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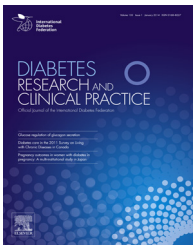

Review

The role of fibroblast growth factor 21 in diabetes and its complications: A review from clinical perspective

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ABSTRACT

Fibroblast growth factor 21 (FGF21) has been well-recognized as a metabolic hormone and a promising target for treatment of metabolic diseases. The level of endogenous FGF21 is elevated in patients with impaired glucose tolerance and progressively increased from patients with overt type 2 diabetes to those with micro- and macro-vascular complications, presumably as a compensation or response to the deterioration of metabolic imbalance. A few exploratory in vivo studies, including a recent clinical trial, showed that exogenous FGF21 mimetics targeting FGF21 signaling can attain beneficial metabolic effects not withstanding the already elevated ambient FGF21 levels. In addition, some clinically available pharmacologic agents such as fenofibrates and metformin may modulate energy and macronutrients metabolism by acting through FGF21. This review mainly focuses on the role of FGF21 in development, progression and treatment of type 2 diabetes from a clinical perspective.

Contents

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1. Introduction

Fibroblast growth factor 21 (FGF21) belongs to the fibroblast growth factor (FGF) superfamily but it lacks the conventional heparin-binding domain of other FGF members. Together with FGF19 and FGF23, these three FGF members are often classified as ''endocrine'' FGFs [1]. Human FGF21 is a 181 amino acid protein well conserved across species and it shares 75% homology to mouse FGF21 [2]. FGF21 is primarily secreted by the liver. Moreover, it is also expressed by adipose tissue, thymus, skeletal muscle and pancreas [3].

The metabolic action of FGF21 was first discovered when it was found to activate 3T3-L1 adipocytes glucose uptake in a high throughput screening [4]. Knowledge of the physiological function of FGF21 was mainly obtained by administration of recombinant FGF21 into animal models and from gain-of-function transgenic mouse [4,5]. FGF21 has now been well-recognized as a metabolic hormone and a promising target for treatment of metabolic diseases [1,6]. The role of FGF21 as a regulator of lipids and glucose metabolism and the mechanisms of its actions on energy metabolism have been reviewed extensively elsewhere [1,3,7]. This review focuses on the role of FGF21 in diabetes and its complications from a clinical perspective. We will also discuss recent preclinical and clinical studies suggesting FGF21 as a therapeutic target for treatment of type 2 diabetes and its associated cardiometabolic risk factors.

2. Association of FGF21 with type 2 diabetes

A hallmark of type 2 diabetes is insulin resistance, namely impaired response to the normal actions of insulin to control glucose and lipids homeostasis in insulin-sensitive organs including liver, fat tissue, and muscle. Insulin resistance also contributes to the progressive failure of the pancreatic islet beta cells insulin production [8]. The pathogenesis of type 2 diabetes involves dysregulation of multiple pathways of energy metabolism. The cardio-metabolic risk factors associated with type 2 diabetes often cluster as ''metabolic syndrome'' [9].

Administration of recombinant FGF21 in obese and diabetes rodent models induces a range of favorable metabolic changes which include amelioration of hyperglycemia and dyslipidemia, reduction in body weight accompanied by enhancement of insulin sensitivity and glucose uptake in peripheral tissue, increase in fat utilization and energy expenditure, and decrease in glucagon production in islet α cells [3,7]. These overwhelming beneficial effects of exogenous FGF21 on metabolic regulation in animal models lead to the expectation that circulating FGF21 may be lower in human subjects with metabolic dysregulations. Paradoxically, the level of circulating FGF21 in obese subjects with components of metabolic syndrome is significantly higher compared to that in those healthy controls, presumably due to FGF21 resistance associated with ''metabolic imbalance'' [10]. Given the close association between type 2 diabetes and metabolic syndrome (presumptively driven by insulin resistance), it is not a surprise to observe that the level of circulating FGF21 in patients with type 2 diabetes is significantly higher than that in controls without diabetes and correlated with insulin resistance [11–13]. In a large prospective study in Chinese subjects, the level of circulating FGF21 is increased progressively with the deterioration of dysglycemia from normal glucose tolerance, prediabetes to diabetes [14]. Interestingly, a high level of baseline FGF21, together with waist circumference and fasting plasma glucose level, was a strong independent predictor of diabetes development (odds ratio 1.79, $p < 0.01$). These observations suggest that FGF21 may have been elevated in response to metabolic imbalance even before the overt manifestation of hyperglycemia and it may be a potential biomarker predicting the risk of type 2 diabetes, especially among those with central obesity.

Although the level of circulating FGF21 is significantly increased in patients with type 2 diabetes and correlated with glycemia level [13], it is unlikely that hyperglycemia itself is a direct cause of increased FGF21 expression and secretion. Firstly, to the best of our knowledge, there are no convincing data showing a linear relationship between the level of plasma glucose and the level of circulating FGF21 independent of other associated metabolic risk factors such as insulin resistance and dyslipidemia. Secondly, the level of circulating FGF21 in obese patients with type 2 diabetes does not differ significantly from obese subjects without type 2 diabetes, although both were higher than that in healthy controls [12]. Thirdly, the level of circulating FGF21 in newly diagnosed type 2 diabetes with non-alcoholic fatty liver disease (NAFLD) is significantly increased. However, the level of circulating FGF21 in newly diagnosed type 2 diabetes without NFALD is similar to that of normal controls [15]. Lastly and most importantly, the level of circulating FGF21 in some subtypes of diabetes, including type 1 diabetes and latent autoimmune diabetes in adults (LADA), as discussed below, are actually lower than that in age- and sex-matched controls without diabetes [16]. A reasonable speculation is that the higher level of circulating FGF21 associated with type 2 diabetes may be secondary to the ''common soil'' shared by components of metabolic syndrome, namely hyperinsulinemia and the consequential increase in increased lipolysis and plasma free fatty acid (FFA) [17]. A recent study showed that the level of circulating FGF21 was increased under supra-physiological level of free fatty acid induced by lipid–heparin infusion (LHI) which is accompanied by mild hyperinsulinemia. However, a mild elevation of FFA resulting from complete insulin deficiency also increased FGF21 levels. These data suggest that higher FFA, which is often observed in patients with type 2 diabetes and presumably secondary to the increased lipolysis, may be one of the main drivers of elevated circulating FGF21 in patients with T2DM [18].