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Original article

Low levels of insulin-like growth-factor-binding protein-1 (IGFBP-1) are prospectively associated with the incidence of type 2 diabetes and impaired glucose tolerance (IGT): The Söderåkra Cardiovascular Risk Factor Study

U. Petersson [a,*,b], C.J. Östgren [b], L. Brudin [b], K. Brismar [c], P.M. Nilsson [d]

[a] *Primary Health Care Centre, Kalmar County Council, Kyrkvägen 28, 38551 Söderåkra, Sweden*
[b] *Department of Medical and Health Sciences, Linköping University, Sweden*
[c] *Department of Molecular Medicine and Surgery, Karolinska Institutet, Solna, Sweden*
[d] *Department of Clinical Sciences, Lund University, University Hospital, Malmö, Sweden*

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Abstract

Aim. – To explore the association between baseline levels of insulin-like growth-factor-binding protein-1 (IGFBP-1), a marker of insulin sensitivity, and the development of type 2 diabetes or impaired glucose tolerance (IGT) in a specifically defined middle-aged population.

Methods. – This cross-sectional population-based screening study was conducted in 1989–1990 and included baseline data for 664 non-diabetic subjects aged 40–59 years. Clinical data were collected and blood samples analyzed for blood glucose, serum lipids and insulin. Blood specimens were frozen at baseline and later analyzed for IGF-I, IGFBP-1 and C-reactive protein (CRP). At the follow-up in 2006, the incidence of type 2 diabetes and IGT was reported based on primary-care medical records.

Results. – During the 17-year observation period, 42 subjects (6.3%) developed type 2 diabetes/IGT. Those in the lowest quintile of IGFBP-1 ($\leq$24 μg/L) at baseline had a diabetes incidence of 12.6% while, in the highest quintile of IGFBP-1 ($\geq$59 μg/L), the incidence was 1.5%. Cox's proportional-hazards model regression analyses were used to determine the incidence of type 2 diabetes/IGT, corrected for age and gender, in relation to IGFBP-1, CRP and waist circumference. Subjects in the lowest IGFBP-1 quintile showed an independently increased risk of type 2 diabetes/IGT [hazards ratio (HR): 3.54; 95% CI 1.18–10.6; $P = 0.024$]. For CRP and waist circumference, the corresponding figures were HR: 6.81; 95% CI 2.50–18.6; $P < 0.001$ and HR: 3.33; 95% CI 1.47–7.6; $P = 0.004$, respectively.

Conclusion. – Low levels of IGFBP-1 predicted the long-term development of type 2 diabetes or IGT in a middle-aged population. The association was independent of CRP and abdominal obesity.

Keywords: CRP; IGFBP-1; Prediction; Screening; Type 2 diabetes; Longitudinal study

Résumé

Des concentrations basses d'*insulin-like growth factor binding protein-1* (IGFBP-1) sont associées au développement du diabète de type 2 et de l'intolérance au glucose. Étude Söderåkra Cardiovascular Risk Factor.

Objectif. – Étudier les liens éventuels entre l'*insulin-like growth-factor-binding protein-1* (IGFBP-1), marqueur de l'insulinosensibilité, à l'inclusion et le développement ultérieur d'un diabète de type 2 (DT2) ou d'une intolérance au glucose (IGT) dans une population d'âge moyen.

Méthodes. – Une étude de dépistage transversale en population a été conduite en 1989–1990 et comportait les données anthropométriques, la glycémie, l'insulinémie et les paramètres lipidiques du sérum à l'inclusion de 664 sujets non diabétiques âgés de 40 à 59 ans. Des échantillons de sang furent congelés pour dosages ultérieurs de l'IGF-I, de l'IGFBP-1 et de la protéine C-réactive (CRP). Au cours du suivi, en 2006, l'incidence du DT2 et celle l'IGT ont été relevées à partir des dossiers médicaux des patients.

Résultats. – Au cours de la période de suivi de 17 ans, 42 sujets (6,3 %) développèrent un DT2 ou une IGT. L'incidence du DT2 chez les sujets dont l'IGFBP-1 à l'inclusion était dans le quintile le plus bas ($\leq$ 24 μg/L) était de 12,6 %, alors que l'incidence était de 1,5 % chez ceux dont l'IGFBP-1 à l'inclusion était dans le quintile le plus élevé ($\geq$ 59 μg/L). Des analyses de régression proportionnelles avec le modèle de Cox entre IGFBP-1 et risque de développer DT2 ou IGT, ajustées sur l'âge, le sexe, la CRP et le tour de taille ont été réalisées. Les sujets situés dans le quintile

* Corresponding author.
E-mail address: ullape@ltkalmar.se (U. Petersson).

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d'IGFBP-1 le plus bas présentaient un risque plus élevé de développer DT2–IGT avec un risque relatif de 3,54 (IC à 95 % 1,18–10,6 ; $P = 0,024$). Ajustés pour la CRP et le tour de taille, les risques relatifs correspondants étaient respectivement de 6,81 (IC à 95% 2,50–18,6 ; $P < 0,001$) et de 3,33 (IC 95% 1,47–7,6 ; $P = 0.004$).

Conclusion. – Des concentrations basses d'IGFBP-1 permettent de prédire le développement ultérieur d'un DT2 ou d'une IGT dans une population d'âge moyen. Cette association est indépendante de la CRP et de l'obésité abdominale.

Mots clés : CRP ; IGFBP-1 ; Dépistage ; Valeur prédictive ; Diabète de type 2 ; Intolérance au glucose ; Étude longitudinale

1. Introduction

Type 2 diabetes is often preceded by insulin resistance. Waist circumference and the homoeostasis model assessment (HOMA) index are well-known surrogate markers of insulin resistance. Also, insulin-like growth-factor-binding protein-1 (IGFBP-1) as part of the insulin-like growth factor (IGF) system, which is involved in the regulation of glucose metabolism, is associated with insulin resistance and glucose intolerance. IGFBP-1 is one of six binding proteins and has been proposed to be an acute regulator of IGF-I bioavailability [1]. Produced in the liver, it peaks at night and in the early morning, as it is highly dependent on insulin concentrations. High levels of insulin are associated with low IGFBP-1 concentrations.

Low levels of IGFBP-1 are also associated with features of the metabolic syndrome such as insulin resistance, obesity and the development of cardiovascular disease [2–6]. It has been suggested that IGFBP-1 facilitates the transport of IGF-I from plasma to tissue, thus potentially increasing the activity of IGF-I in the target tissue [7]. Many of the processes involved in the formation of atherosclerotic lesions are IGF-I-dependent, promoting macrophage chemotaxis and endothelial cell migration [8], as well as vascular smooth muscle cell proliferation and migration [9]. IGFBP-1 also exerts an effect on cellular growth and migration independently of IGF by binding to the cell surface via 5β1 integrins [10,11]. IGFBP-1 reflects free IGF-I [12]. Serum levels of IGFBP-1 (but not IGF-I) correlate with body mass index (BMI), and upper arm fat and muscle areas in the elderly [13], but also vary considerably in healthy individuals [14]. A monozygotic twin study showed that non-genetic factors explained 64% of the variation seen in serum IGFBP-1 levels [15], whereas insulin and IGF-I explained only 28 and 8%, respectively, of such non-genetic variation [16]. This means that approximately 30% of the variation in IGFBP-1 levels remains unexplained, but could be due to dietary and other lifestyle factors, according to a study in healthy men [17]. In addition, one study has shown that high circulating concentrations of IGF-I were associated with a reduced risk of type 2 diabetes/IGT in normoglycaemic individuals [18]. Finally, a recent study found that low levels of IGFBP-1 predicted an increased risk of cardiovascular events [19].

The aim of the present observational study was to explore the association between IGFBP-1 and IGF-I at baseline with the later development of type 2 diabetes and IGT in a specifically defined middle-aged population.

2. Subjects and methods

The Söderåkra Cardiovascular Risk Factor Study was launched in November 1989 and ran until May 1990 as a population-based, cross-sectional cardiovascular risk-factor screening study in which all inhabitants aged 40–59 years, living in the Söderåkra parish in southern Sweden, were invited to participate. Of a total of 782 invited subjects, 705 (90%)—361 men (88%) and 344 women (93%)—agreed to participate. Details of non-participants at baseline have been described elsewhere [20]. At baseline (study entry), participants underwent laboratory tests, a structured health visit with a specially trained nurse, a self-administered questionnaire, and a visit with a physician for clinical examination and completion of the questionnaire. Blood specimens were drawn without venous stasis after an overnight fast with the subject seated after a 15 minutes rest. Blood glucose, serum cholesterol, HDL cholesterol and serum triglycerides were analyzed. LDL cholesterol was calculated using Friedewald's formula. Indeed, only routine laboratory methods were used by the Department of Clinical Chemistry at Kalmar County Hospital. Extra serum samples were frozen and stored for future analyses. Clinical measurements of height (cm), weight (kg), and waist and hip circumferences (cm) were also taken, and the subjects' BMI calculated (kg/m^2).

After analyses of the blood specimens, all but 13 subjects attended a structured clinical visit with a physician who provided feedback information. Three blood-pressure measurements (Korotkoff I and V) were recorded (mmHg) from the right arm, in the sitting position after a five minutes rest, using a mercury sphygmomanometer and the appropriate cuff width. The mean value of the last two measurements was recorded as well as the heart rate (Beats/minutes). Following the physical examination, a questionnaire containing lifestyle questions and dietary habits, focused on physical activity, smoking and alcohol consumption, was completed. Tobacco use was expressed as the number of cigarettes or packs of tobacco used per day. Alcohol consumption was expressed in centilitres (cl) of beer, wine and hard liquor consumed per week, which was converted into grammes of alcohol per week. Physical activity (cycling, walking, swimming and any other activities engaging the large muscles) was divided into three categories:

- daily exercise for half an hour or more;
- exercise two to three times a week for half an hour;
- less exercise than exercising two to three times a week for half an hour.