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Relation Between B-Thalassemia and Atherosclerosis

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Abstract:

β-thalassemia is prevalent in Mediterranean, Middle Eastern, and Asian populations, with clinical forms ranging from asymptomatic carriers to severe transfusion-dependent β-thalassemia major. Advances in transfusion therapy and iron chelation have improved life expectancy, but long-term survivors face complications such as endocrinopathies, liver disease, and cardiac dysfunction. Atherosclerosis, a leading cause of cardiovascular morbidity worldwide, is characterized by endothelial injury, lipid accumulation, and inflammatory cell infiltration in the arterial wall. In β-thalassemia, chronic hemolysis, elevated oxidative stress, abnormal lipid profiles, and iron-mediated endothelial damage may interact with traditional cardiovascular risk factors, altering the trajectory of atherosclerotic disease. Understanding this relationship is important for early detection and targeted prevention strategies.

Keywords: β-thalassemia; atherosclerosis; endothelial dysfunction; carotid intima–media thickness; oxidative stress; iron overload; cardiovascular risk.

Introduction:

β-thalassemia is an inherited hemoglobin disorder caused by mutations in the β-globin gene, resulting in reduced or absent β-globin chain synthesis and chronic microcytic anemia. The disease is highly prevalent in Mediterranean, Middle Eastern, and Southeast Asian populations, with clinical phenotypes ranging from asymptomatic β-thalassemia trait to severe transfusion-dependent β-thalassemia major **(1).** Advances in transfusion protocols and iron chelation therapy have significantly improved survival; however, long-term complications, including endocrinopathies, hepatic dysfunction, and cardiovascular disease, have emerged as important causes of morbidity and mortality **(2).**

Atherosclerosis is a chronic, progressive vascular disease characterized by endothelial dysfunction, lipid accumulation, oxidative stress, and inflammation of the arterial wall **(3).** While anemia in β-thalassemia is associated with low blood viscosity and high cardiac output, potentially offering some protection against atherosclerosis, other disease-related factors may counteract this benefit. These include chronic inflammation, oxidative stress, abnormal lipid metabolism, and transfusion-related iron overload, all of which can contribute to endothelial injury and promote atherogenesis **(4).**

Several studies have investigated subclinical markers of atherosclerosis in β-thalassemia patients, such as carotid intima–media thickness (CIMT), flow-mediated dilation, and coronary artery calcium scores, but the results remain conflicting. Some reports suggest a lower prevalence of atherosclerotic changes compared with the general population **(5),** while others demonstrate evidence of early vascular aging and increased CIMT, particularly in transfusion-dependent individuals with poor iron control **(6).** These discrepancies may be attributed to variations in study populations, transfusion regimens, chelation therapy adherence, and genetic backgrounds.

Understanding the interplay between β-thalassemia and atherosclerosis is crucial for risk stratification and management, especially as life expectancy increases. Further longitudinal and mechanistic studies are needed to determine whether β-thalassemia confers net protection or heightened susceptibility to atherosclerotic cardiovascular disease.

An early indicator of premature atherosclerosis, an increase in carotid intima-medial thickness is seen in children with beta-thalassemia . However, whether, beta-thalassemia and atherosclerotic disease are directly related is unknown **(7)**.

Since beta-thalassemia is a hemolytic anemia with elevated free heme and depleted hemopexin, heme's endogenous scavenger, in the vasculature, we hypothesize that heme-mediated oxidative stress produces a proatherogenic environment in beta-thalassemia (**7**).

About 80 million people worldwide suffer from beta-thalassemia, an autosomal recessive hemoglobinopathy. By preventing iron toxicity and severe anemia, improvements in iron chelation therapy and routine transfusions of blood have helped patients with beta-thalassemia live longer (**8**). However, it is still unclear how much underlying vasculopathy there is in beta-thalassemia **(9).**

Children with beta-thalassemia have higher carotid intimal-medial thickness, a sign of premature atherosclerosis, according to a number of recent clinical association studies **(10)**. According to **Sherief et al. (10)** and **Hahalis et al. (11)**, patients with beta-thalassemia also have dyslipidemia, which is characterized by elevated triglycerides and low- or high-density lipoprotein levels, leading to a high atherogenic index. However, neither the mechanism causing this phenomenon nor whether beta-thalassemia and atherosclerotic disease are directly related are known. Accelerated atherosclerosis in beta-thalassemia may have multiple pathological causes, including anemia, compensatory reactions to the anemia, dyslipidemia, and/or hemolysis of red blood cells. The hallmark of beta-thalassemia is decreased or impaired beta globin synthesis of hemoglobin which causes excess, unpaired alpha hemichromes that lead to erythrocyte instability (**12**).

Ineffective erythropoiesis, which is the hallmark of beta-thalassemia, is characterized by increased but ineffective erythropoiesis, which results in premature destruction of red blood cells, anemia, and the failure of erythroid progenitor precursors to mature. Consequently, this results in increased compensatory mechanisms to improve anemia, including increased gastrointestinal iron absorption, upregulated erythropoietin, decreased hepcidin expression, and extramedullary hematopoiesis (**12**). Mature erythrocytes have shorter survival times and are microcytic, hypochromic, and malformed **(13)**. Intravascular hemolysis, which exposes the vasculature to high levels of hemoglobin and free heme, is a characteristic of beta-thalassemia **(13)**. By activating Tolllike receptor 4 (TLR4), free heme can directly encourage the production of reactive oxygen species (ROS) (Fig.1).

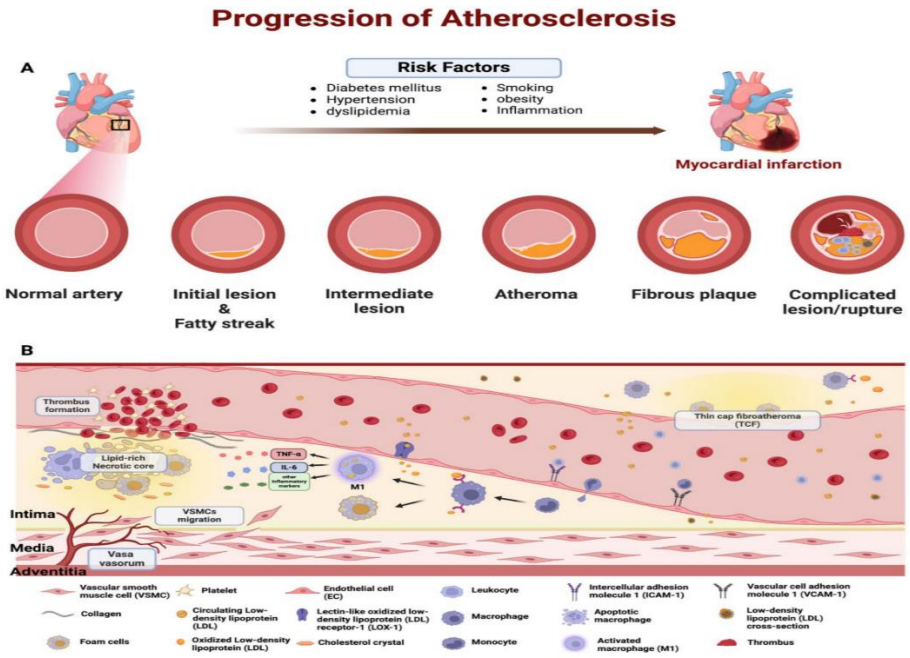

Figure (1): Schematic illustration of the progression of atherosclerosis. (A) The characteristic four pathological stages leading to the rupture of a complicated plaque lesion. (B) The development of atherosclerotic lesions

involves the activation of macrophages and their subsequent foam cells, migration of smooth muscle cells (SMCs), and synthesis of extracellular matrix macromolecules such as collagen **(14)**.

Endostatin

Endostatin, is a 20-kDa antyiangiogenic protein produced by cleavage of collagen XVIII. It has been shown to inhibit endothelial cell proliferation and migration and induce their apoptosis **(15)**.

Endostatin has also been shown to inhibit MMP-2 activity leading to reduced migration of both endothelial cells and tumor cells. Treatment of rats bearing intracranial glioma with endostatin has been shown to prolong survival **(16).**

Gene therapy approaches using endostatin have been explored and delivery of endostatin by human mesenchymal and neural stem cells, adenovirus vectors, plasmid, and alginate encapsulated cells have shown antitumor efficacy **(17)**.

Gene therapy with recombinant endostatin and angiostatin fusion proteins using both viral and non-viral gene transfer using sleeping beauty transposon of mice bearing glioma xenografts with a fusion protein of soluble vascular endothelial growth factor receptor (sFlt-1) and an angiostatin-endostatin fusion protein also showed antitumor activity **(18, 19)**.

Endostatin has a broad spectrum of angiostatic activities on endothelial cells **(20)**. One of the proposed mechanisms is via inhibition of matrix metalloproteinases (MMPs). During angiogenesis, endothelial cell migration and invasion are facilitated by MMPs-mediated proteolytic degradation of the extracellular matrix **(21, 22)**.

In particular, MMP-2, MMP-9 and MMP-13 have been identified as targets for endostatin inhibitory action **(23)**. Furthermore, initial reports described inhibition of human vascular endothelial cell migration by endostatin through its binding to α5- and αV-integrins **(24)**.

Other angiostatic functions of endostatin can be summarized in three major downstream effects: actin disassembly via Src-dependent p190RhoGAP activation **(25)**, inhibition of the FAK/Ras/p38-MAPK/ ERK signaling cascade through α5β1-integrin binding, with suppression of HIF-1α/VEGFA, and signaling-dependent downregulation of β-catenin **(26).**

Moreover, endostatin binds directly to VEGFR2, without binding to its ligand, and inhibits VEGF-induced phosphorylation with consequent down-regulation of this receptor. The VEGF-mediated downstream signaling pathway involving p125FAK, ERK and p38MAP kinase is suppressed by endostatin in human endothelial cells **(23)**.

It is possible that the direct binding to VEGFR2 by endostatin is responsible for the inhibition of VEGF activity, through competitive blockade of VEGF, thereby promoting endostatin's angiostatic effects **(27)**.

In line with this hypothesis is the observation that endostatin blocks vascular endothelial tube formation by suppressing nitric oxide synthase (eNOS) **(28)**. Specifically, endostatin blocks VEGF-induced eNOS phosphorylation at Ser1177 but not VEGF-mediated Akt phosphorylation and Akt-stimulated endothelial cell migration. When a dominant negative inactive construct of the catalytic domain of the phosphatase PP2A, known to inactivate eNOS, is used, endostatin suppresses VEGF-induced endothelial cell migration by activating PP2A, therefore inhibiting eNOS phosphorylation and consequent angiogenesis. Importantly, several studies report endothelial cell apoptosis as a common mechanism of endostatin anti-angiogenic activity (Fig.2) **(29)**.

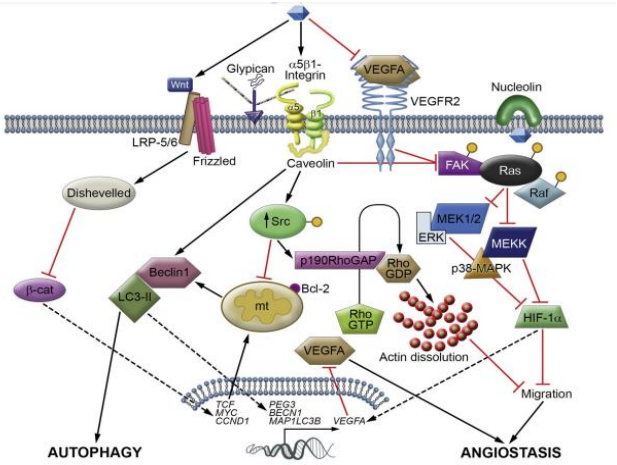

Figure (2): Schematic model of endostatin activity on endothelial cells. A comprehensive model of angiostatic and pro-autophagic activities exerted by endostatin in endothelial cells **(27)**.

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