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Trajectories of plasma IGF-1, IGFBP-3, and their ratio in the Mayo Clinic Study of Aging

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ABSTRACT

Insulin-like growth factor 1 (IGF-1) has been associated with osteoporosis, cardiovascular disease, cancer, neurodegenerative diseases, and mortality in middle and older aged adults. Cross-sectionally, IGF-1 decreases with age and levels of IGF-1 are markedly different between individuals. However, little is known about intra-individual trajectories of IGF-1. We examined baseline and serial measures of plasma total IGF-1, IGF binding protein (IGFBP)-3, and their ratio, which is a proxy for bioavailable IGF-1, among 1618 adults, aged 50–95, enrolled in the Mayo Clinic Study of Aging. At baseline, IGF-1 and IGFBP-3 were strongly correlated ($r = 0.62$, $p < 0.001$). Total IGF-1 and IGFBP-3 decreased across age, while the ratio of IGF-1/IGFBP-3 increased across age. This pattern was consistent across ages at baseline and intra-individually over an average 2.3 years follow-up (range = 10 months–5.6 years). In age-adjusted linear regression models, baseline levels of total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 varied by participant characteristics (sex, BMI, gait speed), medical comorbidities (Charlson comorbidity index score, hypertension, diabetes, and cardiovascular disease), and hormone replacement therapy use in women. High interclass correlation coefficients (ICCs) suggest little intra-individual variability in levels of total IGF-1 (ICC = 0.84), IGFBP-3 (ICC = 0.88), and IGF-1/IGFBP-3 (ICC = 0.81) over time. In mixed effects models that specified age as a time scale, men showed greater decreases in total IGF-1 and IGFBP-3 with age, while more comorbidities and decreasing gait speed were associated with increasing IGFBP-3. In sex-stratified models, trajectories of total IGF-1, IGFBP-3, and IGF-1/IGFBP-3, as a function of participant demographics, health characteristics, and medical conditions, differed between men and women. These results suggest that change in levels of plasma total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 are associated with demographics, health characteristics, and medical conditions, and that the trajectories of change differ by sex. Future research should consider how IGF-1 and IGFBP-3 might be useful in research or clinic, paying particular attention to how sex may impact levels as a function of demographics, health characteristics, and medical conditions.

1. Introduction

Insulin-like growth factor 1 (IGF-1) regulates growth hormone, and is critical during growth and development in childhood (Ghigo et al., 2000). In older adults, IGF-1 levels are associated with multiple medical conditions, including cardiovascular disease, diabetes, osteoporosis, cancer, and neurodegenerative diseases (Yang et al., 2005). Cross-sectionally, IGF-1 levels vary substantially among individuals of the same age (van Dam and Aleman, 2004), but in general decline with age (Ashpole et al., 2015). In the periphery, approximately 99% of circulating IGF-1 is bound to IGF binding proteins (IGFBPs), with > 80% bound to IGFBP-3. The remaining 1% of circulating IGF-1 remains free, in a biologically available form (Favelyukis et al., 2001; Rajaram et al., 1997). IGF-1 bound to IGFBP-3 creates a stable complex that cannot cross the endothelium (Wacharasindhu et al., 2002). The ratio of IGF-1 to IGFBP-3 is a proxy for bioavailable IGF-1 (Rajaram et al., 1997). The majority of circulating IGF-1 is produced by the liver, but it is also generated by peripheral cells and in the brain (Favelyukis et al., 2001). Unbound IGF-1 can cross the blood brain barrier (Anlar et al., 1999; Coculescu, 1999). Within the brain, IGF-1 is associated with

Abbreviations: AD, Alzheimer's disease; BDI, Beck Depression Inventory; BMI, body mass index; CCI, Charlson comorbidity index; CV's, coefficients of variation; HRT, hormone replacement therapy; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor 3; ICC, interclass correlation coefficients; MCSA, Mayo Clinic Study of Aging; MCI, mild cognitive impairment

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neuron proliferation and differentiation, and myelination.

Recently, in the Cardiovascular Health Study (CHS), it was shown that among participants aged 60–100, total plasma IGF-1 levels, measured a maximum of five times over a span of 18 years, remained stable at younger ages and started to decline slightly in the eighth decade (Newman et al., 2016). This was in contrast to related plasma biomarkers (adiponectin, interleukin-6 (IL-6), and cystatin-C), which showed much greater longitudinal intra-individual variability with age. These findings indicate that total IGF-1 levels may not be good time-varying, or state, biomarkers of health status and comorbidities among older adults, particularly when compared to inflammatory markers such as IL-6. However, there is little research on the long-term stability of IGFBP-3 or the IGF-1/IGFBP-3 ratio. In this analysis, we expanded upon the results of the CHS study and examined the intra-individual variations in total IGF-1, IGFBP-3, and the ratio of the two among 1618 adults aged 50–95 at baseline with a maximum of five serial measures. We determined whether these markers changed with age or were affected by demographic variables, health characteristics, and medical conditions over time.

2. Methods

2.1. Participants

The Mayo Clinic Study of Aging (MCSA) is a prospective population-based study aimed at characterizing the incidence and prevalence of mild cognitive impairment (MCI) in Olmsted County, Minnesota (Roberts et al., 2008). In 2004, Olmsted County residents between the ages of 70 and 89 were identified for recruitment using an age- and sex-stratified random sampling design to ensure that men and women were equally represented in each 10-year age strata. In 2008, the study was extended to include those aged 50 and older. This study included 1618 participants, 1387 of whom had at least two IGF measures. Additionally, there were 37 participants who had five serial IGF measures, and a sub-analysis was performed in these individuals. The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

2.2. Participant assessment

MCSA visits included a physician examination, an interview by a study coordinator, and neuropsychological testing (Roberts et al., 2008). All MCSA participant visits are conducted approximately every 15 months. Cognitive test performance on nine tests in four domains (memory, executive function, language, and visual-spatial) and a global average of the four was compared with the age-adjusted scores of clinically normal individuals previously obtained using Mayo's Older American Normative Studies (Ivnik et al., 1992). For the purposes of these analyses, cognitive impairment was defined as a score of < -1.0 SD below age-specific norms. Additional details on participant cognitive assessment were published by Roberts et al. (2008).

Demographic variables (e.g., education) were collected by self-report during the in-clinic exam. Participants' height (cm) and weight (kg) were also measured during the in-clinic exam. These measures were used to calculate body mass index (BMI) (kg/m^2). Self-reported medication use, including hormone (estrogen, progesterone) replacement therapy (HRT), was collected in-clinic and corroborated using information abstracted from the medical records of the record-linkage system. Medical conditions and Charlson comorbidity index (CCI) score (Charlson et al., 1987) were abstracted from the Rochester Epidemiology Project medical records linkage system. Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (Beck et al., 1988); participants with a score of ≥ 13 were considered to have depression. Participants' blood sample collected in-clinic was used to determine APOE genotype.

2.3. Laboratory analyses of IGF-1 and IGFBP-3

Participants' blood was collected in the fasting state at the in-clinic exam, centrifuged, aliquoted, and stored at $-80\,^{\circ}$C. Serum total IGF-1 and IGFBP-3 levels were measured at the Mayo Clinic Immunochemical Core Laboratory. Total IGF-1 was a solid-phase, chemiluminescent immunometric assay on the Siemens Immulite 2000 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL 60015). Intra-assay coefficients of variation (CV's) were 3.5% and 4.2% at 70 and 236 ng/mL, respectively. Inter-assay CV's were 4.9%, 3.5% and 5.0%, at 37, 68 and 225 ng/mL respectively. IGFBP-3 was a solid-phase, chemiluminescent immunometric assay on the Siemens Immulite 2000 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL 60015). Intra-assay CV's were 4.2% and 2.5% at 1.0 and 4.4 μg/mL respectively. Inter-assay CV's were 4.0% and 3.9% at 1.0 and 4.3 μg/mL, respectively. We calculated the ratio of total IGF-1 to IGFBP-3 for each participant as a proxy of free (bioavailable) IGF-1.

2.4. Statistical analyses

Spearman correlations were calculated between total IGF-1 and IGFBP-3 levels at baseline. Wilcoxon ranksum and Fisher's exact tests were used to compare participant baseline variables by sex. We utilized *t*-tests and Wilcoxon ranksum tests to compare total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 ratio levels by participant demographics, health characteristics, and medical conditions. We used ANOVA to compare total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 levels by age group (50–59, 60–69, 70–79, ≥ 80). Interclass correlation coefficients (ICC) were used to assess intra-individual variability of the markers over time in all participants with longitudinal data (N = 1387), separately in those aged 50–69 and 70 and older, by the median CCI score (< 6 vs ≥ 6), and among the 37 participants with five measures. Baseline means and standard deviations plots by decade were created using the mean and standard deviation plot function.

Total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 values were skewed so we natural log-transformed them. We then fit age-adjusted linear regression models to investigate the cross-sectional association between participant demographics, health characteristics, and medical conditions (independent variables) and total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 (dependent variables). Additionally, we fit mixed effects models specifying age as a time scale to investigate the longitudinal association between demographics, health characteristics, and medical conditions and total IGF-1, IGFBP-3, and IGF-1/IGFBP-3. The models included time-varying participant demographics, health characteristics, or medical condition status (indicating average association between participant demographics, health characteristics, and medical conditions and total IGF-1, IGFBP-3, or IGF-1/IGFBP-3 over follow-up), age (indicating change in total IGF-1, IGFBP-3, or IGF-1/IGFBP-3 with age), and the interaction between the demographic/medical variable and age (indicating change in the association between participant demographics, health characteristics, and medical conditions and total IGF-1, IGFBP-3, or IGF-1/IGFBP-3 with age). We specified a random intercept, but not a random slope, and used an unstructured covariance matrix. All statistical analyses and graphing were completed using Stata version 13.0 (StataCorp LLC, College Station, TX).

3. Results

At baseline men, as compared to women, were older, had more years of education, were more likely to have medical comorbidities, had faster gait speed, higher total IGF-1 and IGF-1/IGFBP-3 levels, and lower IGFBP-3 levels (Table 1). IGF-1 and IGFBP-3 were highly correlated ($r = 0.62$, $p < 0.001$). Cross-sectionally, total IGF-1 levels were lower in participants with vs without hypertension and diabetes, slower versus faster gait speed, and among women who used vs did not use HRT (Table 2). IGFBP-3 levels were significantly lower in those with