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Thrombospondin 1, obesity and nonalcoholic fatty liver disease

Konstanza Angelova*
Department of Hygiene and Nutrition, Medical Faculty, Medical University, Bulgaria.

***Corresponding author: Konstanza Angelova**
Department of Hygiene and Nutrition, Medical Faculty, Medical University, 1431 Sofia, Bulgaria.
Email: kchristoangelova@gmail.com

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Short Commentary

The thrombospondin 1 (THBS1 or TSP-1), a subunit of a homotrimeric protein, is a multifunctional adhesive glycoprotein, encoded in humans by *THBS1* gene [1]. It is a member of the thrombospondin family of five extracellular matrix proteins. THBS1 is produced and secreted in extracellular space by endothelial cells, adipocytes, fibroblasts, macrophages, hepatic stellate cells. The function of THBS1 is related to platelet aggregation and angiogenesis [2]. Subsequent studies found a mediation of adipose-derived thrombospondin 1 in insulin resistance and adipose inflammation [3,4]. Expression of *THBS1* gene increases in obesity and insulin resistance [5]. Serum THBS1 has been estimated as biological marker of obesity and metabolic syndrome predominantly in women, with levels of THBS1 associated to abdominal obesity [6].

Obesity is a risk factor for Nonalcoholic Fatty Liver Disease (NAFLD). The prevalence of NAFLD in children and adolescents exceeds 36% in the context of obesity [7]. In most children, NAFLD is associated with insulin resistance, central or generalized obesity, and dyslipidemia with hypertriglyceridemia and low HDL-cholesterol levels [8]. In adult population, the impact of NAFLD shows a rapidly growing contribution to liver morbidity and mortality [9]. NAFLD remains undermanaged and is also lacking effective therapy.

Studies discovered that serum THBS1 levels increase in individuals with NAFLD and are positively correlated with the grades of liver steatosis [10]. Moreover, significant reduction of serum levels of THBS1 have been found with improvement of hepatic steatosis through lifestyle interventions. In experiment, pharmacological administration of recombinant human THBS1 attenuates lipid accumulation in primary hepatocytes and inhibits cleavage and processing of Sterol Regulatory Element-Binding transcription Factor 1 (SREBF1), (that regulates genes related to lipid and cholesterol production), through the mediation of CD36 (cluster of differentiation 36, or platelet glycoprotein 4, fatty acid translocase), involved in fatty acid metabolism.

The diverse functions of thrombospondin proteins have been attributed to several recognition motifs and domains of the genomic structure of *THBS* gene. Proteomics assists in the synthesis of mimetic peptide of THBS1 – ABT-526, which inhibits steatosis in hepatocytes exposed to high glucose and insulin [10].

Other studies confirm that extracellular protein THBS1 may be applied as an indicator of NAFLD [11]. But the pleiotropic functions and interactions of thrombospondin 1, including its role in angiogenesis and cancer development [12], suggest that various implications of THBS 1 as a therapeutic potential agent and risk factor for NAFLD should be further validated.

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