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Original article

Serum fibroblast growth factor 21 concentrations in type 2 diabetic retinopathy patients

Dosage sérique du facteur de croissance des fibroblastes 21 chez les patients atteints de rétinopathie diabétique de type 2

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Abstract

Aims/purpose. – Fibroblast growth factor 21 (FGF21) is a major metabolic regulator in the body that has been shown to be elevated in a number of metabolic disturbances including type 2 diabetes mellitus (T2DM) and the metabolic syndrome. However, little is known regarding the circulating levels of FGF21 in type 2 diabetic retinopathy (T2DR) and its association with the severity of the condition. *Methods.* – In a cross-sectional setting, 142 individuals, consisting of (1) T2DM patients without T2DR, (2) T2DM patients with T2DR, and (3) healthy control subjects were recruited for this study. Various clinical and biochemical parameters were assessed and entered for analysis. *Results.* – Serum FGF21 levels were significantly elevated in T2DM subjects without retinopathy (103.50 [75.75] pg/mL) compared with healthy controls (99.00 [126.75] pg/mL). Circulating FGF21 levels were comparable across different stages of T2DR (233.00 [109.00] for nonproliferative type 2 diabetic retinopathy [NPT2DR] vs. 215.00 [122.00] for proliferative type 2 diabetic retinopathy [PT2DR] groups, $P = 361$). FGF21, triglycerides, and duration of diabetes mellitus were significantly associated with T2DM in baseline models. However, after adjustment for potential confounders, in the final multivariate model, FGF21 emerged as the only significant factor associated with T2DM (OR = 13.772, 95% CI = 3.062–61.948, $P = 001$). *Conclusions.* – Serum FGF21 concentrations are markedly elevated in patients with T2RN. The association between FGF21 and T2DR appears to be independent of the effects of potential confounding variables. These findings may suggest FGF21 as a novel surrogate diagnostic biomarker in initial stages of T2DR (particularly with FGF21 values above 135.5 pg/mL).

Keywords: Fibroblast growth factor 21; Type 2 diabetic retinopathy; Nonproliferative retinopathy; Proliferative retinopathy

Résumé

Objectifs/but. – Le facteur de croissance des fibroblastes 21 (FGF21) est un régulateur majeur du métabolisme dont l'élévation a été mise en évidence dans un certain nombre de troubles métaboliques, notamment le diabète de type 2 (DT2) et le syndrome métabolique. Toutefois, on en sait peu sur les taux circulants de FGF21 dans la rétinopathie diabétique de type 2 (T2DR) et son association avec la gravité de l'état. *Méthodes.* – Dans le cadre d'une analyse transversale, 142 personnes ont été recrutées, réparties de la façon suivante : (1) patients atteints de DT2, sans T2DR, (2) patients atteints de DT2 avec T2DR, et (3) sujets témoins sains. Les différents paramètres cliniques et biochimiques ont été évalués et colligés pour analyse. *Résultats.* – Les niveaux de FGF21 sérique étaient significativement plus élevés chez les sujets atteints de DT2, sans rétinopathie (103,50 [75,75] pg/mL) par rapport aux témoins sains (99,00 [126,75] pg/mL). Les taux circulants de FGF21 étaient comparables selon les différents stades de T2DR: 233,00 [109,00] dans le cadre d'une rétinopathie diabétique de type 2 non proliférante [NPT2DR] vs 215,00 [122,00] pour

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une rétinopathie diabétique de type 2 proliférante [PT2DR], $P = 0{,}361$). Le FGF21, les triglycérides, et la durée du diabète sucré étaient significativement associés à T2DM dans les modèles de référence. Toutefois, après ajustement pour les facteurs confondants potentiels, dans le modèle multivarié, FGF21 a émergé comme le seul facteur significatif associé à T2DM (OR = 13,772, 95 % CI = 3,062 à 61,948, $P = 0{,}001$). *Conclusions.* – Les concentrations sériques de FGF21 sont sensiblement plus élevées chez les patients atteints de T2DM. L'association entre FGF21 et T2DR semble être indépendante des effets des variables de confusion potentielles. Ces résultats suggèrent que le taux de FGF21 est un marqueur potentiel des étapes initiales de développement d'un T2DR (en particulier pour des valeurs de FGF21 supérieures à 135,5 pg/ml).

Mots clés : Facteur de croissance des fibroblastes 21 ; Rétinopathie diabétique de type 2 ; Rétinopathie non proliférante ; Rétinopathie proliférante

1. Introduction

Type 2 diabetic retinopathy (T2DR) is a leading cause of avoidable blindness worldwide [1]. Generally, the incidence of T2DR increases with patient's age and duration of diabetes but its occurrence and progress is appeciably hastened when hyperglycemia is not adequately controlled [2]. Aside from poor glycemic control, a number of modifiable risk factors, often present in patients with type 2 diabetes mellitus (T2DM), also contribute to the progression of T2DR. These treatable risk factors include overweight/obesity, high blood pressure, hypercholesterolemia and hypertriglyceridemia, and presence of other microvascular complications (e.g. diabetic nephropathy) [3,4].

Fibroblast growth factor 21 (FGF21) is an adipokine originating in the liver with extensive local and systemic biological roles in both animals and humans [5]. Released as a signal for global starvation, FGF21 promotes intrahepatic gluconeogenesis, lipoxidation, and lipolysis in white adipose tissues (WATs). While FGF21 is mainly expressed through the peroxisome proliferator-activated receptor-α (PPARα) cascade, its metabolic actions are mediated through binding the complex consisting of its receptors and an obligatory coreceptor, β-Klotho [6]. A lacking FGF21 expression/activation as found in PPARα signaling impairments decreases insulin sensitivity, hepatic lipid oxidation and triglyceride clearance [7]. On the other hand, increased concentrations of FGF21 are paradoxically observed in states of heightened insulin resistance, obesity, hypertension, diabetes, and the metabolic syndrome to name a few. It is suggested that the increase in FGF21 might be due to resistance to its functions, and/or a compensatory phenomenon in response to the dysregulated metabolic state [5,6].

Both macrovascular and microvascular complications of diabetes have been linked to elevated FGF21 concentrations. For example, in a population-based study, FGF21 levels were associated with carotid atherosclerosis independent of traditional cardiovascular risk factors [8]. The association between serum FGF21 and diabetic nephropathy has also been extensively investigated. In a prospective study of 1136 Chinese patients with T2DM, it was shown that FGF21 is a significant predictor of decline in estimated glomerular filtration rate (eGFR) over four years, even in the subgroup of patients with baseline eGFR > 60 and normoalbuminuria [9]. By comparison, a possible association between FGF21 and T2DR (as another prevalent microvascular complication of T2DR) has only received scant attention in the literature [10,11].

With this in mind, in the present study, we sought to investigate the following:

- Are FGF21 concentrations associated with T2DR and its severity?
- Is the association between FGF21 and T2DR independent of other possible risk factors associated with T2DR?

2. Patients and methods

2.1. Study design, population and protocol

The present study was carried out amongst 142 consecutive individuals in three groups: T2DM patients without T2DR, T2DM patients with T2DR and healthy controls. Patients with T2DM were selected from those attending regular follow-up visits at the Diabetes Clinic (Vali-Asr University Hospital, Tehran University of Medical Sciences) who were receiving oral antihyperglycemic agent (OAG) and/or insulin. If antihypertensive and/or lipid-lowering therapies were indicated, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) and statins, respectively, were prescribed. Patients were excluded if they consumed alcohol, smoked cigarette/tobacco, were obese (body mass index [BMI] $\geq 30\,kg/m^2$), had impaired renal function (plasma creatinine > 2 mg/dL and eGFR < 60 ml/min/1.73 m^2) or fatty liver disease (nonalcoholic fatty liver disease or nonalcoholic steatohepatitis), had clinical kidney damage (macroalbuminuria or urinary albumin excretion; UAE > 300 mg/day) and manifested active bacterial and/or viral infection. History of heart failure, ischemia and other acute events (e.g., unstable and stable angina), any previous or current evidence indicative of macrovascular disease (myocardial infarction, coronary artery disease, peripheral arterial disease, revascularization procedure, or coronary artery bypass grafting and established atherosclerosis) and use of drugs known to affect serum FGF-21 levels (e.g., fenofibrate [11]) were the other exclusion criteria to this study. All of the patients received adequate information regarding study aims and protocol and signed informed consent forms prior to enrolment. The study protocol was approved by local ethics committee and was conducted in accordance with the Helsinki declaration.