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Advancing Atherosclerosis Management: Innovative Targeted Cell Therapy Approaches to Reverse Disease Progression and Enhance Vascular Health

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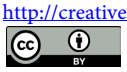

Abstract

Atherosclerosis, which is defined by plaque accumulation within artery walls, is one of the leading causes of cardiovascular disease and mortality. Although they help control symptoms and slow the condition's progression, traditional treatments, including medication, surgery, and lifestyle changes, do not address the underlying pathophysiology. Recent innovations in targeted cell therapy, such as gene editing, stem cell therapy, and exosome-based therapies, present encouraging methods for repairing endothelium damage, lowering inflammation, and restoring vascular health. This study examines how different therapy approaches are related, highlighting the potential of regenerative medicine to stop the progression of atherosclerosis. Despite the potential of these developments, issues such as financial constraints, regulatory obstacles, patient-specific efficacy variability, and safety concerns must be resolved. More research and technical developments are essential to incorporate these treatments into clinical practice, improve patient outcomes, and reduce the prevalence of cardiovascular disease worldwide.

Keywords

Atherosclerosis, Targeted Cell Therapy, Stem Cells, Regenerative Medicine, Endothelial Progenitor Cells (EPCs), Monocyte/Macrophage Modulation, Vascular Repair, Immune Modulation, Gene Therapy

1. Introduction

The accumulation of fatty substances, immune cells, and other materials inside the arterial walls is known as atherosclerosis and is a leading cause of heart failure

and mortality [1]. Although there are techniques to manage it, such as medication, lifestyle modifications, and sometimes surgery, they usually slow it down or address its symptoms [2]. Unfortunately, they usually do not address the underlying cause or completely restore normal artery blood flow and can lead to heart failure and mortality [3]. **Figure 1** demonstrates how atherosclerosis develops from a simple lesion to a complex lesion and potential intervention at the stages. The stages and treatment depicted include:

Initial Lesion: Normal histology, macrophage infiltration. Targeted cell therapy can modulate macrophage behavior by using immune-modulatory cells to promote anti-inflammatory macrophage phenotypes, thereby reducing the initial inflammatory response and preventing the progression of fatty streaks. Stem cell therapy, particularly with endothelial progenitor cells (EPCs), can repair and regenerate the endothelial lining of arteries, preventing the infiltration of LDL cholesterol and other harmful substances that contribute to initial lesion formation. Gene editing techniques like CRISPR/Cas9 can modify genes involved in lipid metabolism and inflammation, such as those regulating LDL receptor function, to enhance the clearance of LDL cholesterol from the bloodstream and reduce its accumulation in arterial walls. Additionally, exosome-based delivery systems derived from stem cells can deliver therapeutic agents directly to the site of initial lesions, carrying anti-inflammatory molecules and growth factors that promote endothelial repair and reduce lipid accumulation.

1) Fatty Streak: Intracellular lipid accumulation. Targeted cell therapy can address the formation and progression of fatty streaks in atherosclerosis by reducing foam cell formation, exerting anti-inflammatory effects, enhancing cholesterol efflux, and utilizing exosome-based delivery. By modulating macrophage activity and promoting the clearance of oxidized LDL cholesterol, these therapies can prevent the buildup of foam cells and the emergence of fatty streaks. Mesenchymal stem cells (MSCs) can reduce local inflammation within the arterial wall, stopping fatty streaks from growing worse to more advanced lesions. Gene editing techniques like CRISPR/Cas9 can increase the expression of the genes that regulate cholesterol efflux, such as ABCA1 and ABCG1, increasing cholesterol removal via decreasing the production of foam cells and macrophages. Additionally, exosomes derived from stem cells can deliver therapeutic agents that promote cholesterol efflux and reduce inflammation, carrying microRNAs and proteins that enhance cholesterol removal from macrophages and prevent fatty streak formation.

2) Intermediate Lesion: Intracellular and extracellular lipid accumulation. For the intermediate lesion stage of atherosclerosis, targeted cell therapy interventions include macrophage reprogramming, endothelial progenitor cell (EPC) therapy, gene editing for inflammation reduction, exosome-mediated cholesterol efflux, anti-inflammatory cytokine delivery, and nanoparticle-based drug delivery. These approaches aim to modulate macrophage behavior, repair endothelial damage, reduce inflammation, enhance cholesterol removal, and deliver therapeutic agents

directly to the affected areas, thereby addressing the progression of atherosclerotic lesions.

3) Atheroma: Extracellular lipid core development. For the treatment of atheroma, several targeted interventions can be employed, including macrophage apoptosis induction, cholesterol efflux enhancement, anti-inflammatory cytokine delivery, gene editing for lipid metabolism, exosome-based anti-inflammatory delivery, and nanoparticle-mediated drug delivery. These strategies aim to reduce the accumulation of lipids, modulate inflammatory responses, and promote the removal of cholesterol, thereby addressing the underlying mechanisms of atheroma formation and progression.

4) Fibrous Plaque: Fibrous/calcific layers. For the treatment of fibrous plaque, several targeted interventions can be utilized, including fibroblast modulation, collagen degradation inhibition, stem cell therapy for plaque stabilization, gene editing for matrix metalloproteinases (MMPs), exosome-based delivery of anti-fibrotic agents, and nanoparticle-based drug delivery. These approaches aim to modulate fibroblast activity, prevent collagen breakdown, stabilize plaques, regulate MMPs, and deliver therapeutic agents directly to the affected areas, thereby addressing the progression and stability of fibrous plaques.

5) Complicated Lesion: For the treatment of complicated lesions or plaque rupture, several targeted interventions can be employed, including plaque stabilization via anti-inflammatory agents, macrophage reprogramming to reduce inflammation, gene editing for thrombosis prevention, exosome-based delivery of anti-thrombotic agents, nanoparticle-mediated ROS scavenging, and targeted mRNA therapy for inflammation modulation. These strategies aim to stabilize plaques, reduce inflammation, prevent thrombosis, and deliver therapeutic agents directly to the affected areas, thereby addressing the underlying mechanisms of lesion complications and rupture.

1.1. Limitations of Current Treatments

Despite major advances in pharmacological and surgical management, current therapies for atherosclerosis remain largely palliative and do not reverse the underlying disease process. Statins, while effective at lowering LDL cholesterol, do not significantly restore endothelial function or remove established plaque deposits [4]. Antihypertensives and antiplatelet agents reduce cardiovascular risk but fail to address the persistent vascular inflammation and immune activation that characterize disease progression [5].

Surgical procedures such as angioplasty and stenting offer mechanical relief of arterial blockages but are inherently invasive and do not eliminate the risk of recurrent events. Furthermore, a considerable number of patients experience adverse outcomes despite adherence to guideline-directed medical therapy, a phenomenon attributed to residual cardiovascular risk [6]. These challenges highlight the clinical need for therapeutic approaches that can directly target the biological drivers of atherosclerosis and potentially induce long-term vascular repair.

1.2. How Targeted Cell Therapies Address These Gaps

Targeted cell therapies offer a promising strategy to overcome the limitations of conventional treatments by focusing on the biological mechanisms driving atherosclerosis. These therapies aim to repair endothelial damage, regulate immune responses, and modulate lipid metabolism approaches not typically achieved with existing pharmacological or surgical interventions.

Stem cell-based therapies, including the use of mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs), have demonstrated immunomodulatory and regenerative capabilities that may enhance vascular healing and stabilize plaques [7]. Gene editing tools such as CRISPR/Cas9 have shown the potential to correct mutations in lipid-handling genes, reduce LDL cholesterol levels, and diminish atherosclerotic burden in preclinical models [8]. In addition, exosome-based therapies derived from stem cells facilitate targeted delivery of microRNAs and proteins to sites of vascular injury, reducing inflammation and promoting endothelial repair with minimal systemic effects [9].

Collectively, these cell-based approaches represent a shift from symptomatic treatment toward modification of disease pathophysiology, providing new opportunities for long-term disease management and potential reversal of atherosclerotic damage [10].

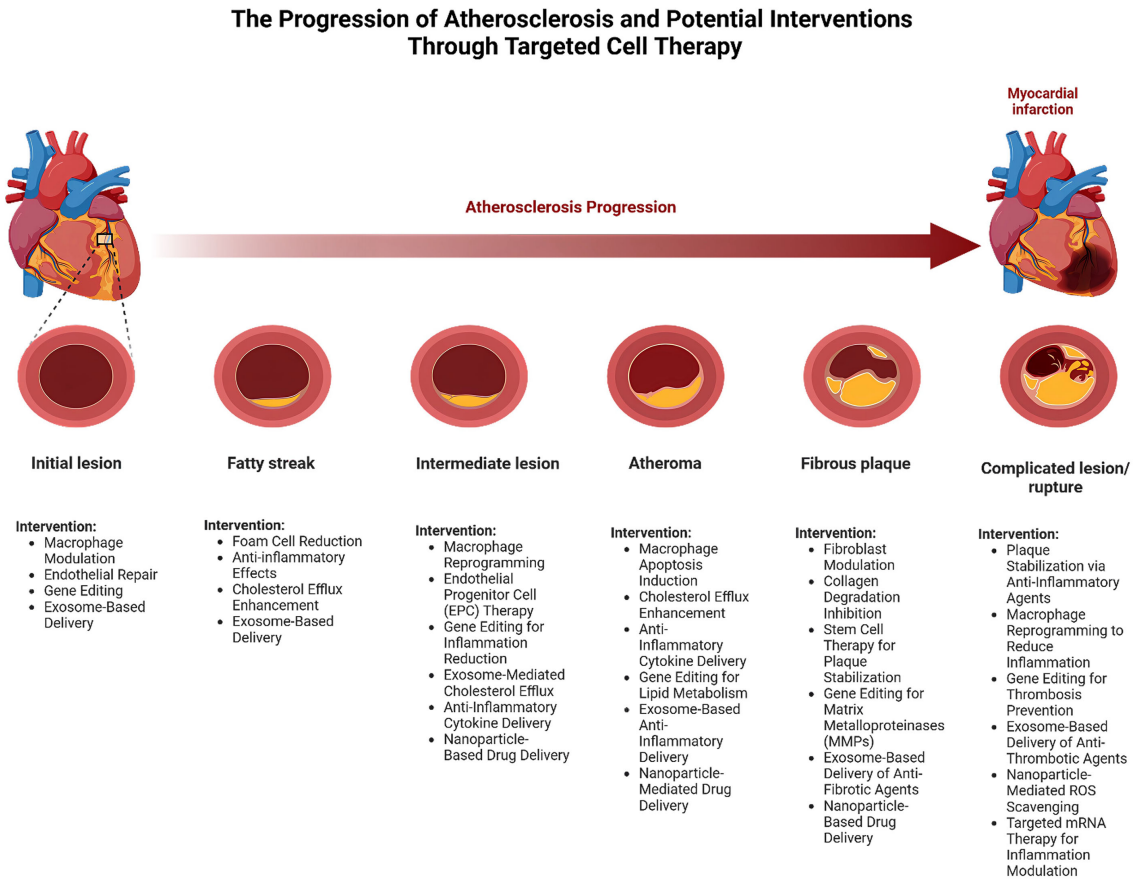

Figure 1. Stages of atherosclerosis and targeted cell therapy intervention.

1.3. Objectives and Significance of the Study

Recent developments in cell-based therapeutics and regenerative medicine have created new opportunities to address the molecular underpinnings of atherosclerosis and treat it at its source. New approaches to targeted cell treatment, including immune-modulatory cells, stem cells, and gene editing techniques, are promising in improving endothelium repair, lowering inflammation, stabilizing plaque, and even reversing arterial thickness [11]. By improving vascular health and restoring normal blood vessel function, these treatments seek to offer a more comprehensive and perhaps therapeutic approach than merely managing atherosclerosis [12].

The objective of the study is to assess how well immune-modulatory cells can lower inflammation and encourage endothelium repair in atherosclerosis. Additionally, it will explore the potential of gene editing techniques to enhance lipid metabolism and reduce plaque formation. By investigating these novel treatments, this research offers cardiovascular medicine an interesting new avenue. Examining the therapeutic potential of different cell types, delivery systems, and mechanisms of action in stopping the progression of the disease, this study explores the most recent advances in targeted cell therapy for atherosclerosis [13]. It also highlights the potential for revolutionary advances in the management of vascular health and addresses the difficulties and potential pathways for these cutting-edge therapies in clinical practice [14].

By advancing our understanding of targeted cell therapies, this research could lead to more effective treatments for atherosclerosis, ultimately reducing the prevalence of cardiovascular diseases and improving patient outcomes. This study is among the first to integrate gene editing techniques with stem cell therapy to address both lipid metabolism and inflammation in atherosclerosis, making a unique and innovative contribution to the field.

1.4. Materials and Methods

Table 1. PRISMA flow diagram illustrating the literature search and article selection process for studies on targeted cell therapy in atherosclerosis.

Identification	Records identified through database searching (n = 1.452)
Screening	Records after duplicates removed (n = 1.234)
Screening	Records screened (title and abstract) (n = 1.234)
Screening	Records excluded (n = 1.073)
Eligibility	Full-text articles assessed for eligibility (n = 161)
Eligibility	Full-text articles excluded (n = 100) Not targeted cell therapy or not relevant
Included	Studies included in final review (n = 61)

To guide the review of targeted cell therapies for atherosclerosis, a multi-step methodology integrating systematic literature identification and researcher map-

ping was employed. The final selection process followed the PRISMA guidelines, as shown in Table 1.

1) Broad Topic Identification and Initial Search: The initial step involved defining the core research area using the primary keyword "atherosclerosis." An exploratory search was conducted in PubMed, Scopus, and Web of Science to gauge the breadth and volume of relevant literature.

2) Keyword Matrix Construction and Iterative Refinement: To develop a robust and targeted search strategy, secondary keywords were generated related to targeted cell therapies—such as "macrophage therapy," "mesenchymal stem cell," "gene editing," "exosome delivery," and "immune modulation." These were structured into a keyword matrix and refined iteratively using Boolean operators. The aim was to balance comprehensiveness with specificity and to reduce irrelevant results.

3) Key Researcher Identification via Author Frequency Analysis: Author metadata was extracted from relevant studies. An author frequency table was compiled to identify recurring contributors and leading research groups in the domain. This enabled deeper insights into influential authors and institutions.

4) Foundational Paper Retrieval: Frequently cited and thematically pivotal studies across different keyword subgroups were prioritized for full-text retrieval. This step ensured that landmark studies were incorporated regardless of slight variations in keyword usage.

5) Paper Outline Generation: Using thematic overlap and keyword relationships, a logical structure was developed for the manuscript. This helped align the literature into coherent subsections: macrophage-targeted therapies and MSC-based interventions.

6) Screening and Inclusion: Articles published in English between 2000 and 2024 were included if they presented original research (in vitro, in vivo, or clinical) specifically on macrophage or MSC-based therapy for atherosclerosis. Reviews were included only for background or context. The final selection process followed PRISMA guidelines. A total of 1.452 records were identified initially, 1.234 remained after duplicate removal, and 61 were ultimately included. See Figure 1 for the PRISMA flow diagram outlining the article screening and inclusion process. outlining the article screening and inclusion process.

2. Understanding Atherosclerosis

Atherosclerosis is a complex, challenging condition affecting the artery walls that results in the development of plaques made of calcium deposits, inflammatory cells, fibrous tissue, and lipids. Normal blood flow is hampered over time by the narrowing, hardness, and loss of elasticity caused by this plaque accumulation. Atherosclerosis is caused by an interaction of lifestyle, environmental, and genetic variables, many of which interact intricately to encourage the onset and progression of the disease. Figure 2 provides a visual summary of the causes, risk factors, symptoms, and treatment options for atherosclerosis, highlighting the multifaceted nature of the disease and the various approaches to its management.

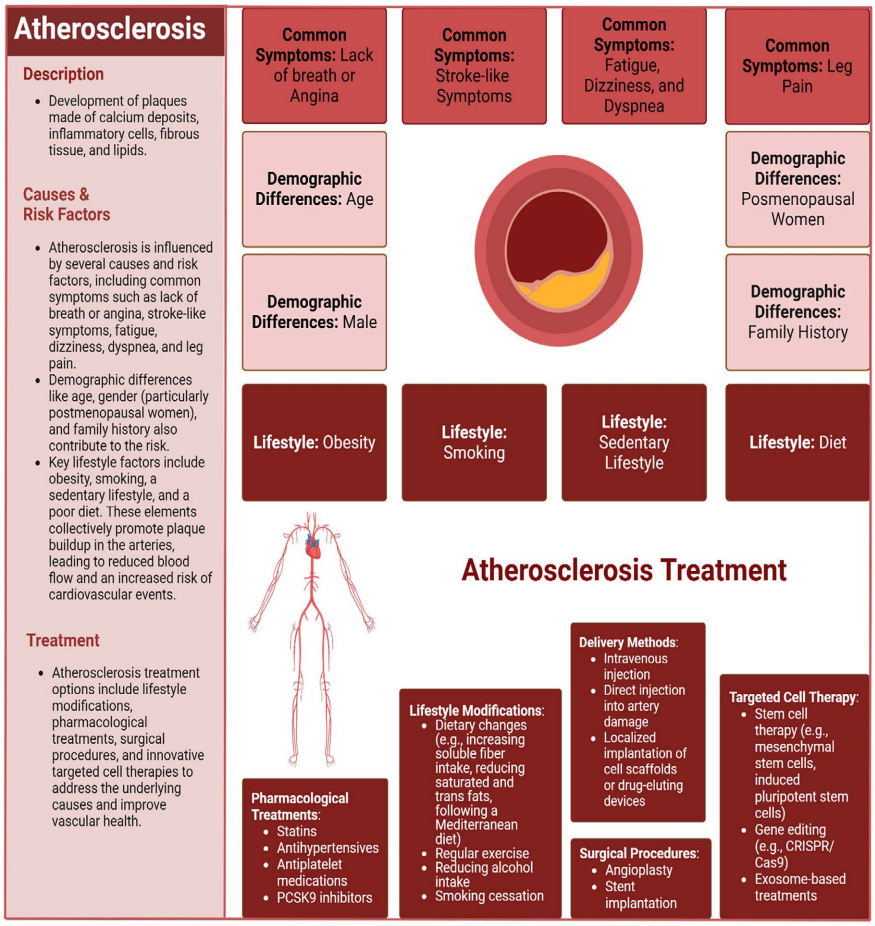

Figure 2. Overview of atherosclerosis.

The primary reasons and risk factors that contribute to the development of atherosclerosis are examined in detail below.

1) High LDL Cholesterol and Lipid Imbalance

One of the primary causes of atherosclerosis is an imbalance in lipid metabolism, namely the accumulation of low-density lipoprotein cholesterol (LDL), sometimes referred to as "bad" cholesterol. Cholesterol is transported to peripheral tissues by LDL particles. But when LDL cholesterol levels are too high, they can penetrate the endothelium and cause fatty streaks to form [15]. Oxidized LDL worsens this process by activating immune cells such as macrophages and causing a local inflammatory response. After failing in their attempt to remove oxidized LDL, these macrophages eventually turn into foam cells, helping to develop plaque [16].

2) High-density lipoprotein cholesterol

High- density lipoprotein cholesterol, sometimes known as "good" cholesterol, aids in the removal of cholesterol from artery walls and its transportation to the liver for waste removal. Therefore, the risk of atherosclerosis is also influenced by low HDL cholesterol levels. A key component that influences vascular health is a good lipid profile, which is defined by low LDL and high HDL. Dyslipidemia is a

known risk factor for atherosclerosis [17].

3) Increased Blood Pressure (Hypertension)

Another significant cause of atherosclerosis is hypertension. The endothelial cells lining the arteries are harmed by mechanical stress brought on by the continuous high blood pressure strain on the artery walls. A series of actions that promote inflammation and the development of atherosclerotic plaques are triggered by this endothelial damage [18]. Furthermore, elevated blood pressure makes the walls more permeable, which makes it easier for lipoproteins—especially LDL—to enter the walls of the vessels. The course of atherosclerosis is gradually accelerated by this cycle of endothelial damage and the inflammatory response.

Furthermore, hypertension has been shown to promote vascular remodeling, which makes the arteries harder and less capable of expanding in response to elevated blood flow, thus making the problem worse. A vicious cycle that accelerates the disease' s progression is produced by endothelial damage, increased lipid infiltration, and arterial stiffening.

4) Smoking

One of the strongest modifiable risk factors for the start of atherosclerosis is cigarette smoking. Nicotine and carbon monoxide, two dangerous chemicals found in tobacco smoke, cause direct injury to the endothelium, increasing susceptibility to lipid infiltration and the start of the inflammatory cascade. As stated above, smoking worsens the formation of plaques by increasing oxidative stress and oxidizing LDL cholesterol. Smoking also lowers HDL cholesterol levels, which makes it harder for the body to remove cholesterol from the arteries.

In addition to its effects on lipids, smoking increases the risk of forming a clot at the site of arterial damage, which can rupture plaques and cause acute cardiovascular events such as heart attacks and strokes.

5) Diabetes Mellitus

Atherosclerosis risk is greatly increased by diabetes, especially Type 2 diabetes. Atherosclerosis is characterized by endothelial dysfunction, which is worsened by hyperglycemia, or elevated blood sugar. The elevated glucose levels result in the generation of advanced glycation end products (AGE), which interact with cellular receptors to encourage inflammation and the formation of collagen and other components of the extracellular matrix in the artery walls. In addition, AGEs disrupt endothelial cell regular function, increasing their vulnerability to damage and promoting lipid deposition.

Furthermore, dyslipidemia, which includes low HDL cholesterol and high triglyceride levels, is frequently seen in people with diabetes and is significantly associated with an increased risk of atherosclerosis. Diabetes increases the chance of getting cardiovascular disease due to the combination of hyperglycemia, dyslipidemia, and endothelial dysfunction, which accelerates the formation of plaque in the arteries.

6) Obesity and Lack of Exercise

Because obesity is linked to both systemic inflammation and metabolic dysfunction, it is an important risk factor for atherosclerosis. Adipokines and inflammatory cytokines produced by excess fat, especially visceral fat, interfere with regular metabolic functions and lead to endothelial dysfunction. Furthermore, insulin resistance, which worsens glucose metabolism and increases the risk of Type 2 diabetes, is frequently associated with obesity, increasing the risk of atherosclerosis.

These risks are increased by physical inactivity. While lack of exercise can lead to the development of obesity, hypertension, and impaired cholesterol metabolism - all of which are critical factors in the initiation of atherosclerosis - regular physical activity is known to enhance lipid profiles, lower blood pressure, and support endothelial function.

The risk of atherosclerosis is increased by obesity, high blood pressure, and high cholesterol, all of which are caused by lack of physical exercise. Frequent exercise can lower cardiovascular risk and aid in controlling these conditions [19]. Physical inactivity and the risk of atherosclerotic cardiovascular disease were found to be significantly correlated in one study [20].

7) Genetics and Heart Disease in Families

An individual may be more vulnerable to atherosclerosis if they have a family history of early heart disease or stroke. Some people may be susceptible to higher levels of LDL cholesterol or other cardiovascular risk factors due to genetic factors [21]. Although there is no way to change these factors, being aware of them can lead to earlier monitoring and intervention [22].

8) Aging

The risk of atherosclerosis increases with age. Significant plaque accumulation and a higher risk of cardiovascular events can result from the long-term cumulative effect of risk factors in older adults. Throughout life, leading a healthy lifestyle can help reduce this risk.

2.1. Common Atherosclerosis Symptoms

1) Lack of breath and Angina in the Chest: A heart attack, loss of breath, or chest discomfort or pressure (angina) can occur if the coronary arteries are affected.

2) Stroke-like Symptoms: If carotid arteries are affected, symptoms such as abrupt numbness or weakness in the arms or legs, difficulty speaking, blurred speech, drooping facial muscles, and rapid changes in vision can resemble those of a stroke [23].

3) Fatigue, dizziness, and dyspnea: When the blood supply to different sections of the body is reduced, general symptoms like fatigue, dizziness, and dyspnea can arise.

4) Leg pain**:** A condition known as claudication occurs when the peripheral arteries are impacted, causing discomfort in the legs or other limbs, particularly when exercising.

5) Other symptoms: It may include a slam (bruit) sound in the affected artery, weakness and numbness in some regions of the body, or decreased blood pressure in one limb, depending on the arteries involved [24].

2.2. Demographic Factors

1) Age. As people age, their risk of atherosclerosis increases. A person in good health has a 50% chance of developing significant atherosclerosis after the age of 40, and the risk increases with age. Although it often begins in childhood, the disease becomes more apparent and severe in older years.

2) Gender Differences

Male incidence. Compared to premenopausal women, men generally have a higher incidence of atherosclerosis. The higher in men of LDL cholesterol levels than in women are partially responsible for this.

Postmenopausal Women. Because estrogen levels decrease after menopause, which used to offer some protection against cardiovascular disease, women' s risk increases dramatically [25].

Sex-Specific Factors. Women are more at risk than men for diabetes and smoking. For example, compared to men, women with diabetes have a 50% higher relative risk of dying from coronary heart disease.

3) Family History. Atherosclerosis is more likely to develop in people who have a family history of early cardiovascular disease. First-degree male relatives who develop premature atherosclerosis before the age of 55 and first-degree female relatives who do so before the age of 65 are considered to have premature atherosclerosis.

2.3. Lifestyle Factors

1) Obesity. By causing high blood pressure, high cholesterol, and diabetes, being overweight or obese increases the risk of atherosclerosis [26].

2) Smoking. Because tobacco destroys the inner lining and raises inflammation, it is a major risk factor for atherosclerosis.

3) Sedentary Lifestyle. Being inactive raises the risk of atherosclerosis by causing obesity, high blood pressure, and high cholesterol levels.

4) Poor Diet. Diet plays a crucial role as an impact of lifestyle on atherosclerosis development and treatment. Dietary intake of saturated fats, trans fats, cholesterol, and refined carbohydrates can raise the risk of atherosclerosis by causing plaque to accumulate in the arteries.

2.4. Demographics' Impact on Atherosclerosis

It is essential to understand these demographic characteristics to identify high-risk individuals and implement concentrated preventive measures in action. For example, more aggressive control of risk factors such as high blood pressure and cholesterol may be beneficial for both men and postmenopausal women. Similarly to this, people who have a family history of bad lifestyle choices or who are cur-

rently doing so should be urged to change to healthier habits and get regular check-ups.

2.5. The Implications for Public Health

Understanding the demographic trends of atherosclerosis may inform public health initiatives to lower the disease's prevalence. This involves promoting lifestyle modifications among all demographics, with a focus on high-risk populations, such as regular exercise, a healthy diet, and avoiding smoking. Clinical recommendations should also incorporate gender-specific factors to ensure that men and women receive care that is appropriate for their individual risk profiles.

3. Prognosis

The degree of plaque accumulation, the existence of other risk factors and the success of therapies are some of the variables that affect the prognosis.

1) Chronic Characteristics

Although atherosclerosis often lasts a lifetime, with the right care, its progression can be delayed or prevented.

2) Cardiovascular Complications

Serious illnesses such as peripheral artery disease, heart attacks, and strokes can result from untreated atherosclerosis. These problems are due to blocked or narrowed arteries that limit blood supply to vital organs.

3) Impact of Lifestyle Modifications and Early Detection

The prognosis can be significantly improved by lifestyle changes and early detection. The risk of problems can be reduced by adjusting, including eating a nutritious diet, getting more exercise, stopping smoking, and controlling blood pressure and cholesterol levels [27].

3.1. Risk Factors

There are two types of risk factors for atherosclerosis: modifiable and nonmodifiable.

3.1.1. Modifiable Risk Factors

1) Diet

Consuming an excessive amount of saturated fat can raise cholesterol and cause plaque to accumulate. This risk can be reduced with a nutritious diet rich in fruits, vegetables, and whole grains.

2) Smoking

Smoking increases inflammation and the risk of atherosclerosis by damaging the inner lining. Reducing cardiovascular risk requires quitting smoking [28].

3) Physical Inactivity

A sedentary lifestyle increases the risk of atherosclerosis by causing obesity, high blood pressure, and high cholesterol. These problems can be managed regular exercise.

with Hypertension, or high blood pressure, can weaken and damage blood vessels, increasing their vulnerability to plaque accumulation.

4) Hypertension or high blood pressure

Hypertension or blood pressure can weaken and damage blood vessels, increasing susceptibility to plaque accumulation. It is critical to control blood pressure using medication and lifestyle modifications [25].

5) High Cholesterol

Plaque can develop because of elevated LDL cholesterol levels. This risk can be reduced by controlling cholesterol levels with food and medicine.

6) Diabetes

Diabetes damages blood vessels and increases inflammation, raising the risk of atherosclerosis. It is critical to manage diabetes with medicine and lifestyle modifications.

3.1.2. Non-Modifiable Risk Elements

1) Age

The risk of atherosclerosis increases with age. Although age cannot be altered, early intervention may be prompted by knowledge of this risk.

2) Gender

Although the risk of atherosclerosis rises considerably, men are generally at a higher risk than premenopausal women.

3) Genetic Inclination

An individual's risk may be elevated if there is a family history of early heart disease or stroke. Although genetics cannot be changed, being aware of this risk may encourage more aggressive management of factors that can be changed.

4. Current Ongoing Atherosclerosis Treatments

Lifestyle modifications are essential for controlling cholesterol and maintaining cardiovascular health in general. These include modifying one's diet, exercising frequently, reducing the use of alcohol, and quitting smoking. Table 2 provides a summary of the various treatment options for atherosclerosis, including lifestyle modifications, pharmacological treatments, surgical procedures, and innovative targeted cell therapies. This table highlights the different approaches to managing the disease and improving vascular health.

Table 2. Treatment options for atherosclerosis.

Category	Treatment Options	Description
Lifestyle Modifications	Dietary changes	Increasing soluble fiber intake, reducing saturated and trans fats, following a Mediterranean diet
	Regular exercise	Maintaining healthy weight, improving lipid profiles, lowering blood pressure
	Reducing alcohol intake	Limiting or refraining from alcohol to manage blood pressure and triglyceride levels
	Smoking cessation	Quitting smoking to improve cardiovascular health

Continued

Pharmacological Treatments	Statins	Lowering LDL cholesterol levels, stabilizing arterial plaques
	Antihypertensives	Reducing blood pressure to prevent arterial damage
	Antiplatelet medications	Lowering the risk of heart attacks and strokes, and prevent blood clots
	PCSK9 inhibitors	Lowering LDL cholesterol by focusing on the PCSK9 protein
Surgical Procedures	Angioplasty	Enlarging narrowed or obstructed blood arteries using a balloon-tipped catheter
	Stent implantation	Inserting a metal mesh tube to keep arteries open after angioplasty
Targeted Cell Therapy	Stem cell therapy	Repairing injured tissue with induced pluripotent stem cells and\ mesenchymal stem cells
	Gene editing	Employing CRISPR/Cas9 to modify genes involved in lipid metabolism and inflammation
	Exosome-based treatments	Delivering therapeutic agents directly to atherosclerotic plaques using exosomes
Delivery Methods	Intravenous injection	Systemic distribution of therapeutic drugs through the bloodstream
	Direct injection	Localized delivery of cells or materials to plaque-forming sites
	Localized implantation	Inserting cell scaffolds or drug-eluting devices inside the vascular wall

4.1. Lifestyle Changes

4.1.1. Dietary Modifications

The lowering of cholesterol depends mainly on dietary changes. Important dietary adjustments consist of the following:

4.1.2. Increasing Soluble Fiber Intake

Consuming foods high in soluble fiber, such as whole grain cereals, fruits (e.g., apples, bananas) and legumes (e.g., kidney beans, lentils), help prevent cholesterol absorption in the digestive tract. The aim is to consume 10 - 15 grams of soluble fiber per day [29].

4.1.3. Reducing Saturated and Trans Fats

Lowering LDL ("bad") cholesterol15 requires avoiding trans fats in baked goods and fried foods and limiting saturated fats in red meat, butter, cheese and whole milk products. Substitute unsaturated fats from foods such as avocados, almonds, and olive oil for these [30].

4.1.4. Mediterranean Diet

Following a Mediterranean diet can help reduce cardiovascular risk and improve lipid levels since it places an emphasis on fresh fruits, vegetables, whole grains, and healthy fats such as nuts, olive oil and seafood.

4.1.5. Increasing Plant Stanols and Sterols

These compounds, which are present in nuts, whole grains, and some fortified foods, aid in preventing cholesterol absorption [31].

4.1.6. Consuming Omega-3 Fatty Acids

Omega-3s can reduce LDL cholesterol and triglycerides and are present in fatty seafood such as salmon and plant sources such as walnuts.

4.1.7. Exercise

Maintaining healthy weight and blood pressure, which are correlated with cholesterol levels, requires regular physical activity. Increased HDL cholesterol from exercise HDL ("good") cholesterol is increased by moderate exercise [32].

4.1.8. Lowers Blood Pressure

Exercise lowers blood pressure by reducing stiffness of the blood vessels.

4.1.9. Promotes Weight Loss

Consistent exercise lowers the risk of cardiovascular disease by helping maintain a healthy weight.

4.1.10. Reducing Alcohol Intake

Although moderate alcohol consumption may marginally increase HDL cholesterol, it is unknown if it has any positive effects on general health. Limiting or refraining from alcohol is frequently recommended because it can increase blood pressure and triglyceride levels.

4.1.11. Avoiding Smoking

Rapid smoking cessation increases HDL cholesterol and improves cardiovascular health in general. An essential lifestyle modification to reduce the risk of heart disease is quitting smoking.

4.2. Pharmacological Treatments

Drugs that treat high blood pressure, high cholesterol, and risk of blood clots are essential for maintaining cardiovascular health. PCSK9 inhibitors, antihypertensives, antiplatelet drugs, and statins are important pharmacological therapies. These medications are crucial for controlling cardiovascular risk factors and preventing serious cardiovascular disease.

1) Statins

Statins are frequently used to lower cholesterol and stabilize arterial atherosclerosis. They reduce LDL (or "bad") cholesterol levels by blocking a liver enzyme required for the synthesis of cholesterol. This activity helps prevent plaque development and rupture, which can cause heart attacks and strokes, in addition to lowering the risk of heart disease.

2) Antihypertensives

Blood pressure is a significant risk factor for cardiovascular disease, and antihypertensive medications are intended to reduce it. Kidney disease, heart failure, and stroke can all be caused by high blood pressure. Diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers are among the families of medications known as antihypertensives; they all lower blood pressure in a different way.

3) Antiplatelet Medications

Aspirin and P2Y12 inhibitors, including ticagrelor and clopidogrel, are examples of antiplatelet drugs that function by stopping platelets from aggregating and creating blood clots. In particular, for those who have a history of cardiovascular events or who are undergoing treatments such as angioplasty with stenting, this is essential to prevent heart attacks and strokes.

Approximately 15% fewer vascular deaths and 30% fewer non-fatal vascular events have been demonstrated with aspirin, the most researched antiplatelet medication.

4) PCSK9 Inhibitors

PCSK9 inhibitors are a more recent family of drugs that decrease cholesterol by specifically targeting the PCSK9 protein. LDL receptors, which are responsible for eliminating LDL cholesterol from the bloodstream, are often broken down by this protein. These inhibitors significantly lower LDL cholesterol levels by blocking PCSK9, increasing the number of accessible LDL receptors. This decrease is frequently between 50% and 60%. For people with familial hypercholesterolemia or those unable to reduce their cholesterol sufficiently with statins alone, PCSK9 inhibitors are especially helpful.

4.3. Surgical Procedures

Angioplasty and Stent Implantation: Removal of obstructed arteries is achieved through minimally invasive techniques such as angioplasty and stent implantation are used to open blocked arteries, increasing blood flow, and lowering the risk of problems linked to more severe blockages. Conditions such as peripheral arterial disease and coronary artery disease respond especially well to these procedures [33].

1) Angioplasty

Angioplasty is the process of enlarging narrowed or obstructed blood arteries with a balloon-tipped catheter. Medical imaging, usually live radiographs, is used to guide the catheter to the obstruction site. The balloon is then inflated to push the plaque aside, expanding the channel, and improving blood flow. This operation can be performed in carotid arteries, peripheral arteries, and coronary arteries, among other places.

2) Stent Implantation

A stent, which is a tiny metal mesh tube, may be inserted into the newly opened route after angioplasty to help maintain its opening. The purpose of stents is to stop restenosis, a condition in which the artery narrows again. Many stents have coatings that release medications over time to assist in preventing restenosis [34].

4.4. Procedure Specifics

1) Preparation

An interventional radiology suite or catheterization laboratory is usually where the operation is performed. Before the procedure, patients are sedated.

2) Catheter Insertion

Using imaging techniques, a catheter is directed to the location of obstruction after being introduced through an artery, usually the groin.

3) Balloon Inflation

To increase blood flow, the catheter's balloon is inflated to enlarge the artery.

4) Stent Placement

To keep the artery open, a stent is securely secured and, if required, enlarged and inserted.

5) Post-Procedure Care

To minimize clotting around the stent, patients may need to take antiplatelet drugs and be monitored for problems following the procedure.

4.5. Advantages Compared to Surgery

When compared to more invasive surgical techniques such as coronary artery bypass grafting (CABG), stent implantation and angioplasty have the following benefits:

1) Minimally Invasive

In contrast to open heart surgery, these techniques use fewer incisions and cause less tissue damage.

2) Shorter Recovery Time

Following surgery, patients usually recover more quickly and feel less pain.

3) Reduced Complication Risk

Compared to open surgery, minimally invasive techniques typically provide a lower risk of infection and other consequences [35]. However, surgery may still be required for more complicated situations or more severe obstructions. The patient's condition and the degree of obstruction determine whether stent insertion, angioplasty, or surgery is the best course of action.

5. Targeted Cell Therapy

By addressing the underlying causes of atherosclerosis rather than just treating its symptoms, targeted cell treatments have paved the way for new developments in cardiovascular care. In general, these innovative therapies can be divided into three primary groups: exosome-based methods, gene editing, and stem cell therapy.

5.1. Stem Cell Therapy

Stem cell therapy has shown remarkable potential in healing damaged tissue and reducing inflammation linked to atherosclerosis, especially when using mesenchymal stem cells (MSC) and induced pluripotent stem cells (iPSC). MSCs have shown the capacity to control inflammation, suppress various components of the immune system, and differentiate into distinct cell types. Research has indicated that allogeneic MSC transplantation, which uses cells derived from different tissues such as the kidney, heart, and brain, may be a useful treatment strategy for

atherosclerosis [36]. Despite the promising preclinical models of MSCs and iPSCs, issues with immunological compatibility, possible carcinogenicity, and inconsistent patient results still exist. Another barrier to broad adoption is the cost and scalability of producing autologous or allogeneic stem cell products.

5.2. Gene Editing

For the treatment of atherosclerosis at the genetic level, gene editing - specifically, the CRISPR/Cas9 system - has become a potent tool. This method has demonstrated encouraging results in preclinical investigations and allows the repair of disease-causing alleles. For example, a study that used AAV-CRISPR/Cas9 to fix the Ldlr gene mutation in a mouse model showed that serum levels of LDL cholesterol, triglycerides, and total cholesterol were significantly reduced. Furthermore, the aorta showed fewer macrophage infiltrations and smaller atherosclerotic plaques [37]. Although the CRISPR/Cas9 platform makes precise genome alterations possible, questions about long-term safety, off-target effects, and ethical issues still exist. Because of these unknown hazards, regulatory approval for genome editing in cardiovascular diseases is still strict.

5.3. Exosome-Based Treatments

Exosome-based treatments have shown potential as transporters for the direct delivery of medicinal agents to atherosclerotic plaques. Exosomes made from stem cells, namely human umbilical cord mesenchymal stem cells (hUCMSCs), limit eosinophil migration treated with ox-LDL, lower levels of inflammatory cytokines, and encourage apoptosis [38]. Exosomes provide a low-immunogenicity, non-cellular approach to targeted administration; however, limitations in bio-distribution efficiency, batch uniformity, and dose consistency restrict their use in clinical settings. Moreover, methods for large-scale production are still being developed.

5.4. Methods of Delivery

Delivery strategies have a significant impact on how well targeted specific cell therapies work. Therapeutic drugs can be distributed systemically through the bloodstream by intravenous injection. The localized distribution of cells or materials to plaque-forming sites is made possible by direct injection into artery damage. Furthermore, localized implantation involves inserting cell scaffolds or drug-eluting devices inside the vascular wall to continuously release therapeutic agents [39].

1) Intravenous Injection: Enables systemic distribution of therapeutic agents through the bloodstream, which may lead to widespread effects but can suffer from limited accumulation at plaque sites.

2) Local Injection: Allows precise delivery to specific lesion sites; however, this method is invasive and may result in uneven therapeutic distribution or localized tissue trauma.

3) Localized Implantation: Involves inserting biomaterial-based scaffolds or drug-eluting devices into the vascular wall to achieve sustained local release. Integration into host tissue and biodegradability present ongoing challenges.

4) Biomaterials: Serve as scaffolding matrices or controlled-release systems for cellular or molecular agents. These enhance localization but face issues related to biocompatibility, vascular integration, and potential immunogenic responses.

5) Nanotechnology: Provides high specificity through functionalized nanoparticles capable of targeting atherosclerotic plaques directly. This method minimizes systemic exposure but is currently limited by reproducibility, biodistribution accuracy, and regulatory complexities.

Together, these approaches illustrate the current landscape and future potential of delivery technologies for advanced cell-based cardiovascular therapies.

6. Challenges and Future Directions

There are still several obstacles to these focused cell treatments' tremendous potential. Careful observation is required due to safety concerns about the long-term implications of stem cell and gene editing treatments. Patients, particularly those with advanced diseases, may have varying degrees of efficacy. Since cell-based treatments are still regarded as experimental and require extensive clinical trials, regulatory hurdles provide significant hurdles. Furthermore, access to these cutting-edge treatments may be limited due to financial concerns.

To ensure effective targeting of cells, future research should focus on assessing the long-term effects of these treatments while improving delivery methods. Developing methods to lower the prices of these treatments will be critical for increased accessibility and improving scalability will be critical for greater applicability [40] (**Table 3**).

Table 3. Clinical trials of targeted cell therapy approaches.

Therapy Type	Study/Trial Reference	Target/Mechanism	Key Findings	Challenges
MSC therapy	*Frodermann et al.*, 2015	Immune modulation, Tissue Repair	Reduced Lesion size, lowered inflammation	Immune rejection, cost scalability
iPSC Therapy	*Wang et al.*, 2015	Endothelial regeneration	Elevated T-reg cells, reduced foam cells.	Tumor risk, regulatory hurdles
CRISPR/Cas9 Therapy	*Zhao et al.*, 2020	LDLR gene correction	Decreased LDL, smaller plaques.	Off-Target effects, delivery specificity.
Exosome Delivery	*Xu et al.*, 2019	Macrophage polarization	Reduced inflammation, improved function.	Standardization, Manufacturing challenges

7. Conclusion

In conclusion, by addressing the fundamental pathophysiological mechanisms linked to the disease, targeted cell treatments provide a new treatment option for atherosclerosis. Although this sector has seen tremendous advancements, more studies and clinical validation are required to determine the safety, effectiveness, and viability of these medications in the management of atherosclerosis. These

treatments have the potential to completely change how this common and deadly cardiovascular disease is treated when it develops further.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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