

Review

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# Obesity and atherosclerosis: the exosome link

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## Abstract

Obesity is a global public health issue with serious health consequences and rising prevalence. It is a risk factor for a broad range of diseases, particularly atherosclerosis and cardiovascular disease. Long-term weight loss is difficult to achieve, even with diet, life-style changes and anti-obesity drugs. The causes of the association between obesity and atherosclerotic cardiovascular disease are the subject of ongoing investigation. It is known that a chronic surplus in nutritional intake results in expansion and remodeling of adipose tissue, leading to chronic inflammation. Lipid overloaded adipocytes secrete pro-inflammatory adipokines and other mediators that produce this inflammatory state that may in turn, promote atherosclerosis, which is considered an inflammatory disorder. This review discusses the potential role of exosomes from adipose tissue in accelerating atherosclerosis in the setting of obesity. Exosomes are small membrane-bound vesicles that circulate in body fluids and are important participants in intercellular communication both locally and at a distance. They can transfer their cargo of protein, DNA, RNA and microRNA between cells, thus impacting cellular function and signaling. Adipose tissue-derived exosomes may be involved in heightening of the atherogenic environment and, if so, suggests a therapeutic target for the treatment and prevention of cardiovascular complications of obesity.

**Keywords:** Obesity, atherosclerosis, adipocyte, macrophage, exosome

## INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide<sup>[1-3]</sup>. Obesity increases the risk of ASCVD and death even after accounting for other known risk factors such as dyslipidemia, smoking, and hypertension<sup>[4]</sup>. The underlying mechanisms that produce the added harmful effects of obesity are poorly understood. Elucidating the mechanisms behind differences between obese individuals with and without atherosclerosis<sup>[5,6]</sup> could reveal therapeutic targets for treating



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the harmful cardiovascular consequences of obesity as an alternative or adjunct to weight-loss programs, which are known to have limited long-term success.

Adipose tissue acts as an active metabolic endocrine organ that releases not only hormone-like adipokines and inflammatory cytokines, but also cargo-carrying vesicles such as exosomes that may be considered a form of adipokine that contributes to the development of atherosclerosis<sup>[7-10]</sup>.

Adipose tissue in obese subjects is inflamed as compared to lean subjects and displays greater macrophage infiltration<sup>[11]</sup>. In the obese state, adipose tissue can no longer accommodate excess energy stores and among the maladaptive changes that occur are infiltration by a variety of inflammatory immune cells that interact with adipocytes to promote chronic inflammation<sup>[12]</sup>. Atherosclerosis progression is driven by inflammation and the pro-inflammatory environment fostered by excess adiposity is thought to be a critical link between obesity and ASCVD<sup>[13,14]</sup>. Sequential steps in atherosclerosis are: circulating monocyte adhesion to endothelium, penetration through the compromised barrier, differentiation into macrophages and excessive uptake of lipids<sup>[15]</sup>. Each of these steps may be vulnerable to interference by exosomes. This review will discuss the connection between adipose tissue and atherosclerosis and the potential role of exosomes in communicating atherogenic signals from fat depots to the arterial wall. Understanding these relationships may be invaluable in the understanding, prevention and treatment of ASCVD.

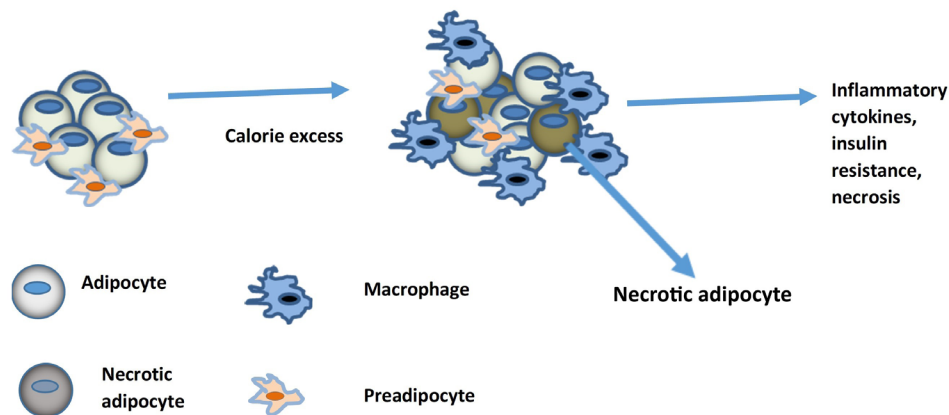
## ATHEROSCLEROSIS, INFLAMMATION AND LIPIDS

Atherosclerosis is a process that takes place in the arterial wall and its earliest stage involves a breach of the vascular endothelium by monocytes, which settle in the subendothelial space and become macrophages<sup>[16]</sup>. In an inflammatory environment, these macrophages in the subendothelial intima may exhibit impairment of cholesterol efflux, which leads to intracellular accumulation of modified low-density lipoprotein (LDL) and subsequent formation of plaque-forming lipid-rich foam cells<sup>[17,18]</sup>. Macrophages may become classically or alternatively activated to the M1 or M2 phenotype, respectively. During atherogenesis, monocytes enter the atheroma and differentiate into the M1 macrophage subtype and it is these M1 macrophages that play a crucial role in the initiation and progression of atherosclerosis<sup>[19]</sup>. M1 macrophages are considered pro-atherogenic because they easily transform into cholesterol-overloaded foam cells while the M2 subtype is less atherogenic and has a lesser propensity to form foam cells. M2 macrophages are associated with tissue repair and are enriched in regressing plaques<sup>[20]</sup>.

Macrophage cholesterol homeostasis is a delicate balance among influx, endogenous synthesis, esterification/hydrolysis and efflux<sup>[21]</sup>. The low grade chronic inflammation associated with obesity is a likely driver of dysregulated macrophage cholesterol homeostasis. It has also been shown to adversely affect expression of the proteins responsible for cholesterol influx and efflux by our group and others<sup>[22-29]</sup>.

A variety of cytokines may stimulate the atherosclerotic process, including interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , and interleukin (IL)-1 $\beta$ <sup>[30,31]</sup>. TNF- $\alpha$  and IL-1 $\beta$  induce cytokine and adhesion molecule expression and also encourage the migration of vascular smooth muscle and endothelial cells<sup>[32,33]</sup>. IFN- $\gamma$  promotes foam cell formation<sup>[25,34]</sup>.

One of the most compelling clinical challenges of our time is the increasing prevalence of obesity and its detrimental effects on the cardiovascular system. Obesity influences inflammation and the pathophysiological processes involved in atherosclerotic disease development<sup>[35]</sup>. Obesity and overweight are accompanied by unfavorable blood lipid profile patterns<sup>[36,37]</sup>. Dyslipidemia is a major risk factor for coronary artery disease. Among obese patients, the estimated prevalence of hypertriglyceridemia is twice as high as in non-obese individuals<sup>[38]</sup>. In addition, the atherogenic combination of hypertriglyceridemia with high LDL and low HDL is more prevalent in obese and overweight patients<sup>[39,40]</sup>. Unfortunately, high



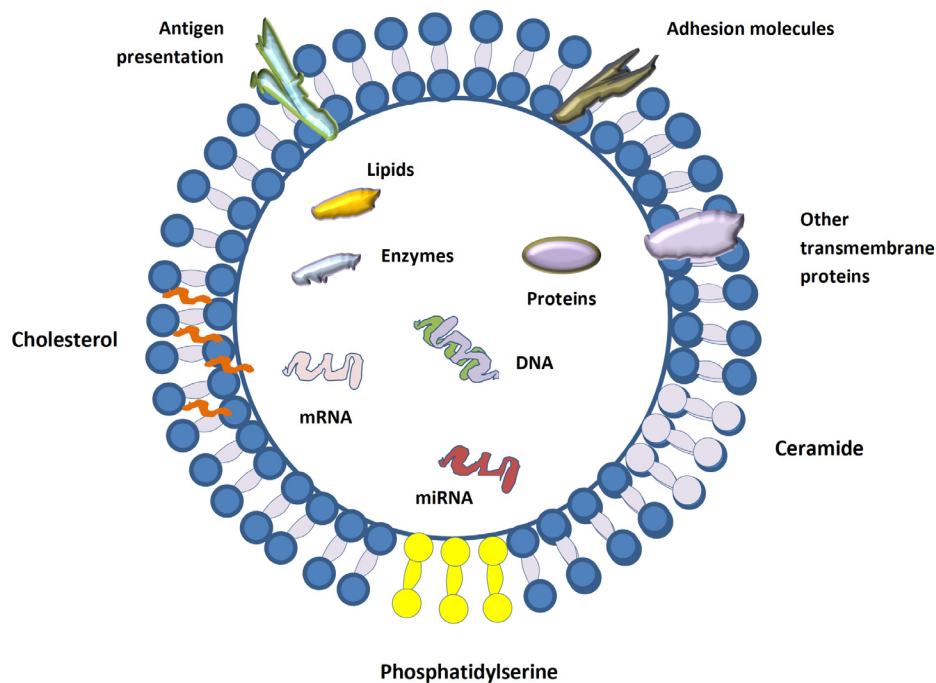
**Figure 1.** Change in white adipose tissue with unhealthy weight gain. Excess calorie intake results in dysfunctional adipose tissue characterized by a chronic inflammatory state with macrophage infiltration and phenotypic switching, inflammatory cytokine secretion, adipocyte necrosis, reduced insulin sensitivity and hypoxia

residual ASCVD risk remains even when LDL cholesterol is reduced to target levels and comorbidities are optimally treated<sup>[41-44]</sup>. Pathological processes within the arterial wall may continue despite statin and other pharmacologic therapies. The standard lipid profile would not be sensitive to this type of regional arterial process because it measures liver metabolism of cholesterol and other systemic effects not localized at sites of atherosclerosis. Lipid dyshomeostasis at the cellular level within the artery is not reflected.

## ADIPOSE TISSUE

Adipose tissue is not simply an inert tissue for storing excess energy and a thermal insulator. It is an active endocrine organ at the center of metabolic dysfunctions associated with obesity<sup>[45,46]</sup>. Adipose tissue contains a variety of cell types including adipocytes, preadipocytes, pericytes, fibroblasts, endothelial cells and macrophages. The biology of adipose tissue is complex as it can exist in different forms and is classified as white adipose tissue (WAT) or brown adipose tissue (BAT) based on morphology and function<sup>[47]</sup>. WAT holds energy in the form of triglycerides as a buffer against starvation and is the largest free cholesterol reservoir in the body, while BAT is more energetically active, with a greater number of mitochondria and higher energy production<sup>[48]</sup>. Mature WAT adipocytes each contain a single large lipid droplet. Obesity induces changes in WAT leading to increased lipolysis, insulin resistance, adipocyte hypertrophy and regions of hypoxia [Figure 1]. WAT secretes into the bloodstream many adipokines, which are bioactive molecules that are thought to contribute to the inflammatory milieu, thus promoting atherosclerosis<sup>[49-52]</sup>. However, anti-inflammatory treatments have failed to reduce ASCVD, indicating that factors other than inflammatory mediators are involved in the interplay between adipose tissue and blood vessels<sup>[53,54]</sup>. Exosomes may be one of the links that contribute towards development of ASCVD in obesity<sup>[55]</sup>.

Over the last few years, BAT has also been recognized as a potential therapeutic target in the prevention of atherosclerosis<sup>[56-58]</sup>. BAT consumes energy and generates heat through the action of uncoupling protein 1, which disconnects the electron transport chain from ATP synthesis<sup>[59]</sup>. The distribution of brown adipocytes in the body maximizes the cytoplasmic-lipid interface, making their involvement in fatty acid metabolism more effective than white adipocytes. In mice, brown adipocyte-derived endocrine factors significantly diminish body weight via elevation of oxygen consumption and decrease in total body fat mass<sup>[60]</sup>. Activation of endogenous brown adipocytes induces intracellular lipolysis of triglycerides and



**Figure 2.** Exosome structure. Exosomes are microvesicles delineated by a membrane enriched in phosphatidylserine and contain DNA, mRNA, miRNA, proteins and lipids

thus, leads to release of fatty acids and glycerol in the cytoplasm with reduced plasma triglyceride levels and obesity<sup>[61,62]</sup>.

Adipose tissue is a key organ that controls lipid metabolism and energy distribution, as well as regulation of endocrine function related to cardiovascular disease. Endocrine functions of adipose tissue are mostly attributed to their ability to secrete adipokines, hormones and cytokines that regulate energy homeostasis and satiety<sup>[7]</sup>. There are over 600 known adipokines but the most well-studied are the anti-inflammatory adiponectin, which is decreased in obesity, and leptin, which is secreted mostly by WAT and is present unbound in the circulation at higher levels in obesity<sup>[63-65]</sup>. Adipokines are carried by human adipocyte exosomes and leptin has been detected in mouse serum exosomes while adiponectin has been found in rat adipose tissue exosomes<sup>[66-68]</sup>.

## EXOSOMES AND ADIPOCYTE-DERIVED EXOSOMES

Exosomes are a type of extracellular vesicle with a size of 30-150 nm and a specific density of 1.13-1.21 g/mL. They are found in blood and other biological fluids. Exosomes are released into the extracellular space when multivesicular bodies fuse with the cellular plasma membrane<sup>[69,70]</sup>. Exosomes carry nucleic acids such as microRNA (miRNA), messenger RNA (mRNA) and mitochondrial DNA as well as proteins and lipids [Figure 2]. These exosome components are encased in a phospholipid membrane rich in ceramides, cholesterol and sphingomyelin, often with high phosphatidylserine content<sup>[71-73]</sup>. Exosomes help mediate signal transduction and provide a means for cell-to-cell communication over a distance and between organ systems<sup>[74]</sup>. Signaling pathways can be impacted by exosomes through the miRNAs they carry. miRNAs are small non-coding RNAs that negatively regulate gene expression by impeding translation or inciting instability of complementary mRNA targets, thus inhibiting protein formation<sup>[75]</sup>. Exosomes carrying miRNAs can be taken up via endocytosis or pinocytosis into recipient cells<sup>[76]</sup>.

It should be noted that there are different circulating particles in the blood and bodily fluids, collectively known as extracellular vesicles. These are heterogeneous in size and include not only exosomes, but also

microparticles, which are larger in size but have similar composition and structure<sup>[77]</sup>. It is difficult to differentiate between these, but we have tried to confine this discussion as much as possible to exosomes. The appearance of adipose-derived exosomes in the circulation has been documented in humans and mice<sup>[78,79]</sup>. Adipocyte-derived exosomes may be considered a form of adipokine<sup>[79]</sup>. In mice, adipose tissue is an important source of circulating exosomal miRNAs in the obese state<sup>[79]</sup>. The miRNA cargo of adipocyte-derived exosomes may influence pathways involved in obesity and atherosclerosis<sup>[80-82]</sup>. Many miRNAs have been shown to be differentially expressed in obese adipocyte exosomes, compared to lean adipocyte exosomes in both mouse and human<sup>[83]</sup>. Adipocyte-derived exosomes affect insulin resistance<sup>[84]</sup>. Mice with adipose tissue-specific knockout of Dicer, a large multi-domain ribonuclease enzyme responsible for the biogenesis of miRNA, produce exosomes with low miRNA content and exhibit a form of lipodystrophy marked by loss of WAT and whitening of BAT, as well as insulin resistance and dyslipidemia<sup>[79,85]</sup>. When WAT from wild type mice is transplanted into Dicer knockouts, circulating miRNAs are restored and glucose tolerance improves. Phenotypic change of cultured Dicer knockout brown preadipocytes to a white adipocyte-like state was modulated by specific miRNAs miR362, miR365 and miR346. Exosomes from adipose tissue macrophages of obese mice confer poor glucose tolerance and insulin resistance when transferred to lean mice<sup>[86]</sup>. A comparison of miRNA content of adipose tissue macrophage exosomes of obese versus lean mice showed that miR155 was much more abundant in exosomes from obese mice and this miRNA was shown to inhibit insulin signaling via downregulation of peroxisome proliferator-activated receptor  $\gamma$ , a key regulator of adipocyte differentiation, glucose and lipid metabolism. Mice with knockout of miR155 fed a high fat diet for 12 weeks exhibited less obesity-induced glucose intolerance and insulin resistance, compared to wild type mice on a high fat diet. When wild type bone marrow was transplanted into miR155 knockouts, glucose tolerance and insulin sensitivity were impaired with feeding of high fat diet.

In mice, fibroblast growth factor (FGF)-21, a member of the FGF family with hormone-like actions that regulates glycolipid metabolism, can be downregulated in liver by miRNA29b carried in exosomes<sup>[87,88]</sup>. This effect of adipose tissue exosomes on FGF21 may be pro-atherogenic since FGF21 is considered atheroprotective and improves the cardiometabolic profile in obesity and diabetes<sup>[89]</sup>. Exosomes released from adipose tissue of obese mice and injected into wild type mice induce activation of monocyte differentiation to macrophages in the latter, causing inflammatory cytokine production through the toll-like receptor (TLR) 4 pathway<sup>[90]</sup>. Macrophages in atherosclerotic lesions express TLRs, including TLR4, a type of pattern recognition receptor that is known to mediate inflammatory activation and TLR4-deficient mice are protected from forming atherosclerotic lesions<sup>[91]</sup>. Both pro-inflammatory/pro-atherosclerotic (M1) and anti-inflammatory (M2) macrophage phenotypes were induced by adipose tissue exosomes. The obese mouse adipose exosomes also caused insulin resistance in wild type mice. Mouse exosomes derived from visceral adipose tissue cause foam cell formation in a mouse macrophage cell line, likely due to inhibition of cholesterol efflux due to decreased expression of ATP binding cassette transporter (ABC) A1 and ABCG1, reverse cholesterol transport proteins that are needed to prevent lipid overload<sup>[92,93]</sup>. Adipocyte exosomes affect macrophage function in humans as well<sup>[94]</sup>.

Exosomes from adipose tissue may also influence vascular endothelial cells, but this is not as well-studied as in macrophages. Vascular endothelial cells take up adipose tissue exosomes and it is postulated that obese adipose tissue may secrete exosomes with pro-inflammatory cargo that could then activate the endothelium<sup>[95-97]</sup>. Confirmation of the interaction of adipocyte exosomes and vascular endothelium awaits further study.

Pericytes are pluripotent contractile cells embedded in the basal membrane surrounding endothelial cells that directly interact with endothelium, and are increasingly recognized for their involvement in atherosclerosis<sup>[98,99]</sup>. At this time, there is no data on adipocyte exosome effect on pericytes or pericyte-

endothelial interaction, but it is known that pericytes can affect the endothelium through exosomes and so, adipocyte-to-pericyte communication via exosomes may merit investigation<sup>[100]</sup>.

Both proteins and miRNAs within exosomes may be involved in their effects. Adipocyte exosomal miRNAs can influence macrophages resident within adipose tissue towards an inflammatory direction and can be delivered to the vasculature where *in vitro* studies have shown that they induce pro-atherogenic changes in macrophages<sup>[101,102]</sup>. One example is miR-34a, which is expressed at a higher level in adipose tissue of obese compared to lean mice and also, in obese compared to lean humans<sup>[101]</sup>. In mice, miR-34a downregulated Kruppel like factor 4, a transcription factor that drives M2 macrophage polarization, and this resulted in less M2 and more M1 macrophages in adipose tissue. In human studies, the number of circulating adipocyte-derived extracellular vesicles has been found to correlate with insulin resistance in obese subjects and with serum triglyceride levels<sup>[103,104]</sup>.

## CONCLUSION

The link from obesity to adipose tissue dysfunction to adipose-derived exosome influence on atherosclerosis is only being explored now. Many of the experiments cited in this review utilize particles produced *in vitro* and then introduced into *in vivo* animal models. Even though this is a useful initial approach towards understanding the effects of different particles, it does not provide cause-and-effect evidence of what is occurring in humans *in vivo*. Rather, it guides direction for future studies.

Exosomes from adipose tissue are formed by inward budding of the limiting membrane of late endosomes, fuse with the plasma membrane and released into the blood or extracellular fluid<sup>[105]</sup>. We now have the technology to isolate exosomes of adipocyte origin directly from the blood for analysis of their content and sequencing of their miRNAs<sup>[105]</sup>. As more miRNA sequences are found to affect specific signaling pathways, we can expect further elucidation of how they impact multiple aspects of atheroma formation and maturation. A working hypothesis is that obesity induces chronic low-grade inflammation within adipose tissue leading to specific changes in exosome cargo from both adipocytes and resident macrophages. The miRNA and protein in these exosomes enter the circulation, reach the blood vessels and influence the endothelial monolayer, macrophages and the stability of the plaque. The adipocyte exosomes may also indirectly foster atherosclerosis by playing a role in insulin resistance and type 2 diabetes. Exosomes from adipose stem cells may exert protective, anti-inflammatory effects on macrophages, suggesting a means to develop countermeasures to the pro-inflammatory influence of adipose tissue<sup>[106]</sup>. While it is clear that macrophages are integral to the atherosclerotic process, their precise role is still uncertain. Macrophages may be part of the formation of a plaque, or they may be attracted to lipid deposits within the arterial wall and act as phagocytes absorbing these lipids, as has been observed in early atherosclerotic changes, and may participate either way<sup>[107]</sup>. Whatever the context, the effect of exosomes on macrophages in atherosclerosis is worthy of further study. Knowledge of processes through which adipose tissue exosomes may accelerate atherosclerosis progression would open up an opportunity to mitigate these negative effects, even in persons who do not lose weight. One such approach would be to design and produce exosomes harboring antagomirs to neutralize undesirable and overexpressed miRNAs<sup>[108]</sup>.

## DECLARATIONS

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### Authors' contributions

Researched data for the article, discussed its content, and wrote, reviewed, and edited the manuscript: Reiss AB, Kasselmann LJ, De Leon J

Researched data for the article, discussed its content, and edited the manuscript: Voloshyna I, Glass DS, Glass AD

### Availability of data and materials

Not applicable.

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None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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