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LETTER TO EDITOR

Diabetes, Insulin Resistance, Fetuin-B and Exercise Training

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DEAR EDITOR

Diabetes represents a major global public health threat and, together with obesity, constitutes an important contributor to a decline in life expectancy (1). The pathophysiology of type 2 diabetes is complex. In addition to impaired insulin secretion from pancreatic cells, a reduced insulin sensitivity is found to play a predominant role in the pathogenesis of the disease (2). Several circulating proteins are involved in the regulation of insulin sensitivity; such as, adiponectin, retinol binding protein 4, and fetuin-A (3). The fetuin family consists of a set of orthologous plasma proteins found in humans, sheep, pigs, cows and rodents. Fetuin-A has been identified as a major protein during fetal life and is also involved in important functions such as inhibition of insulin receptor tyrosine kinase activity, protease inhibitory activity and the development of associated regulation of calcium metabolism and osteogenesis. Furthermore, fetuin-A is a key component in the recovery phase of an acute inflammatory response. There is a second protein of the fetuin family, called fetuin-B, which is found at least in human and rodents. Fetuin-B was discovered in mice prone to diabetes. Based on domain homology, overall conservation of cysteine residues and chromosomal assignments of the corresponding genes in these species, fetuin-B is a unambiguously paralogue of fetuin-A (3, 4). Recently, fetuin-B has also been identified as a novel adipokine/hepatokine which is significantly increased in hepatic steatosis and which mediates impaired insulin action, as well as glucose intolerance (4). Meex et al. demonstrated that secretion of fetuin-B by isolated hepatocytes is augmented in mice with hepatic steatosis as compared to control littermates and it impairs glucose homeostasis in both humans and rodents (4). Most interestingly, short hairpin RNA-induced knockdown of plasma fetuin-B improved glucose tolerance in mice as compared to controls without any effect on body weight (4). Previous studies have shown that Fetuin-B is in high levels

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in patients with Type 2 diabetes. In an experimental trial, patients were found to have high levels of Fetuin-B only if they were also pre-diabetic or diabetic. Moreover, another study demonstrated that fetuin-B levels are increased in women with gestational diabetes mellitus compared with healthy pregnant control women (5). Also Fetuin-B protein has been shown to impair the action of insulin in the body (5). This evidence collectively provides a clear and causal link between the development of non-alcoholic fatty liver disease (NAFLD) and the development of Type 2 diabetes. If we can develop a drug that can block this protein perhaps we may be able to prevent the development of diabetes in patients with NAFLD (5, 6).

On the other hand, exercise training is well noted as one of the most effective behavioral factors in the prevention of diabetes and inflammation. Numerous studies have examined the effect of exercise training on diabetics, obese patients, and cardiovascular patients, confirming that exercise training is able to reduce insulin resistance, obesity, inflammatory markers and adipokines such as leptin, retinol binding protein 4, resistin (associated with insulin resistance), while at the same time increasing adiponectin (7-11). The aforementioned points highlight the positive effect of exercise training on obesity, diabetes and inflammation risk factors (12); and, in turn, suggest the effect of exercise training on fetuin-B research is highly warranted – and as of yet remains unexamined. The study of fetuin-B and exercise may provide new insight and important understanding about the connections between, and prevention of diabetes, insulin resistance, and related diseases. We encourage exercise immunology and physiology researchers to examine the theoretical constructs present here and test the premise put forward.

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