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Tracking and Cumulative Lifetime Exposure to Circulating IGF-I in 6,459 Healthy Individuals and in SGA Children Treated with GH

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Background: /objective: Insulin-like-growth-factor-I (IGF-I) levels in the lower or upper normal range have been proposed as a biomarker of risk for later disease in healthy adults, specifically cardiovascular disease and cancer. In addition, concern has been raised about the frequently observed supraphysiological IGF-I levels in non-growth-hormone-deficient children treated with growth hormone (GH). However, whether a single IGF-I measurement is a valid indicator of cumulative lifetime exposure to IGF-I and thus disease risk is not established. We aimed to evaluate intra-individual longitudinal tracking of IGF-I and IGF-binding-protein-3 (IGFBP-3) levels and to estimate cumulative lifetime exposure to IGF-I in healthy and GH-treated individuals. We hypothesized that individuals follow a certain IGF-I trajectory throughout life and that GH therapy in childhood does not increase lifetime IGF-I exposure substantially. **Methods:** We performed a combined cross-sectional (n=5,326) and longitudinal (n=1,133) study of 6,459 healthy participants (49% male) aged 0–76 years recruited as part of six Danish

population-based studies, resulting in a total of 9,963 serum samples. In addition, we included 238 samples from nine short children born small-for-gestational-age (SGA) before, during and after GH treatment.

Serum samples were analyzed for IGF-I and IGFBP-3 with the IDS-iSYS immunoassay and anthropometric measures were obtained. Intra-individual tracking was determined by intraclass correlation coefficients (ICC) derived from a linear mixed model with IGF-I (SDS) or IGFBP-3 (SDS) as dependent variable and subject as random effect, unadjusted and adjusted for BMI-changes. Cumulative lifetime exposure to IGF-I was estimated by calculating area under the curve of the predicted SD trajectory from 0-76 years.

Results: Sex- and age-specific reference curves for IGF-I and IGFBP-3 were established. For IGF-I, ICCs were 0.50 (95% CI: 0.47–0.53) and 0.53 (0.50–0.56) for male and female participants, respectively. ICCs for IGFBP-3 were 0.52 (0.49–0.55) for male participants and 0.59 (0.56–0.62) for female. Cumulative lifetime IGF-I exposure was significantly higher in female (mean ± SD, 12,723 ± 3,691) than in male participants (12,563 ± 3,393); p=0.02. The SGA patients had a mean (range) GH-treatment duration of 9.2 years (5.2–11.9). Treatment caused an increase in estimated cumulative lifetime IGF-I exposure of 1,759 ± 556 shifting them from a mean estimated lifetime exposure without treatment of 9,512 ± 1,889 to 11,271 ± 1,689 with treatment. This corresponded to a rise in IGF-I trajectory (SDS) of 0.55 SD ± 0.18, from -0.89 SD ± 0.57 to -0.35 SD ± 0.49.

Conclusion: Our results suggest that IGF-I and IGFBP-3 levels are tracking throughout life and that a single measurement reliably reflects lifetime exposure. We, for the first time, estimated lifetime exposure to IGF-I in healthy individuals and show that pediatric GH therapy only slightly increases lifetime exposure and not beyond levels commonly found in the reference population.

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