Growth Hormone & IGF Research 22 (2012) 1–5

Contents lists available at SciVerse ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

The association between insulin-like growth factor-I and cardiac repolarization

Till Ittermann [a,b,*,1], Charlotte van Noord [d,1], Nele Friedrich [a], Marcus Dörr [c], Stephan B. Felix [c], Matthias Nauck [a], Henry Völzke [b], Albert Hofman [d], Jacqueline C.M. Witteman [d], Bruno HCh Stricker [d,e,1], Henri Wallaschofski [a,1]

[a] Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany
[b] Institute for Community Medicine, University of Greifswald, Germany
[c] Department of Medicine, University of Greifswald, Germany
[d] Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands
[e] Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 15 June 2011
Received in revised form 17 October 2011
Accepted 20 November 2011
Available online 11 December 2011

Keywords:
IGF-I
IGFBP-3
QTc interval
Cardiac repolarization
Population-based studies

ABSTRACT

Objective: Previous studies reported associations between insulin-like growth factor I (IGF-I) serum concentration and cardiac morbidity and mortality, but the association between IGF-I serum concentration and cardiac repolarization has not been investigated in a population-based study so far. Therefore, we analyzed the impact of IGF-I concentrations on QTc, QT and RR intervals in two population based studies, The Study of Health in Pomerania (SHIP) and the Rotterdam Study.

Design: 457 individuals from SHIP and 155 individuals from the Rotterdam Study older than 55 years and without cardiovascular diseases and a left ventricular hypertrophy were investigated. IGF-I was determined by automated two-site chemiluminescence immunoassays and electrocardiograms were recorded by an ACTA electrocardiograph at a sampling frequency of 500 Hz. The association of IGF-I with QTc, QT and RR intervals was investigated by multivariable linear regression analyses adjusted for age, gender, diabetes mellitus, myocardial infarction, hypertension, body mass index, serum potassium and calcium in both studies separately and in pooled analysis.

Results: There were no significant associations between log-transformed IGF-I and QTc interval in the single populations, whereas a significant inverse association was detectable in the pooled population (β, −15.6; 95%-confidence interval, −25.7, −5.5). The QTc interval was significantly higher in the first tertile of IGF-I compared to the third tertile (β, 5.4; 95%-confidence interval, 9.5–1.3) in the pooled analysis.

Conclusion: The inverse association between IGF-I serum concentrations and QTc interval in our study is suggestive of a higher risk for cardiac arrhythmias and thus might provide additional evidence for increased cardiovascular mortality in subjects with low IGF-I secretion.

1. Introduction

Insulin-like growth factor I (IGF-I), which is mostly transported by IGF binding protein 3 (IGFBP-3), is generally accepted as a central mediator of endocrine and metabolic effects of the growth hormone (GH) [1]. Both disorders of the GH/IGF-I axis, GH deficiency (GHD) characterized by low IGF-I serum values [2–5] as well as acromegaly caused by GH and consequent IGF-I oversecretion [6,7], are associated with increased cardiovascular morbidity and all-cause mortality. In a recent meta analysis [2] low as well as high IGF-I serum values were associated with all-cause but not with cardiovascular mortality. However, data was not analyzed sex-stratified in this meta analysis [2]. Another study [3] demonstrated significant associations between low IGF-I concentrations and all-cause as well as cardiovascular mortality in males but not in females. In agreement with this, a further study [8] showed an inverse association between IGF-I concentrations and the intima-media thickness of the carotis in males, whereas IGF-I concentrations were positively associated with this endpoint in females. Moreover, another study [9] demonstrated that GHD is associated with an altered lipid profile, insulin resistance, and glucose intolerance due to an increase of visceral fat mass. Therefore, GHD is strongly linked to the metabolic syndrome which might be one explanation for the observed higher cardiovascular mortality that has been observed in GHD patients [3–5]. In contrast to these findings, a previous analysis based on data from the Study of Health in Pomerania (SHIP) did not reveal a significant association between IGF-I concentrations and left ventricular hypertrophy as a potential intermediated phenotype for increased morbidity and mortality [10].

* Corresponding author at: Institute for Clinical Chemistry and Laboratory Medicine, Ernst Moritz Arndt University, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany. Tel.: +49 3834 867539; fax: +49 3834 865502.
E-mail address: till.ittermann@uni-greifswald.de (T. Ittermann).
[1] Contributed equally.

1096-6374/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ghir.2011.11.001

Cardiac repolarization disturbances are strongly linked to ventricular arrhythmias and cardiovascular mortality [11] and thus might provide another explanation for the reported association between alterations of growth hormone levels with increased morbidity and mortality. However, this relation has not been investigated so far. We therefore investigated the associations between IGF-I and IGFBP-3 concentrations and cardiac repolarization as defined by electrocardiographic QT, QTc, and RR intervals using data from two population-based studies conducted in Western Europe.

2. Material and methods

2.1. Study populations

2.1.1. The Rotterdam Study

The Rotterdam Study is a population-based cohort study, which started with a baseline visit between 1990 and 1993. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and over, were invited to participate (n = 10,275). Of them, 7983 (78%) gave their written informed consent and took part in the baseline examination (Rotterdam Study). Objectives and methods of the Rotterdam Study have been described in detail elsewhere [12]. At baseline, all participants were visited at home for a standardized questionnaire, and 7151 were subsequently examined at the research center. The cohort is continuously being monitored for major morbidity and mortality through linkage of the Rotterdam Study database with general practitioner and municipality records.

A group of 346 subjects aged between 55 and 79 years was studied for the present investigation; they comprised two different subsamples from the Rotterdam Study: (i) the first study group consisted of 196 subjects who were randomly selected; (ii) the second study group of 150 healthy subjects had been selected based on their IGF-I genotype as previously described by Vaessen et al. [13]. Participants with an IGF-I measurement for whom an ECG was available, were included in the study population.

2.1.2. The Study of Health in Pomerania (SHIP)

SHIP is a population-based study in a region in northeast Germany, comprising three cities Greifswald, Stralsund, Anklam and 29 surrounding communities, with a total of 212,157 residents [14]. A representative sample aged 20 to 79 years was invited to participate. For the SHIP baseline study a sample from the population aged 20 to 79 years was drawn from population registries. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects. The population of the baseline SHIP finally comprised 4308 participants (2117 men and 2193 women) corresponding to a final response of 68.8%. Examinations were conducted between 1997 and 2001.

Both studies obtained informed written consent from all participants, and followed the recommendations of the Declaration of Helsinki. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. The SHIP study was approved by the Ethics Committee of the University of Greifswald.

2.2. Exclusion criteria

Of the 346 subjects in the subpopulation of the Rotterdam Study, 191 were excluded because of missing ECGs, missing information on left ventricular hypertrophy (n = 158), or intake of QTc prolonging drugs (n = 7), and/or digoxin (n = 7). Furthermore all participants with a left ventricular hypertrophy as assessed by echocardiography using previously described criteria (calculated by dividing left ventricular mass by height$^{2.7}$) [15] (n = 9), or a left or right branch block (n = 10) were excluded from further analysis resulting in a population of 155 individuals (71 women).

From SHIP, we excluded 807 individuals due to missing data as well as participants <54 years (n = 1925) in order to obtain comparable study populations with respect to age. In addition all participants with intake of QTc prolonging drugs (n = 29), digoxin, and digitoxin (n = 125) were excluded. Moreover all participants with a left ventricular hypertrophy or non-available echocardiograms (n = 606), a pacemaker (n = 2), or a left or right branch block (n = 34) were excluded. Since the QTc interval differed significantly between groups of individuals without left ventricular hypertrophy and those for which data on left ventricular hypertrophy was missing (p = 0.030), all individuals with missing data in the left ventricular hypertrophy variable (n = 325) were excluded from further analysis resulting in a population of 457 individuals (236 women).

2.3. Assessments

2.3.1. Rotterdam Study

Serum was separated by centrifugation and quickly frozen in liquid nitrogen. Blood measurements were performed on fasting blood samples, unless otherwise specified. Total IGF-I was determined by a commercially available RIA ((Medgenix Diagnostics, Brussels, Belgium) with intra-assay and inter-assay coefficients of variation of 6.1 and 9.9%). Commercially available IRMAs were used for the measurement of IGFBP-3 ((Diagnostic System Laboratories Inc., Webster, TX, USA) intra-assay and inter-assay coefficients of variation for IGF-1 4.0 and 6.0% respectively, and for IGFBP-3 1.8 and 1.9% respectively)).

2.3.2. SHIP

Blood samples were taken in supine position between 7 a.m. and 4 p.m., and were analyzed in the core laboratory of the University Hospital Greifswald. Serum IGF-I and IGFBP-3 concentrations were determined by automated two-site chemiluminescence immunoassays (Nichols Advantage; Nichols Institute Diagnostica GmbH, Bad Vilbel, Germany). Details on the assays and their performance have been reported previously [3]. Serum potassium, and calcium were determined using a commercial colorimetric test (Roche Diagnostics, Mannheim, Germany) on a Hitachi 717 autoanalyzer. Serum alanine aminotransfarase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) were measured photometrically at 37 °C as previously described [16].

2.3.3. Rotterdam Study and SHIP

Socio-demographic characteristics, history of smoking, medication, history of myocardial infarction, diabetes, and alcohol consumption were assessed by computer-assisted personal interviews. Smokers were categorized into three categories (lifetime non-smokers, former smokers, current smokers). Alcohol consumption in g/day was defined according to Alte et al. [17]. Information on determination of blood pressure related variables and definition of hypertension can be find elsewhere [18,19]. Height and weight were measured for the calculation of the body mass index: BMI = weight (kg)/height^2 (m^2).

The endpoints were the duration of the QTc, QT and RR intervals in ms. In both studies a 12-lead resting ECG was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs from both studies were centrally processed in Rotterdam using the Modular ECG Analysis System (MEANS) to obtain ECG measurements, in agreement with the FDA guidance for clinical evaluation of QT/ QTc interval prolongation [20]. The MEANS program has been evaluated and validated extensively [21–24]. In one of these validation studies [24], ECGs with selected abnormalities were analyzed by 5 cardiologists and 11 different computer programs of which MEANS performed as one of the best. In a study in which QT intervals by manual measurement were compared with QT measurement by ECG machines [25], manual and automated measurements generated similar numerical results in