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Review Article

Clinical syndromes associated with acquired antithrombin deficiency via microvascular leakage and the related risk of thrombosis

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ABSTRACT

Antithrombin (AT) is a 65 kDa glycoprotein belonging to a group of inhibitory factors known as serpins (serine protease inhibitors). It plays a critical role in the inhibition of coagulation and inflammation processes within the environment of the vascular endothelium.

Inadequate levels of functional AT in plasma results in an increased risk of thrombotic events, both venous and arterial. AT deficiency can be inherited or acquired. Congenital AT deficiency is the most severe inherited thrombophilic condition with an odds ratio of 20 for the increased risk of venous thrombosis. Acquired AT deficiency occurs in a variety of physiologic and pathologic medical conditions with similar risks of increased thrombosis.

In this article, we review clinical settings characterized by an acquired AT deficiency largely or partly subsequent to protein microvascular leakage. Other different mechanisms of AT depletion are implied in some clinical conditions together with endothelial loss, and, therefore, outlined. In addition, we provide a description of the current knowledge on the specific mechanisms underlying endothelial AT leakage and on the consequences of this protein decrease, specifically looking at thrombosis. We identify potential directions of research that might prove useful in patients with acquired AT deficiency.

Contents

Abbreviations: AT, antithrombin; OHSS, ovarian hyperstimulation syndrome; HCG, human chorionic gonadotropin; IVF, in-vitro fertilization; RAS, renin-angiotensin system; VEGF, vascular endothelial growth factor; vW, von Willebrand; VTE, venous thromboembolism; PIATD, pregnancy-induced antithrombin deficiency; AFLP, acute fatty liver of pregnancy; rhAT, recombinant human AT; OLT, orthotopic liver transplantation; CVT, central venous thrombosis; DIC, disseminated intravascular coagulopathy; SIRS, systemic inflammatory response syndrome; NS, nephrotic syndrome; IBDs, inflammatory bowel diseases.

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Introduction

Antithrombin (AT) is a 65 kDa glycoprotein belonging to a group of inhibitory factors known as serpins (serine protease inhibitors) [1]. It plays a critical role in the regulation of coagulation, being the major inhibitor of thrombin (factor IIa), factor Xa and, to a lesser extent, factors XIIa, XIa, IXa and VIIa. It is estimated that AT provides 80% of the natural anticoagulant effect against thrombin [2], and its broad spectrum of inhibition makes it a key regulator of the coagulation system [3]. Inhibition of proteinases by AT occurs by formation of an equimolar complex between the reactive site of AT and the active site of the proteinase. Heparin has an appreciable accelerating effect on the formation of the AT-proteinase complexes [4], and its clinical efficacy is related to interaction with AT [5].

Evidence suggests a pivotal role of AT in the inhibition of inflammation within the vascular endothelium and a subsequent regulatory effect on microvascular leakage. AT binding to glycosaminoglycans on endothelial cells leads to inhibition of IL-6, a pro-inflammatory cytokine, and to an increase in prostacyclin. Specifically, the anti-inflammatory cytokine prostacyclin inhibits leukocyte activation and platelet aggregation, thus preventing the leukocyte-mediated endothelial cells injury and subsequent vascular leakage [8]. AT inhibition of thrombin and factor Xa blocks their pro-inflammatory actions due to IL-6 and IL-8 generation. Moreover, AT hampers thrombin-mediated increase in microvascular permeability related to platelet and intra-endothelial Rho-GTPase activation [9–13,7,14–19]. In addition, AT reduces vascular leakage by interacting with the syndecan-4 receptor [20,21], preserving the endothelial glycocalyx [22], and inhibiting endothelial cell activation and contraction [23].

AT is synthesized chiefly in the liver, but also in vascular endothelium [2,24]. In normal conditions, a plasma concentration of about 112–140 μg/mL is maintained with a half-life of 2–3 days; this equates to approximately 100 IU/dL of AT activity [25]. Results of both antigenic and activity assays are expressed as a percentage of the normal level. For most assays the normal range of two standard deviations from the mean is around 80–120 IU/dL [2].

Understanding the clinical significance of AT levels just at or below the lower limit of the reference range is challenging [4]. Indeed, the level at which AT deficiency becomes clinically relevant is not clear and may also depend on the cause of depletion.

AT deficiency can be inherited, most often for heterozygosity, or acquired. The congenital form is the most severe thrombophilic condition with an odds ratio of 20 for venous thrombosis in the heterozygous state in general. These patients have a particularly high risk of thrombosis in the presence of specific risk factors, e.g. pregnancy, post-partum state, use of oral contraceptives, major trauma, surgery, immobilization, and metastatic cancer [26,27,28–30]. Specifically, affected individuals have plasma levels of AT ranging from 25 to 60% of normal value [31]. However, only half of these patients present thrombotic episodes, regardless the specific value of AT. Indeed, the first thrombotic event is more related to the type of genetic mutation, the presence of predisposing conditions, as reported above,- and the patient's age than to AT plasma levels [31–35]. The point of transition between the normal and the heterozygous state is reported to be 65-80% [36,37].

Acquired AT deficiency has been associated with an increased thrombotic risk or a worse clinical outcome in several clinical settings [4,38–64]. Different mechanisms are implied in causing protein depletion, such as reduced hepatic synthesis, increased consumption, abnormal leakage, blood dilution, and drug effect [14,38,39].

In this article, we review clinical settings with an acquired AT deficiency largely or partly subsequent to protein microvascular leakage. Other different mechanisms of AT depletion are implied in some of these settings together with endothelial loss, e.g. increased consumption due to coagulation activation or decreased hepatic synthesis, and are therefore outlined. In addition, we provide a description of the current knowledge on the specific mechanisms underlying endothelial AT leakage and on the consequences of this protein decrease, specifically looking at thrombosis. Further research is necessary to better define the potential benefit of AT assessment and AT replacement in clinical settings of AT deficiency.

Materials and Methods

We performed a Medline search of all clinical conditions with an acquired AT deficiency, focusing on settings with protein microvascular leakage as one of the main mechanisms of AT decrease.

We used Mesh headings "antithrombin", "antithrombin III", "acquired antithrombin deficiency", "thrombosis", "thromboembolism" "ovarian hyperstimulation syndrome", "pregnancy", "pregnancy edema", "third spacing", "preeclampsia", "HELLP syndrome", "acute fatty liver of pregnancy", "ascites", "chylothorax", "chylous effusions", "sepsis", "thermal injury", "burn injury", "renal diseases", "nephrotic syndrome", "intestinal diseases", "inflammatory bowel diseases", "ischemic colitis", "vascular permeability", "endothelial leakage", "plasma derived antithrombin", "recombinant human antithrombin". All English, French, and Italian language articles in the aforementioned clinical settings and its relation with thrombosis were retrieved. Moreover, manuscripts about mechanisms underlying protein leakage and the potential use of AT as replacement therapy were evaluated.

Results

Table 1 displays several clinical conditions associated with acquired AT deficiency and the proposed mechanisms causing protein depletion.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is an iatrogenic complication of supraphysiologic ovarian stimulation. Human chorionic gonadotropin (HCG) is thought to play a crucial role in the development of this syndrome, being the severe forms almost always restricted to cycles using exogenous HCG or to endogenous pregnancy-derived HCG in the setting of in-vitro fertilization (IVF) procedures [65].

A classification system for OHSS has been proposed and applied. It is based on clinical and laboratory parameters and recognizes four classes of severity, subsequent to capillaries leak and "third spacing" (Table 2) [66]. Clinical symptoms become evident in the moderate form. Hypovolemia, hemoconcentration, generalized edema, ascites and pleural effusion are observed in the severe and critical forms