



## SERUM AMYLOID A: A KEY MEDIATOR IN INFLAMMATION, METABOLIC DISORDERS AND CARDIOVASCULAR DISEASE

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### ABSTRACT:

**Introduction:** Serum Amyloid A (SAA) is a critical acute-phase protein involved in a range of physiological and pathological processes, including inflammation, lipid metabolism, and the regulation of the immune system. Recent investigations have underscored its significant role in various pathological conditions, such as cardiovascular diseases (CVD), type 2 diabetes mellitus, obesity-related disorders, and amyloidosis.

**Objective:** This review aims to elucidate the structural characteristics of serum amyloid A while assessing its pathological implications in metabolic and cardiovascular diseases. Additionally, we will evaluate its potential utility as a biomarker for disease diagnosis and management.

**Methods:** A systematic literature review was conducted utilizing reputable databases, including PubMed, Scopus, and Science Direct.

**Results:** The evidence presented indicates that SAA plays a significant role in the pathogenesis of atherosclerosis by disrupting high-density lipoprotein (HDL) metabolism, fostering oxidative stress, and enhancing vascular inflammation. In the contexts of obesity and type 2 diabetes mellitus, SAA produced by adipose tissue contributes to chronic inflammatory processes that promote insulin resistance and impair pancreatic  $\beta$ -cell function. Furthermore, persistently elevated levels of serum amyloid A in amyloidosis can lead to the misfolding and deposition of amyloid fibrils, which subsequently results in progressive organ dysfunction.

**Conclusions:** The diverse pathological effects of serum amyloid A underscore its importance as a key mediator in the pathogenesis of various diseases. Its potential as a biomarker for early diagnosis and monitoring warrants further exploration. Future research should prioritize elucidating the precise molecular mechanisms underlying serum amyloid A's actions and developing targeted strategies to mitigate its detrimental effects.

**Keywords:** serum amyloid A, cardiovascular diseases, type 2 diabetes mellitus, obesity-related conditions, amyloidosis,

### INTRODUCTION

Serum amyloid A (SAA) is a protein that is synthesized mainly in the liver, but can also be formed in the presence of an inflammatory process in the gastrointestinal tract, breast, prostate, thyroid, lungs, pancreas, kidneys and brain neurons. Serum amyloid A is secreted in response to pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF- $\alpha$ ). Similar to C-reactive protein (CRP), SAA is an acute-phase reactant involved in systemic inflammation. During the acute phase of inflammation, serum amyloid A levels can temporarily increase by more than a thousand fold in the circulation. After this phase is over, it returns to normal values (SAA is usually found at 20-50 mcg/ml) [1-4]. As a highly conserved protein, SAA serves as a dynamic component of the immune and metabolic systems, modulating diverse physiological and pathological processes. Initially identified as a marker of inflammation, its functions extend far beyond simple acute phase reactants. [1, 2, 4] SAA is intricately involved in lipid metabolism, immune system modulation, and inflammatory responses, making it a key player in a number of diseases, including metabolic syndromes, diabetes mellitus, cardiovascular disease and amyloidosis.

Given its broad functional implications, SAA has emerged as a potential biomarker for inflammation-related diseases, including cardiovascular disease, metabolic disorders, and amyloidosis. Understanding the mechanisms by which SAA contributes to these pathologies is critical for the development of targeted therapies aimed at mitigating its deleterious effects [1-3]. This review will explore the structural features of SAA, its role in metabolic and cardiovascular diseases (CVD), and its contribution to the pathogenesis of amyloidosis, highlighting its importance as a biomarker and potential therapeutic target in inflammatory diseases.

## METHODS

For the present review, a search was conducted on PubMed, Google Scholar, and Science Direct. Only articles written in English were included. The reference lists of the selected articles were subjected to a hand search to identify additional articles.

## RESULTS AND DISCUSSION

### *Structure of SAA subtypes*

Structurally, SAA proteins are small (12-14 kDa) and composed of amphipathic alpha-helices, which facilitate their interaction with lipoproteins. SAA proteins exist in 4 different isoforms: serum amyloid A1 and serum amyloid A2 (SAA1 and SAA2)- isoforms are associated with acute-phase inflammations process [1, 2, 3, 5], serum amyloid A3 (SAA3)- isoform is associated with immune responses in animals [4] and serum amyloid A4 (SAA4)- constitutive form of SAA and have important role in lipid transport and homeostasis [1-5].

The gene encoding human SAA1 is one of 4 SAA genes mapped to a region on the short arm of chromosome 11 (11p15.1) [2, 3, 6]. In its functional form, SAA1 exists as a hexamer, with each subunit adopting an antiparallel four-helix bundle structure. This structure forms a cone-shaped shape, with its apex serving as a binding site for HDL and heparin [2, 3, 6, 7]. Variations in the coding region have resulted in five different isoforms of SAA1 (SAA1.1 to SAA1.5). Multiple genetic studies have linked certain single nucleotide polymorphisms (SNPs) in SAA1 to susceptibility to a number of human diseases, including familial Mediterranean fever and coronary artery disease [2, 3].

Serum Amyloid A2 (SAA2) is an acute-phase protein predominantly produced by the liver in response to inflammatory stimuli, such as infection, tissue injury, or malignancy. Upon release into the bloodstream, SAA2 associates with HDL, influencing lipid metabolism and transport. Beyond its role in lipid transport, SAA2 exhibits cytokine-like properties, modulating immune responses. It acts as a chemoattractant for immune cells, including neutrophils and macrophages, guiding them to sites of inflammation. SAA2 also induces the production of various inflammatory cytokines, such as interleukin-8 (IL-8), thereby amplifying the inflammatory response. Elevated levels of SAA2 are associated with several pathological conditions. Prolonged high concentrations can lead to the deposition of amyloid A fibril in tissues, resulting in a condition known as secondary amyloidosis. Additionally, increased SAA2 levels have been linked to chronic inflammatory diseases, such as atherosclerosis and

rheumatoid arthritis [3, 4].

Serum Amyloid A3 (SAA3) is an acute-phase protein primarily studied in mice, as the human SAA3 gene is considered a pseudogene and does not produce functional protein. In mice, SAA3 shares structural similarities with other SAA isoforms, such as SAA1 and SAA2. SAA3 is expressed in various tissues beyond the liver, including adipose tissue, indicating its involvement in systemic inflammatory processes [1-4, 8].

SAA4 shares similarities with other SAA proteins, featuring a four-helix bundle configuration. This structure facilitates its association with HDL particles, implicating SAA4 in lipid metabolism and transport. Unlike the acute-phase SAA proteins (SAA1 and SAA2), which are upregulated during inflammation, SAA4 is consistently present in the bloodstream under normal physiological conditions [1-3, 5, 6].

### *SAA in metabolic and obesity-related disorders*

SAA plays a key role in metabolic diseases, including obesity and type 2 diabetes mellitus (T2DM). Chronic low-grade inflammation is a hallmark of metabolic disorders, and SAA, secreted by adipose tissue in addition to the liver, is a major contributor to this inflammatory state [3, 4].

### *SAA and obesity*

Obesity is characterized by an increase in adipose tissue, which acts as an endocrine organ secreting inflammatory mediators such as SAA. Elevated levels of SAA in obese individuals correlate with increased macrophage infiltration into adipose tissue, promoting chronic inflammation and insulin resistance. Furthermore, SAA affects lipid metabolism by modifying the composition of HDL, reducing its protective effects, and contributing to dyslipidaemia [3, 4, 9].

SAA functions as a pro-inflammatory component, influencing various metabolic processes: production of inflammatory cytokines and lipolysis and release of free fatty acids. SAA induces the release of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 from adipocytes and immune cells, exacerbating systemic inflammation. SAA promotes lipolysis in adipose tissue, leading to increased release of free fatty acids into the circulation. This may lead to ectopic fat deposition and additional metabolic complications. Given its role in obesity and related metabolic disorders, SAA serves as a potential biomarker for assessing inflammation and cardiovascular risk in obese individuals. Interventions aimed at reducing SAA levels, such as weight loss and anti-inflammatory therapies, may help mitigate obesity-related complications [3, 4, 10, 11].

### SAA and type 2 diabetes mellitus (T2DM)

Serum Amyloid A (SAA) plays a critical role in the pathogenesis of T2DM through its effects on chronic inflammation, insulin resistance, pancreatic  $\beta$ -cell dysfunction, and lipid metabolism. Chronic low-grade inflammation is a hallmark of T2DM, and SAA is a key mediator in this process. SAA interacts with toll-like receptors (TLRs) and activates nuclear factor-kappa B (NF- $\kappa$ B), leading to the upregulation of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ . These cytokines contribute to insulin resistance by impairing insulin signalling pathways, reducing glucose uptake in peripheral tissues, and promoting hepatic gluconeogenesis [3, 4, 12].

In addition to classical inflammatory pathways, SAA also impairs insulin signalling through the activation of c-Jun N-terminal kinase (JNK). SAA induces increased phosphorylation of JNK, which in turn leads to serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby disrupting the normal activation of the phosphoinositide 3-kinase/ protein kinase B (PI3K/Akt) signalling pathway. This impairs the translocation of glucose transporter type 4 (GLUT-4) to the plasma membrane, ultimately reducing glucose uptake in insulin-responsive tissues [13].

Furthermore, SAA induces the infiltration of macrophages into adipose tissue, exacerbating local and systemic inflammation. This results in increased production of free fatty acids (FFAs) and inflammatory mediators, which further impair insulin sensitivity in skeletal muscle and the liver [14].

SAA promotes lipolysis in adipocytes, resulting in excessive release of FFAs into circulation. Elevated FFAs contribute to lipid accumulation in insulin-sensitive tissues, promoting lipotoxicity and further impairing insulin signalling [14, 15].

Patients with T2DM are at an increased risk of developing cardiovascular disease, and SAA contributes to endothelial dysfunction by increasing oxidative stress, reducing nitric oxide (NO) bioavailability, and promoting the expression of adhesion molecules. This enhances monocyte adhesion to the endothelium, initiating the early stages of atherosclerosis and increasing the risk of vascular complications in diabetes [6, 14, 16].

### Role of serum amyloid in the pathogenesis of amyloidosis

Amyloidosis is a group of disorders characterized by the deposition of misfolded protein fibrils in tissues and organs, leading to structural and functional impairment. Serum Amyloid A, an acute-phase protein, plays a central role in the pathogenesis of amyloid A (AA) amy-

loidosis, a subtype of systemic amyloidosis associated with chronic inflammation. Persistently elevated levels of SAA lead to its misfolding and aggregation into insoluble amyloid fibrils, which deposit in various tissues, causing organ dysfunction [6, 17].

Chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, chronic infections, and malignancies lead to sustained elevation of SAA levels. When the normal clearance mechanisms are overwhelmed, SAA undergoes conformational changes, resulting in amyloid fibril formation [18].

Under physiological conditions, SAA is cleared from circulation through proteolysis and uptake by macrophages. However, in chronic inflammatory states, excess SAA undergoes partial proteolysis, exposing amyloidogenic regions, particularly in its N-terminal region. This facilitates the self-assembly of SAA fragments into insoluble  $\beta$ -sheet-rich amyloid fibrils. These fibrils are resistant to degradation and accumulate in extracellular spaces, particularly in the kidneys, liver, spleen, and adrenal glands, leading to progressive organ dysfunction [18, 19].

**Renal Amyloidosis:** The kidneys are the most commonly affected organs in AA amyloidosis, with amyloid fibrils depositing in the glomeruli, leading to proteinuria, nephrotic syndrome, and progressive renal failure [19, 20].

**Hepatic and splenic amyloidosis:** Accumulation of amyloid in the liver and spleen results in hepatomegaly, splenomegaly and altered liver function [21].

**Cardiac involvement:** Although less common in AA amyloidosis, amyloid deposits in the heart can cause restrictive cardiomyopathy and arrhythmias [22, 23].

The deposition of SAA-derived amyloid fibrils disrupts normal cell-matrix interactions, leading to tissue stiffness, impaired perfusion, and hypoxia. Additionally, amyloid deposits trigger oxidative stress and activate apoptotic pathways, further contributing to tissue degeneration [18, 21, 24].

Genetic variations in the SAA1 gene influence an individual's susceptibility to AA amyloidosis. Certain polymorphisms in SAA1 are linked to a higher risk of amyloid deposition. Additionally, the persistence of inflammatory stimuli determines the rate and extent of amyloid formation, making early management of underlying inflammatory diseases crucial in preventing AA amyloidosis [3, 25].

### Role in cardiovascular disease

SAA1 and SAA2 are acute phase reactants involved in inflammation and are associated with lipid metabolism and immune responses in cardiovascular disease. Their

influence on atherosclerosis, endothelial dysfunction, and plaque instability highlights their critical role in the progression of CVD [4, 6, 16, 26].

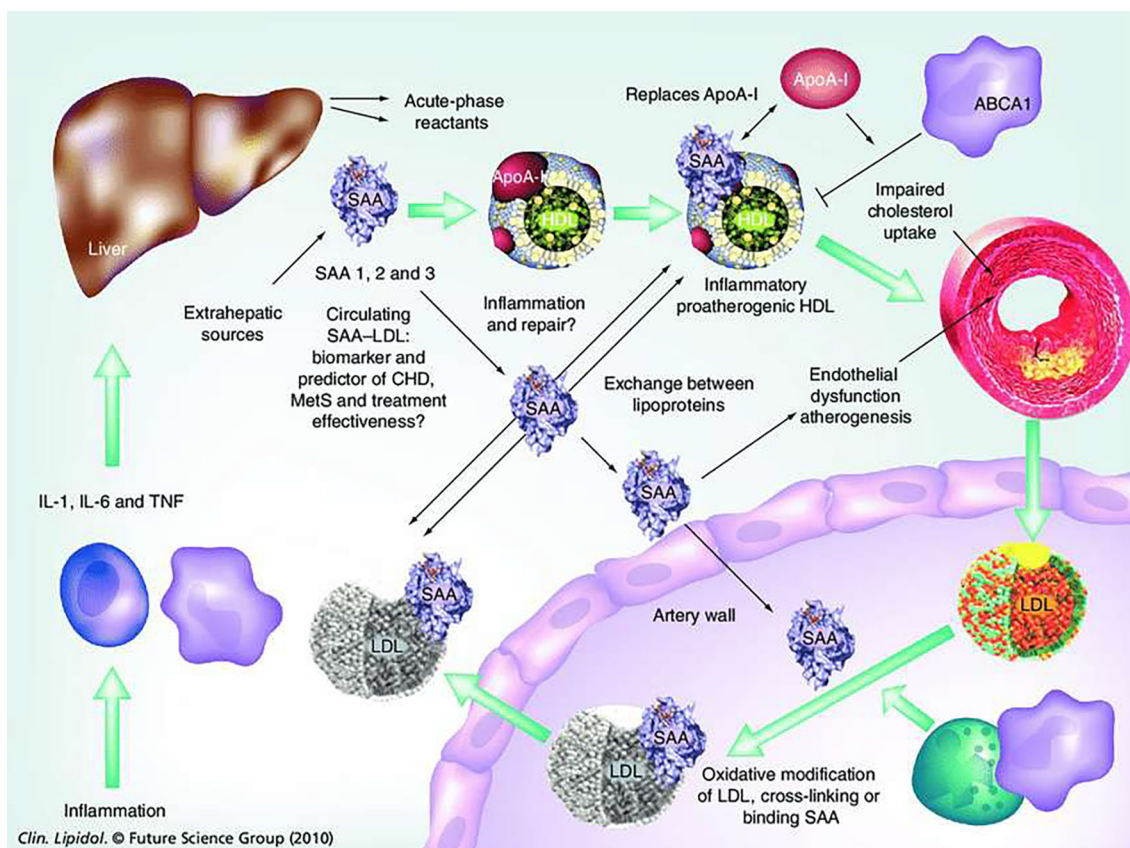
#### SAA1 and SAA2 in atherosclerosis development

Atherosclerosis, a leading cause of CVD such as coronary artery disease and myocardial infarction, is a chronic inflammatory condition characterized by lipid accumulation and plaque formation in the arterial wall. SAA1 and SAA2 contribute to this process through several interrelated mechanisms. During the acute phase of the reaction, elevated levels of SAA lead to a significant substitution of apolipoprotein A-I in HDL, with SAA constituting up to 87% of the total HDL protein content. This structural remodeling transforms HDL from an atheroprotective particle to a dysfunctional one [27].

SAA-enriched HDL exhibits increased affinity for binding to vascular proteoglycans, leading to its retention in the vessel wall and reduced access to the cell surface. This retention impairs the anti-inflammatory and antioxidant functions of HDL [28]. Furthermore, SAA promotes the phenotypic switch of vascular smooth muscle cells from a contractile to a synthetic, proliferative state, a crucial process in the progression of atherosclerosis.

In addition to these mechanisms, complexes between SAA and low-density lipoproteins (LDL) have been described as a potential novel biomarker for cardiovascular risk. These complexes represent a modified, inflammation-associated form of LDL that correlates with metabolic risk and may serve as an adjunct to traditional markers in the assessment of cardiovascular risk [29,30]. (fig. 1.)

**Fig. 1.** Role of Serum Amyloid A (SAA) in Inflammation and Atherogenesis.



The figure illustrates how inflammatory cytokines stimulate the liver to produce Serum Amyloid A (SAA), an acute-phase reactant that integrates into lipoproteins such as HDL and LDL. During inflammation, SAA displaces ApoA-I from HDL, converting it into a pro-atherogenic particle. In the arterial wall, oxidative and inflammatory conditions promote the formation of SAA-modified LDL, contributing to endothelial dysfunction and the progression of atherosclerosis [30].

Endothelial dysfunction is a key event in the pathogenesis of cardiovascular disease, characterized by reduced nitric oxide (NO) bioavailability, increased oxidative stress, and a pro-inflammatory state [31, 32]. Elevated levels of SAA1 and SAA2 have been shown to

induce oxidative stress by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to the production of reactive oxygen species (ROS) [31]. This oxidative stress contributes to endothelial cell apoptosis, increased vascular permeability, and impaired

vasodilation [32]. SAA1 and SAA2 also increase the expression of adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, on endothelial cells. This enhances the recruitment and adhesion of monocytes to the endothelium, an early event in atherosclerosis [16]. Once adherent, monocytes differentiate into macrophages that engulf oxidized LDL, forming foam cells that contribute to plaque growth and instability [33].

## CONCLUSION

Serum Amyloid A plays a pivotal role in inflammation-driven diseases, particularly cardiovascular conditions, metabolic disorders, type 2 diabetes mellitus, obesity-related complications, and amyloidosis. As a key modulator of lipid metabolism and chronic inflammation, SAA contributes to endothelial dysfunction, insulin resistance, and amyloid deposition, making it a critical factor in disease progression. Its elevated levels serve as an early biomarker for metabolic and cardiovascular risk, providing valuable prognostic insight for clinicians.

Given its strong association with metabolic disturbances, therapeutic strategies aimed at reducing SAA levels—such as lifestyle modifications, weight loss, anti-inflammatory interventions, and pharmacological approaches—may offer new avenues for disease prevention and management. Targeting SAA could not only improve cardiovascular outcomes but also mitigate complications related to chronic inflammation and metabolic dysfunction. Further clinical and experimental studies are essential to fully elucidate the molecular mechanisms underlying SAA impact and to develop targeted therapies that could modify its pathological effects, ultimately improving patient outcomes in inflammatory and metabolic diseases.

## Abbreviation list:

CVD - cardiovascular diseases  
SAA - Serum Amyloid A  
HDL - High-density lipoprotein  
IL-6 - Interleukin-6  
IL-1 - interleukin-1  
TNF- $\alpha$  - tumour necrosis factor-alpha  
CRP - C-reactive protein  
SAA1 - Serum amyloid A1  
SAA2 - Serum amyloid A2  
SAA3 - Serum amyloid A3  
SAA4 - Serum amyloid A4  
SNPs - Single nucleotide polymorphisms  
IL-8 - Interleukin-8  
T2DM - Type 2 diabetes mellitus  
TLRs - Toll-like receptors  
NF- $\kappa$ B - Nuclear factor-kappa B  
JNKs - c-Jun N-terminal kinase  
IRS-1 - Insulin receptor substrate-1  
GLUT-4 - Glucose transporter type 4  
PI3K/Akt - Phosphoinositide 3-kinase/ protein kinase B  
FFAs - Free fatty acids  
NO - nitric oxide  
AA - amyloid A  
LDL - Low-density lipoproteins  
NO - Nitric oxide  
NADPH - Nicotinamide adenine dinucleotide phosphate  
ROS - oxygen species

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