Normal IGF-bioactivity and low free IGF-I in patients with Prader-Willi syndrome with high total serum IGF-I: *immunoreactive IGF-I concentration poorly reflects IGF bio-activity and bio-availability*

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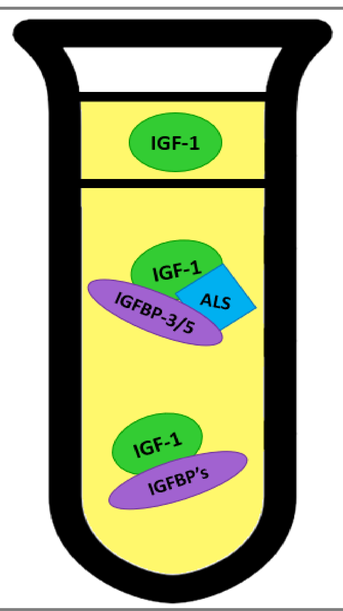
INTRODUCTION

Recombinant Growth Hormone (GH) has changed the lives of many patients with Prader-Willi Syndrome (PWS). GH treatment has beneficial effects on body composition, physical performance, cognition, psychomotor development, respiratory function and quality of life of patients with PWS (1,2). Due to the narrow therapeutic range, GH treatment is subject to strict limits. Clinicians measure serum immunoreactive Insulin-like Growth Factor 1 ('total IGF-I') levels to titrate the dose of GH. However, in patients with PWS, IGF-I levels are often much higher than expected based on GH dose. As a result, clinicians have to reduce the GH dose, with consequent loss of beneficial effects. Based on our previous data (3) and the observation that patients with PWS seem to benefit from relatively high GH doses, we hypothesize that IGF might be less active, or less available, in PWS. Low IGF bioactivity or bio-availability would imply that high total IGF-I levels might not have negative side effects in patients with PWS. In that case, GH dose reduction might not be needed.

CONCLUSION: Our results indicate that total IGF-I is a poor marker of IGF-bioactivity in PWS patients, as IGF-bioactivity in PWS patients with high total IGF-I concentrations was comparable to IGF-bioactivity in controls. It suggests that clinicians might not need to lower GH dose in patients with a high total IGF-I. Further studies are needed to confirm our data and find more reliable parameters for GH dose titration in PWS.



1-5% Free IGF-I

95-99%
IGF-I in ternary and binary complexes

Fig. 1 Distribution of bound and free IGF-I in serum

1. Impaired cognition
2. Typical facial features
3. Hyperphagia
4. Scoliosis
5. Short stature
6. Obesity
7. Hypogonadism
8. Hypotonia
9. Small hands and feet

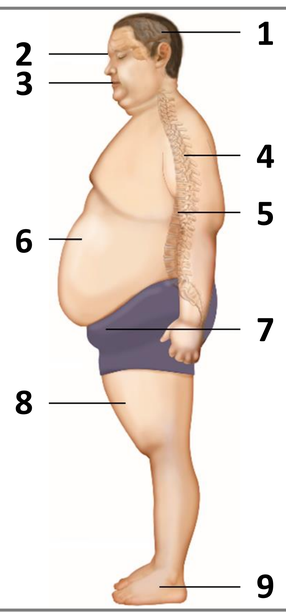


Fig. 2 Features of Prader-Willi syndrome

GH treatment dose

- Increased risk of malignancies
- Acromegalic features
- Narrow therapeutic dosage range
- Increased body fat
- Loss of muscle mass and strength
- Fatigue/poor exercise tolerance
- Neurocognitive deterioration
- Impaired QoL
- Poor growth

Fig. 3 Effects of too much or too little GH

METHODS

We measured total IGF-I, bioactive IGF and free 'bio-available' IGF in 22 PWS patients and 112 healthy controls. IGF-I bioavailability ('free' IGF-I) was measured by commercially available ELISA (Ansh Labs, Webster, TX). IGF-bioactivity was measured by an in-house IGF-I receptor kinase activation assay (KIRA), a cell-based system in which IGF bioactivity is reflected by phosphorylation of the IGF receptor. Both IGF-I bioavailability and IGF-bioactivity were compared with total (immunoreactive) IGF-I values.

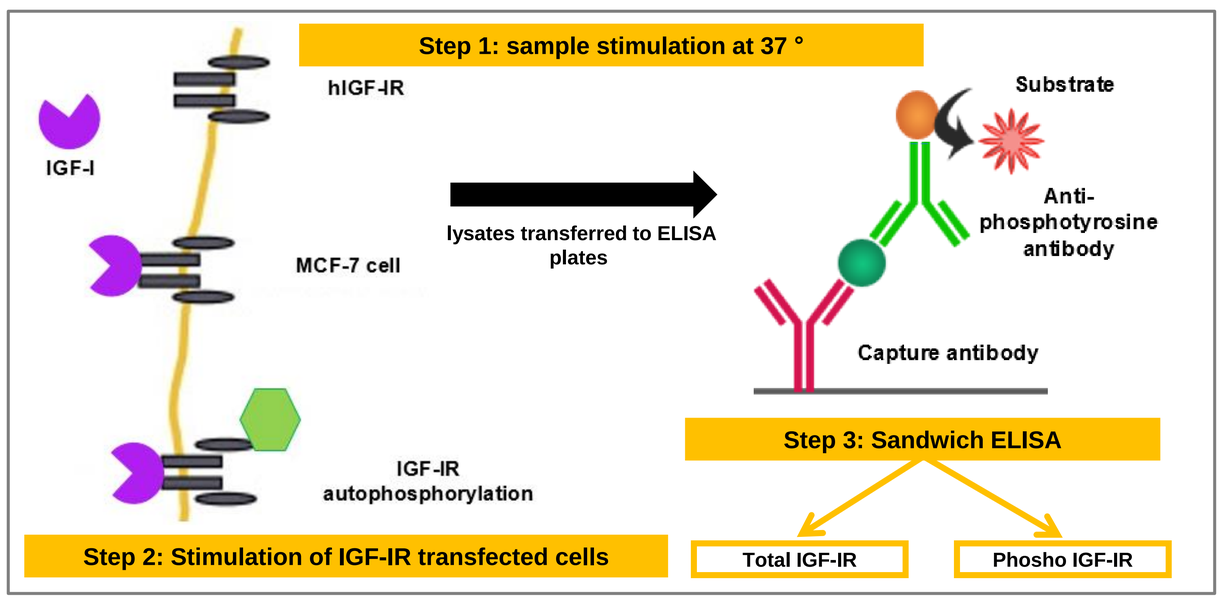


Fig. 4 Principle of the bioactive IGF measurement using KIRA

Bioactive IGF	Free IGF-I	Total (immunoreactive) IGF-I
- KIRA Cell based system & ELISA - 650 µl of serum - Labour intensive - Results available after 4 days cell culture + 2 days ELISA	- New ELISA - 100 µl of serum - Results available after 1 day	- Chemiluminescent immunometric assay IDS-iSYS - 300 µl of serum - Fully automated system - Results available after 1 day

Fig. 5 Three methods used to measure IGF

RESULTS

Correlation between IGF-bioactivity and total IGF-I was very low (**Fig. 6**). Most importantly, PWS patients with high immunoreactive IGF-I during GH treatment showed normal IGF-bioactivity.

Preliminary analysis of free IGF-I values showed that free IGF-I correlated poorly to total IGF-I levels. Moreover, free IGF-I levels in PWS samples were strikingly lower than in controls (data not shown).

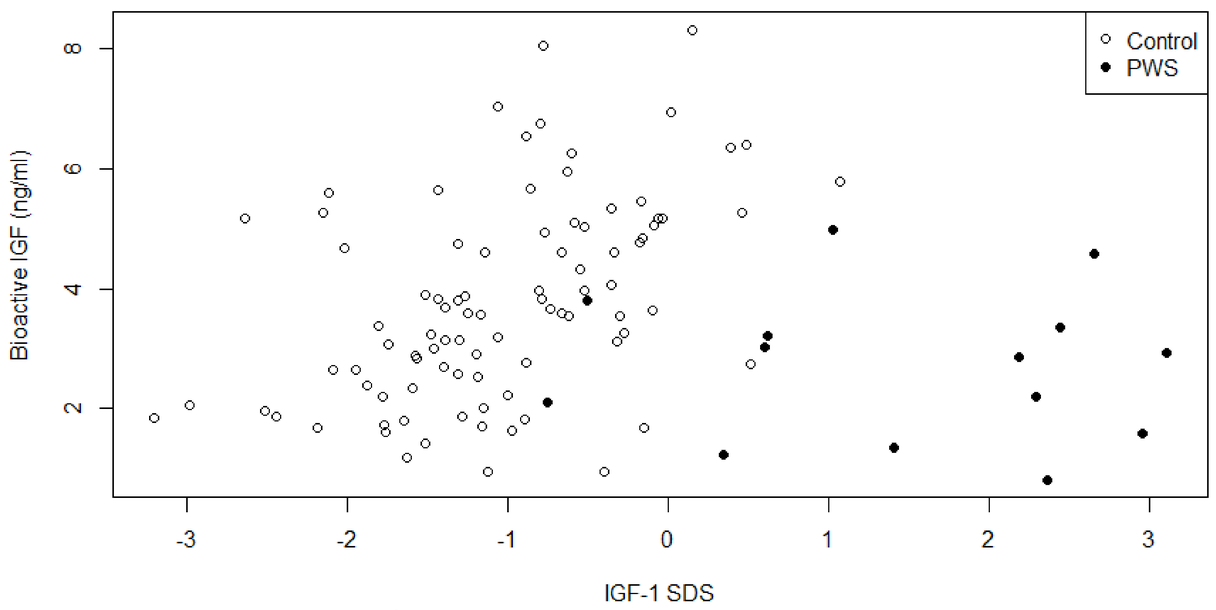


Fig. 6 Bioactive IGF according to IGF-1 SDS

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