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Review Article

A Short Review on ANGPTL-8 as an Important Regulator in Diabetes

Maryam Esfahani[1], Mohamad Taghi Goodarzi[2*]

[1]Ph.D. in Clinical Biochemistry, Nutrition Health Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[2]Professor of Clinical Biochemistry, Department of Biochemistry, Shahrood Branch, Islamic Azad University, Shahrood, Iran

*Corresponding author:
Mohamad Taghi Goodarzi, Department of Biochemistry, Shahrood Branch, Islamic Azad University, Shahrood, Iran.
Tel: +98 23 32390360
Fax: +98 23 32390077
Email: mtgoodarzi@yahoo.com

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Abstract
ANGPTL8, a new hormone, is regarded as a novel target for type-2 diabetes and associated metabolic disorder. Nutritional state and hormonal factors are involved in the regulation of ANGPTL-8 expression. This protein is associated with some myokines or adipokines. Several studies confirmed the function of ANGPTL-8 in glucose metabolism and diabetes complications; however, there are opposite results. The accurate function of ANGPTL-8 in T2D remains unclear. Further strictly controlled studies including measuring methods, nutritional state, diagnostic criteria of overweight/obesity, age, and ethnicity may help to resolve discrepancies. In addition, more studies are demanded to clarify the potential role of ANGPTL-8 in humans, a cause or an effect of this protein in association with insulin resistance, the regulatory mechanism of ANGPTL-8 expression, and the association of ANGPTL8 with other adipokines or myokines. In this mini review, we described various roles of ANGPTL-8 in diabetes.
Keywords: Type 2 diabetes, Angiopoietin-like protein 8, Dyslipidemia, Adipokine, Hepatokine

Background

ANGPTL-8 (angiopoietin-like protein 8), also known as RIFL (refeeding-induced fat and liver), Lipasin, and betatrophin, is regarded as a new object for the treatment of type 2 diabetes (T2D) and associated metabolic disorders (1). The in vitro and in vivo experiments documented the role of ANGPTL-8 in glucose metabolisms (2); however, human studies indicated different results (3,4). Indeed, the accurate role of ANGPTL-8 in diabetes and insulin resistance is far from being well perceived. In this review, we indicated some of diverse or even opposite roles of ANGPTL-8 in diabetes. Therefore, it is required to clarify the accurate relationship between ANGPTL-8 and diabetes.

ANGPTL8 is mainly expressed in the liver, white and brown adipose tissue (5,6). Nutritional states, thyroid hormone, insulin receptor antagonists, sterol regulatory element-binding protein (SREBP) isoforms: SREBP-1a, SREBP-1c, LXR agonists, carbohydrate-responsive element-binding protein (ChREBP), 5 adenosine monophosphate-activated protein kinase (AMPK), and mitogen-activated protein kinase (MAPK) have major roles in the regulation of ANGPTL-8 expression (7). In vitro and in vivo studies indicated that ANGPTL-8 regulates lipid metabolism. This protein plays a major role in the regulation of serum triglycerides (TG) level via interaction with ANGPTL-3 and -4 (6, 8), as well as lipoprotein lipase blocking; therefore, ANGPTL-8 increases TG level (9). It is noted that dyslipidemia is a characteristic of T2D and insulin resistance; the high level of TG, cholesterol, and low-density lipoprotein as ordinary facets of dyslipidemia is reported in T2D (10,11). This protein, as a hepatokine (12), is associated with hepatocellular lipid content (13). In animal and human studies, the level of ANGPTL-8 increased in subjects with non-alcoholic fatty liver disease (NAFLD) compared to the control subjects (14). It is reported that 90% of obese patients with T2D have NAFLD; this indicates a major association between NAFLD and T2D (15). Patients in both disorders have insulin resistance.

Several experiments reported a cross-talk between insulin, glucose, and ANGPTL-8 expression (2). Researchers documented that ANGPTL-8 regulated glucose metabolism through AKT/GSK3beta (glycogen synthesis) and AKT/FOXO (inhibition of gluconeogenesis), which are important in the glucose-lowering effect of the insulin signaling pathway (16). The weighted gene co-expression network analysis indicated that MAPK8, PIK3R2,

PIK3R4, MAP3K11, FLOT1, PIK3C2G, SHC1, and RAPGEF1, which are involved in insulin signaling, are co-expressed genes with ANGPTL8 (7).

In vivo studies showed that ANGPTL-8 improved insulin resistance in obese mice, ANGPTL8 had an effect on macrophage infiltration, decreased monocyte chemoattractant protein-1, IL-1β and inhibited NF-ƙβ activation (17). Therefore, ANGPTL8 may improve insulin resistance via attenuating inflammation.

The other issue is the association of ANGPTL8 with other proteins which have a role in diabetes. Irisin, as a myokine, and adiponectin, as an adipokine, are involved in the management of diabetes and metabolic disorders (18,19). Irisin increased mRNA expression of ANGPTL-8 in 3T3-L1 cells and adipose tissue, and irisin-ANGPTL-8 axis had a role in insulin resistance (20). The positive association of Irisin with ANGPTL-8 is shown in type 1 diabetes (21). However, other studies indicated no association (22). Moreover, ANGPTL8 increased adiponectin expression (17). More studies are needed to depict these issues.

Based on previous in vitro and in vivo studies, there are some controversial data on the association of ANGPTL-8 with insulin resistance in human: positive (4,23), negative (3,24) or even no correlation (25-27). A null mutation in human ANGPTL-8 gene had no association with fasting glucose, glucose tolerance or T2D (28). Some studies reported a decrease in ANGPTL8 level in diabetic patients (3), obese patients, and subjects with insulin resistance (29). The high level of ANGPTL-8 in diabetic patients had no association with fasting blood sugar and insulin resistance (30). Additionally, ANGPTL-8 level had no significant correlation with glucose or HbA1C in disturbed glyco-metabolism (31). Large scale genomic studies in humans have indicated that sequence variants in the gene encoding of ANGPTL-8 are not associated with glucose homeostasis markers (32,33).

On the other hand, the high level of ANGPTL-8 is reported in diabetic subjects (34,35). This protein may be beneficial in glucose tolerance in diabetic patients (7). Human studies showed that ANGPTL-8 plasma level increases in IGR (impaired glucose regulation) patients and gestational diabetic women (36,37) and may be a possible biomarker for predicting novel onset diabetes (38). This is a physiological response to increase beta-cell proliferation in order to counteract high insulin demand (39). Therefore, ANGPTL-8 may play a role before developing into diabetes mellitus (5,7). Some recent studies showed that ANGPTL-8 might be a predictive factor for diabetic complications, especially nephropathy and retinopathy (40).

Conclusion

Some of the discrepancies in the roles of ANGPTL-8 come from the diversity in ELISA kits, sample size, diagnostic criteria of overweight/obesity, age, ethnicity or other factors. Further controlled studies are demanded to define the potential role of ANGPTL-8 in humans. Some issues need to be clarified as follows: association of ANGPTL-8 with insulin resistance is a cause or an effect, physiological and pathophysiological factors which regulate ANGPTL-8 expression, the association between ANGPTL8 and other proteins such as adipokines or myokines, and the positive effect of ANGPTL-8 on hepatocellular lipid content and T2D.

Conflict of Interest Disclosures

The authors declare no conflict of interests.

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