse experimental	AMPKβ1 signaling	Loss of macrophage AMPKβ1 promoted M1 polarisation, inflammation, and insulin resistance.	Demonstrated that macrophage metabolism regulates systemic metabolic homeostasis.
Moon et al. (2021)[15]	Mouse experimental	ANT2-mediated mitochondrial dysfunction	ANT2 deletion reduced mtROS, NF-κB activation, and inflammatory cytokine levels, and improved insulin sensitivity.	Suggested mitochondrial modulation as a therapeutic strategy for obesity-associated CVD.

Author (Year)	Study Design	Key Mechanism	Major Findings	Clinical Relevance
Moreno-Viedma et al. (2016) [16]	Animal study	Shared inflammatory pathways	Identified 22 overlapping dysregulated pathways between obese adipose tissue and atherosclerotic plaques.	Supports common molecular mechanisms linking obesity and atherosclerosis.
Radushev et al. (2024)[17]	Human cross-sectional	Hyper-glycolytic immunometabolism	Obesity-induced glycolytic reprogramming, ROS production, and IL-8 secretion in monocytes.	Demonstrated metabolic rewiring contributes to chronic inflammation and ASCVD risk.
Smeehuijzen et al. (2024)[18]	Human observational	Monocyte metabolic flexibility	Insulin resistance shifted monocytes toward oxidative metabolism with reduced CXCL11.	Linked altered immune-cell metabolism to metabolic dysfunction independent of BMI.
Strand et al. (2022)[19]	Human cross-sectional	Macrophage polarization	Increased VAT M1-like macrophages correlated with insulin resistance; identified novel markers (CD85a, CD48, CD371).	Suggested new biomarkers and therapeutic targets for adipose inflammation.
Apovian et al. (2008)[20]	Human cross-sectional	Crown-like structures (CLS)	Inflamed adipose tissue (CLS+) was associated with insulin resistance and impaired endothelial function.	Demonstrated that adipose inflammation predicts vascular dysfunction independent of BMI.
Farb et al. (2011)[21]	Human cross-sectional	Metabolically healthy obesity	Approximately 30% of obese individuals lacked adipose inflammation and maintained normal vascular function.	Highlighted adipose tissue quality, rather than obesity alone, determines cardiovascular risk.
Makkonen et al. (2007)[22]	Human cross-sectional	Adipose inflammation & liver fat	Macrophage markers correlated with hepatic steatosis and insulin resistance.	Demonstrated the adipose–liver inflammatory axis in obesity.
Ahlin et al. (2013)[23]	Human cross-sectional	Macrophage gene expression	Macrophage markers remained associated with insulin resistance and dyslipidemia after adjustment for BMI.	Indicates inflammation contributes to metabolic disease beyond adiposity alone.
Kunz et al. (2021)[24]	Human cross-sectional	ATM burden & mitochondrial dysfunction	Increased macrophage infiltration correlated with systemic inflammation, reduced insulin sensitivity, and impaired mitochondrial respiration.	Reinforced the link between adipose inflammation and metabolic dysfunction.
Parvaresh Rizi et al. (2016)[25]	Randomized crossover trial	Postprandial immunometabolism	Carbohydrate-rich meals elicited exaggerated NF-κB-mediated inflammatory responses in obese insulin-resistant subjects.	Diet composition influences obesity-associated inflammation and cardiovascular risk.
Tercan et al. (2024)[26]	Human cohort	Clonal hematopoiesis (CHIP)	CHIP increased systemic IL-6 but was not associated with obesity-related metabolic complications.	Suggests clonal hematopoiesis modifies inflammation independently of obesity.
Valero-Muñoz et al. (2025)[27]	Mouse experimental	SIRT3-mediated mitochondrial protection	Preserved mitochondrial function reduced fibrosis and improved cardiac remodelling despite obesity.	Demonstrates that metabolic health influences cardiovascular outcomes in obesity.

All of the studies included in this review have shown that accumulation of adipose tissue macrophage (ATM), metabolic reprogramming, and chronic low-grade inflammation are mechanisms that are often implicated in the aberrations of the immunometabolic regulatory system in obesity. Previous studies have shown that obesity increases the number of macrophages infiltrating the adipose tissue via CCR2/CCL2, which also leads to an increase in the production of pro-inflammatory cytokines (such as, TNF-α, IL-6, and MCP-1), insulin resistance and metabolic abnormalities [10, 11]. The studies identified a number of metabolic sensors required for metabolic regulation on a long-term basis associated with mitochondrial dysfunction and reduced fatty acid oxidation, increased activation of mitochondria derived reactive oxygen species (mtROS), activation of NF-κB and JNK activation and polarization towards pro-inflammatory M1 phenotype.

Recently, human studies have confirmed that obesity causes reprogramming of metabolic pathways in immune cells at a glycolytic level as well as an oxidative level. In circulating monocytes, Radushev et al. found increased glycolysis, increased oxidative stress and increased secretion of IL-8, and Smeehuijzen et al. found increased oxidative dependency of the monocytes independent from BMI with increased insulin resistance. Strand et al., (2022) [17] found that the densities of M1 like macrophages was higher and three new surface markers CD85a, CD48 and CD371 were found to be associated with insulin resistance in adipose tissue, particularly VAT.

There are numerous studies related to clinical implications of Adipose tissue inflammation. Other studies have shown [18, 19] that the atherosclerosis scoring system, crown-like structures (CLS) and inflamed adipose tissue is associated with poor vascular function and insulin resistance and cardiovascular risk, but about 30 percent of the obese population was metabolically healthy in that minimal inflammation was observed in adipose tissue and positive vascular function was observed. Further studies have also found that adipose inflammatory

changes correlate with hepatic steatosis, the adipose inflammatory change shows a correlation with mitochondrial function, adipose inflammatory change has a correlation with dyslipidaemic changes, and even adipose inflammatory change and insulin-sensitivity.Others experiments have also established a correlation between adipose inflammatory changes, hepatic steatosis, adipose inflammatory change and mitochondrial function, adipose and dyslipidaemic change, and indeed adipose inflammatory change and insulin sensitivity. Moreover, at the molecular level, there were several common inflammatory pathways that were discovered by Moreno-Viedma et al. (2016) [14] to be shared between the obese adipose tissue (OAT) and atherosclerotic plaques (APs), which helps elucidate the relationship between obesity and cardiovascular diseases (CVDs).

All of these findings indicate that it is changes in immune and metabolic states and not adiposity per se that exert a greater influence on inflammation of adipose tissue. The genes, macrophage recruitment (CCR2/CCL2) and macrophage metabolic regulators (AMPKβ1 and ANT2), inflammatory signaling pathways and mitochondrial dysfunction are possible therapeutic targets for reducing obesity-related insulin resistance and cardiovascular diseases.

Macrophage recruitment and polarization in obesity and in fat

Adipose tissue (AT) was found to be a source of leukocytes that function as macrophages and were expanded in obese mice and to a certain degree in obese human subjects, detecting the first connection between immunity and obesity by Weisberg et al. who found the presence of adipose tissue macrophages (ATMs), and reported that in obese mice up to 50% of the stromal vascular cells and in obese humans about 40% of all adipose tissue cells were macrophages. Bone marrow-derived monocytic component of the ATMs was found to accumulate in ATMs in response to CSF-1, suggesting that ATMs actively recruit monocytic cells that provide pro-inflammatory mediators including tumour necrosis factor alpha (TNF-α), interleukin 6 (IL6) and inducible nitric oxide synthase (iNOS) which explains the active inflammatory status of the ATMs instead of passive fat accumulation [12,13]

Similar findings were seen in subsequent human research. Significantly elevated macrophage markers (CD68 and ITGAM) in obese. These correlated with liver fat and insulin sensitivity, but were not associated with BMI, suggesting adipose tissue inflammation is not necessarily related to obesity and rather tied to metabolic dysfunction. Next, they found that, on their own, the obese and lean individuals in the study were not different when it came to inflammatory responses from macrophages [20]. Similarly, Ahlin et al. demonstrated increased expression of 18 macrophage markers in obese subjects, and among these markers, they identified associations with insulin resistance, dyslipidemia, and type 2 diabetes independently of BMI [23].

Macrophages have been found to surround dead adipocytes in crown-like structures (CLS), which have become a feature of adipose tissue inflammation. Insulin resistance and endothelial dysfunction were significantly higher among CLS-positive obese individuals than among CLS-negative individuals (with similar BMI) [19]. Building on this, Farb et al. (2011) [19] showed that the presence of the CLS+AT was independent of decreased endothelial function and antioxidant gene expression, and was associated with impaired vascular function and increased inflammatory gene expression [21].

In addition, it seems that macrophage polarization in obesity goes beyond the current dichotomous M1/M2 view. Kunz et al. (2021) [22] determined that BMI was directly correlated to the overall macrophage infiltration; however, changes in the M1/M2 ratio did not correlate with BMI, whereas adipose tissue IL-6 and CD68 expression were more strongly associated with systemic inflammation and insulin sensitivity [24]. On the other hand, in visceral adipose tissue (VAT), Strand et al. (2022) [22] found that M1 macrophages were dominant and that the M1:M2 ratio was positively correlated with insulin resistance and less healthy lipid profiles, independent of BMI, whereas M2 macrophages appeared to have protective metabolic properties [19].

Immunometric reprogramming of monocytes and macrophages in obesity

Obesity alone causes profound immunometabolic changes to circulating monocytes and tissue glucose sensors (resident macrophages) that activate of a pro-inflammatory, metabolic phenotype. Several characteristics of a hyper-glycolytic phenotypes of monocytes from obese subjects were identified by Radushev et al., (2024) [15] such as higher glycolytic activity, decreased mitochondrial mass and respiration, increased ATP production, lipid droplet accumulation and LPS-induced formation of Reactive Oxygen Species (ROS) and Interleukin 8 (IL-8) production upon stimulation. Obesity is associated with an increase in classical monocytes and myeloid-derived suppressor cells, and proteomic analyses revealed that glycolysis, migration, and phagocytosis pathways were altered, suggesting that monocyte metabolism is associated with foam cell formation and atherosclerosis [17].

Smeehuijzen et al. (2024) [16] also revealed that insulin resistance, but not BMI, correlates with the metabolic switch of glycolysis to oxidative metabolism of monocytes. We observed that decreased ECAR/OCR values were associated with insulin resistance, and that higher circulating CXCL11 levels were positively associated with glycolytic activity and negatively associated with insulin resistance, indicating that circulating CXCL11 can serve as a biomarker of metabolic health in monocytes. The study also revealed sex differences, with males having higher glycolytic activity, and speculated that oxidative metabolism in macrophages associated with lipids may be another mechanism for atherosclerosis [18].

One such study in lean and obese Chinese males revealed that markers of inflammation such as NF- KB and TGF- β were increased in obese insulin resistant men following a meal. They experienced increased inflammatory markers, such as NF-κB and TNFα after consuming a high carbohydrate meal. Lean and insulin-sensitive individuals in contrast had blunted inflammatory reactions, including a decrease in TNFα and increase in IL6. Similar differences were not observed with high-protein and high-fat meals; thus, postprandial hyperglycemia could play a critical role in immunometabolic dysfunction and may be responsible for the obesity-related exacerbation of cardiovascular risk [14].

Clonal Hematopoiesis and immunometabolic dysregulation in obesity

Obese individuals have an identified alternative pathway that leads to immunometabolic imbalance and cardiovascular risk: clonal hematopoiesis of indeterminate potential (CHIP), which includes somatic mutations in a subset of their hematopoietic stem cells. Tercan et al (2024) [24] measured the mutation frequency of CHIP in 297 individuals with overweight/obesity and found mutations in 28% of their subjects (mostly DNMT3A, 73, and TET2, 7) [26]. The presence of CHIP was associated with increases in leukocyte and neutrophil counts and in circulating IL-6 levels. Paradoxically, the ex vivo production of the same cytokine by peripheral blood mononuclear cells (PBMCs) stimulated with TLR ligands was low, suggesting immune tolerance. Interestingly, there was no correlation between CHIP and metabolic syndrome, insulin resistance/obesity or adipose tissue inflammation. But, inflammation is believed to play a role in metabolic issues linked to obesity. Interestingly, CHIP carriers had fewer carotid plaques (38% vs 59%), suggesting that CHIP may affect plaque destabilization and that they tended to be stiffer (as indicated by augmentation index). These effects were observed to vary between sexes, with decreased cytokine production in women and increased neutrophil-to-lymphocyte ratio (NPR) in men. This yielded essentially similar data when analyzed in the same manner with DNMT3A-specific analyses, and whether there is an increase in inflammation in adipose tissue in CHIP carriers [16]. These findings give no support to the idea that CHIP promotes metabolic or atherosclerotic diseases in obesity and rather suggest that there are complex, sex-specific associations between CHIP and cardiovascular diseases.

Mitochondrial dysfunction and oxidative stress in immune-metabolic regulation

Key mechanisms underlying the association of obesity-induced immune system dysfunction with insulin resistance and cardiovascular disease are mitochondrial dysfunction and oxidative stress. In humans and mice, Moreno-Viedma et al. (2016) [14] found molecular changes in common, such as increased inflammatory pathways in adipose tissue and the atherosclerotic aorta in obese mice, and decreased oxidative phosphorylation pathways. The number of significant genes shared between inflammatory and mitochondrial

pathways was considerable, indicating shared mechanisms underlying obesity, insulin resistance, and atherosclerosis. However, interestingly, the pathways affected were those of IL-6/JAK/STAT3, TNF-α/NF-κB, interferon gamma signaling, fatty acid metabolism, mTORC1 signaling, apoptosis, angiogenesis, coagulation, unfolded protein response and hypoxia, thus suggesting that there may be potential therapeutic targets here for both type 2 diabetes and cardiovascular disease [16].

In obese mice with heart failure with preserved ejection fraction (HFpEF) they found that decrease in cardiac fibrosis and improvement of metabolic phenotype were caused by preservation of mitochondrial function achieved by overall increase of mitochondrial protein MITOF Activator in adipose tissue without changing the obesity itself in mice. These enhancements encompassed mitochondrial dysfunction improvement, the enhancement of antioxidant mechanisms, activation of an enzyme (namely SIRT3) involved in the regulation of mitochondrial metabolic activity, higher utilization of ketone bodies, decreased insulin resistance, and increased adiponectin levels, indicating mitochondrial quality control as a potential therapeutic target in obese HFpEF [27].

Galic et al. [12] pointed out the protective function of the AMP activated protein kinase (AMPK) β1 in macrophages. AMPK β1 deficiency led to a body-weight-independent reduction in mitochondria content, a decrease in fatty acid oxidation, an increase in M1 (inflammatory) macrophage polarization, production of inflammatory cytokines, macrophage infiltration in adipose tissue and liver, as well as insulin resistance in the liver. Based on these findings, a new potential role for macrophage AMPK as a mediator of inflammatory pathways and particularly in insulin sensitivity has been proposed and this could be important to limit over-ingestion of nutrients for adaption [14].

Moon et al. (2021) [13] found that the adenine nucleotide translocase 2 (ANT2) is another important immunometabolic regulator in macrophages, the deficiency of which in myeloid cells improved glucose tolerance and insulin sensitivity, and prevented accumulation of pro-inflammatory macrophages and inflammation in adipose tissue. Mechanistically, the ANT2 increased the levels of mitochondrial ROS, the HIF-1α and NF-κB signaling pathways, and mitochondrial dysfunction, and decreased metabolic flexibility. Overall, the results in the current study combined with others indicate that the ANT2–mitochondrial ROS–HIF-1α signaling pathway is a viable therapeutic target in obesity-related inflammation and insulin resistance, a field that will benefit from the development of novel therapeutics that counter the effects of ANT2 depletion [15].

Chemokine axis CCR2/CCL2 in the context of Adipose tissue inflammation

The CCR2/CCL2 axis is a validated target identified in obesity-associated inflammation and a significant contributor to the recruitment of monocytes to adipose tissue. As shown by Weisberg and his co-workers, a Ccr2-deficient diet resulted in decreased food consumption and the loss of fat-overload obesity. In the obese mice with the same amount of adiposity, Ccr2-deficient mice had 35% fewer ATMs, increased insulin sensitivity (50% less HOMA-IR), ATMs contained 50% less hepatic triglycerides, plasma levels of adiponectin were elevated, ATM levels of adiponectin gene expression were increased, and 71 inflammatory gene ontologies were reduced, and 52 metabolic gene ontologies were increased [19]. The administration of an inhibitor of CCR2 (INCB3344) for a short period (17 days) resulted in animals feeding less and becoming more insulin-sensitive, with a 25% reduction in ATM content without any changes in body mass, indicating the therapeutic potential of inhibiting this pathway. The CCR2 antagonist did not consistently reduce inflammatory gene expression or hepatomegaly, indicating partial effects [13]. Interestingly, CCR2 regulates feeding via the central nervous system, a novel mechanism linking immune signals to energy balance. CCR2-dependent insulin sensitivity is not entirely adiponectin-dependent; the half-life of ATM turnover is about 1 month, suggesting a potential window for therapeutic intervention. These results show two definitive roles for CCR2 blockade: reducing inflammation and affecting appetite, making CCR2 an attractive drug target in obesity-related metabolic disease [12].

Inflammation, Vascular Dysfunction and Cardiovascular Risk in Adipose Tissue

Many studies have documented a close relationship between inflammation in adipose tissue and vascular disease, thus offering a likely mechanism of how obesity and cardiovascular disease come together. Also, Apovian et al. (2008) [18] initially found that obese patients with crown-like structure (CLS) positive adipose showed an impaired vasodilation that was endothelium-dependent, as well as increasing levels of adipose tissue, both CD68+ and tumor necrosis factor (TNF)-α, insulin resistance, and hs-CRP and decreasing adiponectin levels than CLS-negative subjects. Interestingly, there was no serum inflammatory cytokine differences between groups, although these local inflammatory cytokines within adipose tissue may play a more significant role in the vascular dysfunction process [20].

Farb et al. (2011) [19] extended this observation and similarly showed that obese subjects who were not CLS had endothelial function similar to that of lean subjects. In contrast, those who were CLS had marked endothelial dysfunction with decreased flow-mediated dilation. Not only the amount of fat was important; the CLS status predicted endothelial dysfunction and was associated with an increased prevalence of diabetes and hypertension, suggesting that adipose tissue quality is also relevant to cardiovascular risk. These findings also corroborate the idea of metabolically healthy obesity and suggest that obesity without adipose inflammation can prevent metabolic and vascular complications [21].

Kunz et al. (2021) [22] further confirmed adipose tissue inflammation as a common denominator of obesity, insulin resistance, and mitochondrial dysfunction. Adipose IL-6/macrophage infiltration was strongly associated with insulin sensitivity but not with BMI, and serum (systemic) CRP/TNF-α was tightly correlated with impaired skeletal muscle mitochondrial respiration. As BMI increased, there was a corresponding decrease in mitochondrial oxidative capacity; but ATP production was maintained, inferring compensatory mitochondrial adaptations. These data support the role of adipose inflammation in the link between inflammatory signaling and a decrease in metabolic function unrelated to obesity itself [24].

These observations were built upon by Radushev et al., (2024) [15] who showed that in obese subjects, the monocytes contained an increased amount of lipid droplets and were selected for enhanced glycolysis, sustained oxidative burst, and higher secretion of IL-8, all promoting the formation of foam cells as well as their penetration into the arterial wall during atherosclerosis. Enhanced reactive oxygen species intake and impaired immune function were observed and linked to the expansion of myeloid-derived suppressor cells, providing a direct link between altered monocyte immunometabolism and cardiovascular disease and identifying drug targets [17].

Therapeutic implications:

Together, these data highlight several therapeutic targets for amelioration of cardiovascular risk in obesity, and provide the mechanism underpinning clinical intervention. In obese monocytes, inhibition of NADPH oxidase (NOX2) by GSK2795039 reduced IL-8 secretion, suggesting a novel anti-inflammatory strategy [14]. Another possibility for regulating the metabolic balance of monocytes, suggested by Smeehuijzen et al., (2024) [16] is the CXCL11/ACKR3/PKM2 axis. The interventions that seem promising for preserving mitochondrial function in HFpEF, as shown by Valero-Muñoz et al (2025) [25], are SIRT3 activation and modulation of ketone body metabolism [18]. Evidence suggests that pharmacological activation of macrophage AMPK with A-769662 reduces inflammatory responses, including IL-1β and CXCL1 release, and promotes M2 macrophage polarization. However, because A-769662 also inhibits Na^+-K^+-ATPase as an off-target effect, these findings should be interpreted with caution, and the observed anti-inflammatory effects may not be exclusively AMPK-mediated [28]. ANT2 inhibition, mtPTP blockade, and mitochondria-targeted ROS scavengers (MitoTEMPO) were effective in decreasing obesity-related inflammation and insulin resistance in preclinical models [17]. The CCR2 antagonist (INCB3344) decreased ATM and enhanced insulin sensitivity. Also, there is evidence that

macronutrient manipulation, especially reducing the consumption of high-glycemic-load meals in insulin-resistant obese people, may reduce post-meal immunometabolic dysfunction [27].

Moreover, lifestyle changes and weight loss seem to reverse immunometabolic dysfunction. Makkonen et al. (2007) [20] clearly demonstrated that there is no intrinsic difference between monocyte-derived macrophages from obese subjects and from non-obese subjects, either in basal cell culture or in LPS-stimulated cells, and that the adipocyte environment is responsible for the inflammatory phenotype, which is reversible without an immune cell reprogramming process [22]. The finding has profound implications for therapeutic strategies: the immunometabolic derailment in obesity does not appear irreversible and can be modified by environmental and lifestyle factors. The presence of metabolically healthy obese individuals with reduced adipose inflammation further suggests that targeting adipose inflammation may benefit cardiovascular health outcomes even without weight reduction [21].

The parallel pathways demonstrated by Moreno-Viedma et al (2016) [14] simultaneous increase (upregulation) of inflammatory response and accompanying decrease (downregulation) in oxidative phosphorylation both in adipose tissue and atherosclerotic aorta, provide a joint view of these two processes and offer a single mechanism to account for obesity-related cardiovascular disease and to postulate that targeting common molecular pathways may resolve both cardiovascular and metabolic disease[16]. Results from Valero-Muñoz et al (2025) [25] also highlight the active role of metabolic health in disease severity, proposing that insulin resistance status should be considered when stratifying patients in clinical trials testing treatments for obesity-associated cardiovascular disease [27].

Discussion

The current review highlights the steadily increasing evidence that links obesity to cardiovascular disease (CVD) through important immunometabolic mechanisms. Our results align with previous reviews, which identified low-grade chronic inflammation as a hallmark of obesity, but also showed that changes in the metabolism, function, and quality of immune cells or adipose tissue are relevant to the cardiovascular risk associated with obesity.

Our results corroborate those of Kardinal & Wachten (2025) [26] who stated that obesity is a state of chronic inflammation characterised by elevated concentrations of pro-inflammatory cytokines, such as TNF-α and IL-6, that trigger insulin resistance [29]. Similarly, the vital functions of Adipose tissue Macrophages (ATM) in the obesity-related inflammatory response were highlighted by Jaroch, (2026) [27]. This phenomenon was observed further throughout the present review, with evidence highlighting that the recruitment of macrophages into adipose tissue is an active immune response rather than a passive response to fat expansion, with circulating monocytes recruited to adipose tissue. Moreover, the association between macrophage accumulation and inflammatory gene expression in adipose tissue and insulin resistance and dyslipidemia persisted when comparing graphs by BMI, even suggesting that inflammation of adipose tissue is a more important factor in metabolic dysfunction than obesity itself [30].

A significant addition to this review is up-to-date evidence on immunometabolic reprogramming of monocytes and macrophages. Previous reviews, such as Hinojosa Vera et al., (2025) [28] have mainly focused on macrophage polarization towards pro-inflammatory phenotypes during obesity. By contrast, the studies analyzed in this review showed that obesity is associated with extraordinary alterations in the metabolic properties of immune cells, including elevated glycolytic activity, reduced mitochondrial respiration, lipid droplet accumulation, oxidative stress, and chronic inflammatory activation. All of these metabolic adaptations foster foam cell formation, infiltration of the arterial wall, and atherosclerosis, and provide a mechanistic account of the putative higher risk of heart disease associated with obesity [31]. Our review would also facilitate the understanding of previous knowledge on mitochondrial dysfunction. Previous reviews have concluded that oxidative stress plays a role in obesity-related metabolic disease.

Subramaniyan et al., (2026) [29] have gathered evidence that proportionate mitochondrial regulatory pathways, such as AMP-activated protein kinase (AMPK), SIRT3, MitoNEET and adenine nucleotide translocase 2 (ANT2), have been identified as key modulators of macrophage activation, insulin sensitivity and cardiac remodelling. In experimental studies, three consistent findings emerged: preservation of mitochondrial integrity reduced inflammation, improved insulin sensitivity, and reduced cardiac fibrosis, with no effect on body weight. With this finding, attempts to restore mitochondrial function could be a therapeutic strategy per se, independent of weight loss [32].

Findings of the present study also support the existence of the adipose–vascular axis, first established by Turner L et al. (2025) [30], which connects inflammation in adipose tissue with endothelial dysfunction and cardiovascular disease. Individual studies reviewed showed that in addition to similar BMI, there was an independent association between the presence of crown-like structures (CLS) in adipose tissue and impairment of endothelial function, insulin resistance, and vascular dysfunction [33]. Notably, obese individuals without adipose inflammation are similar to "metabolically healthy" obese people, as described by Wong et al., (2025) [31] who displayed vascular function similar to that of lean individuals. These values suggest that there may be a relationship between parameter of the quality and/or inflammatory profile of the adipose tissue and the cardiovascular risk which may be more clinically relevant than the BMI [34]. The overall evidence suggests that a number of mechanisms play a role in the pathogenesis of CVD in obesity, such as adipose tissue inflammation, metabolic reprograming of immune cells, and dysfunction of mitochondria, oxidative stress and injury to the endothelial cells. In addition, this review incorporates recent mechanistic analyses which reveal a number of remarkable therapeutic targets that have not been addressed in prior reviews such as AMPK, SIRT3, ANT2, mitochondrial reactive oxygen species (ROS) and immune-metabolic signaling pathways. All these results indicate unconditioned of the management approach focused on weight and the incorporation of interventions that are able to restore immune and mitochondrial homeostasis without weight loss.

However, several caveats must be noted. Much of the mechanistic evidence comes from animal models or relatively small observational studies, which do not allow causality to be established and limit generalizability across different patient populations. Further, such variation across studies could have resulted from heterogeneity in study designs, methods for characterizing immune phenotypes, and definitions of metabolic health. Thus, longitudinal studies and RCTs designed to assess the efficacy of immunometabolic pathway targeting to this end are needed. Finally, the current review reinforces and further extends previous findings and confirms that immunometabolic dysfunctions are not only an epiphenomenon of obesity, but also a crucial mechanism in obesity-associated cardiovascular diseases. New data suggest that changes in the metabolism of immune cells and their mitochondria are key to vascular dysfunction and offer opportunities for precision therapeutics to mitigate cardiovascular complications of obesity.

Conclusion

This review highlights a shift in paradigm from “don't blame the fat” to the immunometabolic dysfunction of the fat to cause cardiovascular disease as a result of obesity. Adipose tissue macrophages (ATMs) are known to be recruited and polarized to promote pro-inflammatory effects through the CCR2/CCL2 axis, metabolic reprogramming, mitochondrial dysfunction, oxidative stress, or activation of inflammatory signaling pathways such as NF-κB and JNK. These leads to an increase in pro-inflammatory cytokines which results in insulin resistance, endothelial dysfunction, hepatic steatosis, and rapid atherosclerosis. This also hints there may be metabolically healthy obesity and it's the inflammation of the fat that correlates with metabolic and cardiovascular risk – not obesity alone. There are new players in inflammation, such as CCR2, AMPKβ1, ANT2 and metabolic pathways of macrophages; they are very promising to tackle chronic inflammation and cardiovascular complications. More longitudinal and clinical studies are needed, however, to validate these goals even more and apply metabolically personalized medicine approaches to the treatment of obesity-related cardiovascular disease

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