

Association of serum IGF-1 concentration with cardiovascular function in adults with GH deficiency with different GH treatment regimes: a randomized clinical trial

Christa C. van Bunderen¹, Rick I. Meijer², Paul Lips¹, Mark H. Kramer³, Erik H. Serné², Madeleine L. Drent¹

¹ Department of Internal Medicine, section Endocrinology, Neuroscience Campus Amsterdam, VU University Medical Center
² Department of Internal Medicine, Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center
³ Department of Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands

Introduction

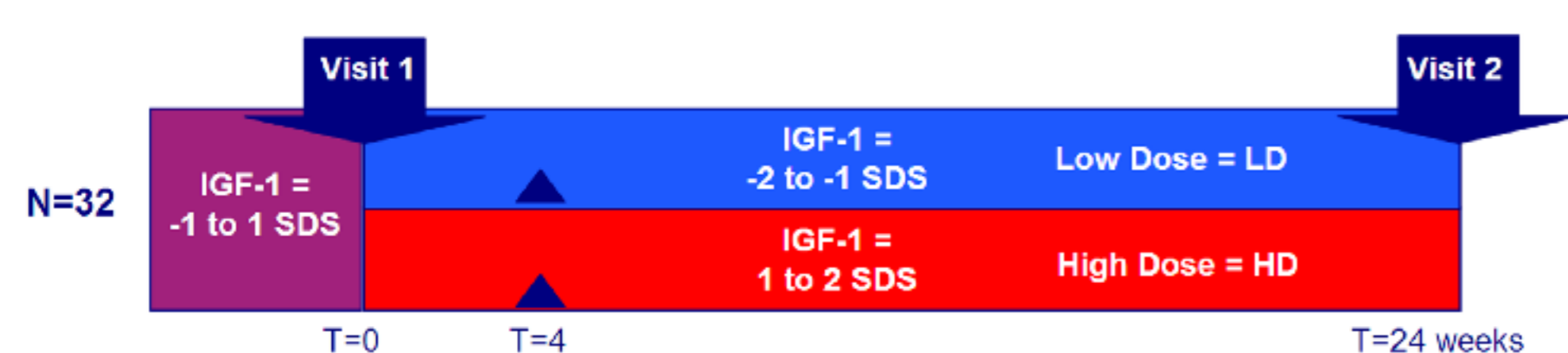
Epidemiological evidence for a link between IGF-1 concentration and cardiovascular (CV) disease in the general population and in patients with growth hormone (GH) deficiency or hypersecretion has been demonstrated. However, the underlying mechanisms remain unresolved.

Aim

To explore the effect of change in IGF-1 levels within the reference range on different measures of CV function in substituted GH deficient adults.

Methods

Randomisation (↓↑GH dose):



Inclusion criteria:

Age 20–65 year, GH treatment >1 year, “stable” disease

Results

Table 1. Baseline characteristics

	LD	HD	P value
No. of patients	16	16	
Age, year (SD)	47.4 (10.8)	46.4 (9.3)	0.80
Sex, no. of females (%)	6 (37.5)	5 (31.2)	0.71
Onset of GHD, CO (%)	10 (62.5)	3 (18.8)	0.01
Cranial radiotherapy (%)	1 (6.2)	2 (12.5)	1.00
Pituitary surgery (%)	2 (12.5)	8 (50.0)	0.02
GH dose, mg/day (SD)	0.30 (0.23)	0.28 (0.18)	0.78
Duration GH treatment, yr (SD)	15.0 (9.3)	10.7 (6.7)	0.15

Figure 1. Treatment regimes

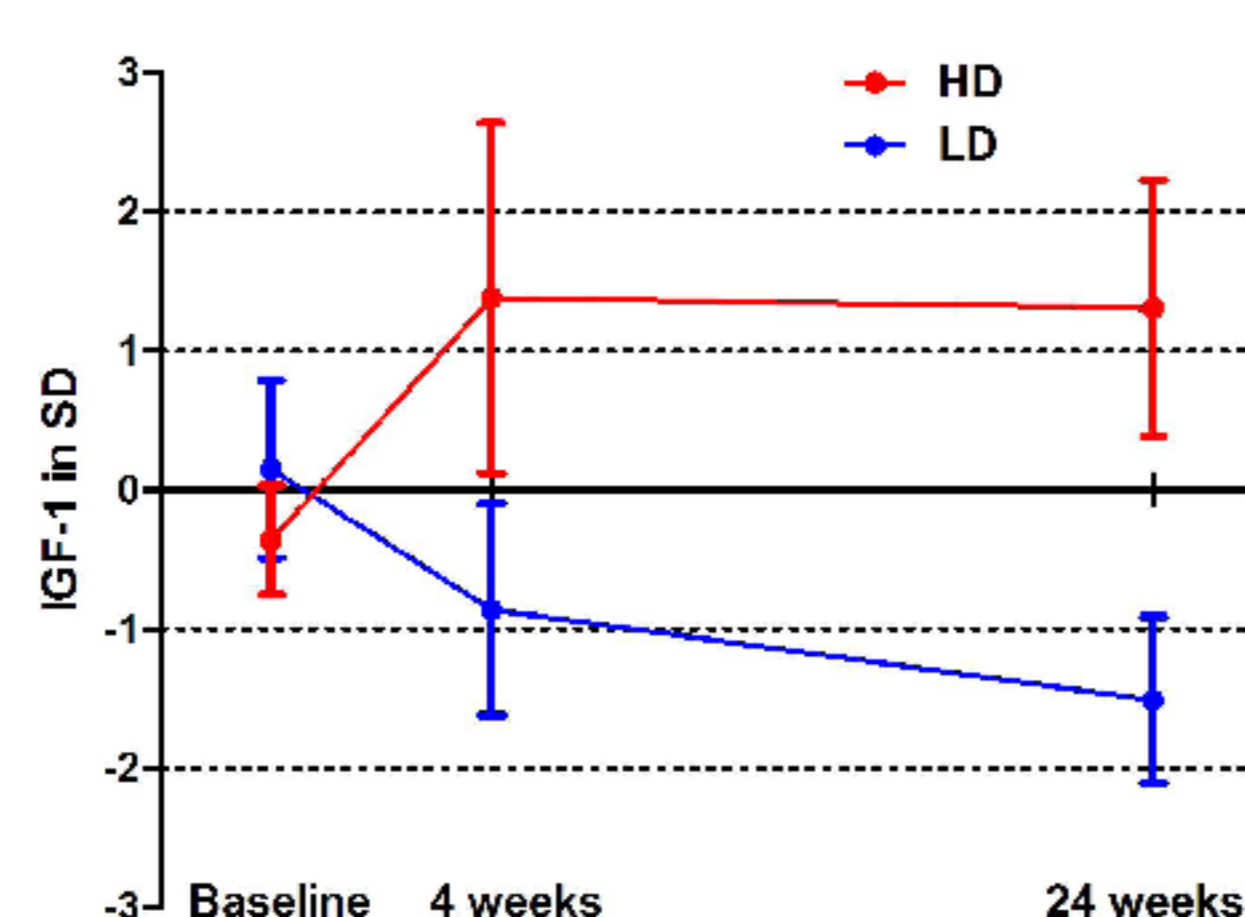


Table 2. Macrovascular measurements

	LD (n=15) Baseline (SD)	Change (SD)	HD (n=15) Baseline (SD)	Change (SD)	P value
Systolic blood pressure, mmHg	129 (18)	-2 (10)	126 (14)	-2 (9)	0.92
Diastolic blood pressure, mmHg	80 (8)	-2 (6)	77 (9)	-3 (7)*	0.37
Heart rate, beats/min	68 (8)	-4 (7)**	59 (8)	2 (9)	0.42
Pulse wave velocity, m/s	7.2 (1.0)	0 (0.5)	7.1 (1.2)	0 (1.0)	0.87
Augmentation index	24 (18)	1.0 (6.4)	20 (15)	-2.7 (8.6)	0.06
Cardiac index, l/min/m ²	3.0 (0.5)	0.01 (0.4)	2.7 (0.5)	0.1 (0.3)	0.52
Stroke volume index, ml/m ²	45.7 (5.6)	1.6 (6.1)	46.8 (6.2)	-0.3 (3.1)	0.29
Syst. vasc. resist. index, dyn.s.m ² /cm ⁵	2916 (552)	-42 (460)	3120 (618)	-236 (653)	0.56
Pulse pressure, mmHg	56 (11)	-1 (13)	57 (11)	-1 (9)	0.84
dP/dtmax, mmHg/s	922 (174)	-72 (259)	987 (316)	-95 (283)	0.89

P value for difference between change in the LD and HD group
 * P value <0.10 for change from baseline
 ** P value <0.05 for change from baseline

Table 3. Lipid profile, inflammation, and insulin resistance

	LD (n=15) Baseline (SD)	Change (SD)	HD (n=15) Baseline (SD)	Change (SD)	P value
Free fatty acids, mmol/L	0.42 (0.18)	0 (0.15)	0.45 (0.22)	0.06 (0.16)	0.26
Apolipoprotein A, g/L	1.37 (0.29)	0.06 (0.08)**	1.39 (0.25)	0.06 (0.16)	0.95
Apolipoprotein B1, g/L	0.98 (0.23)	0 (0.16)	1.06 (0.28)	-0.04 (0.20)	0.96
hsCRP, mg/L (IQR)	0.86 (4.97)	1.49 (3.84)**	1.29 (2.42)	-0.26 (1.27)	0.04
TNF-alpha, pg/mL	1.86 (0.57)	0.12 (0.27)	1.55 (0.30)	0.07 (0.15)	0.88
Adiponectin, mg/L	8.0 (4.9)	0.7 (2.5)	8.9 (5.0)	-0.9 (2.7)	0.16
Insulin resistance, HOMA-IR (IQR)	0.80 (1.24)	-0.12 (0.35)	0.79 (0.57)	0.38 (0.52)**	0.01

P value for difference between change in the LD and HD group
 ** P value <0.05 for change from baseline

Figure 2. Skin blood flow responses to assess endothelial (in)dependent vasodilatation (in perfusion units) by laser Doppler after iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP)

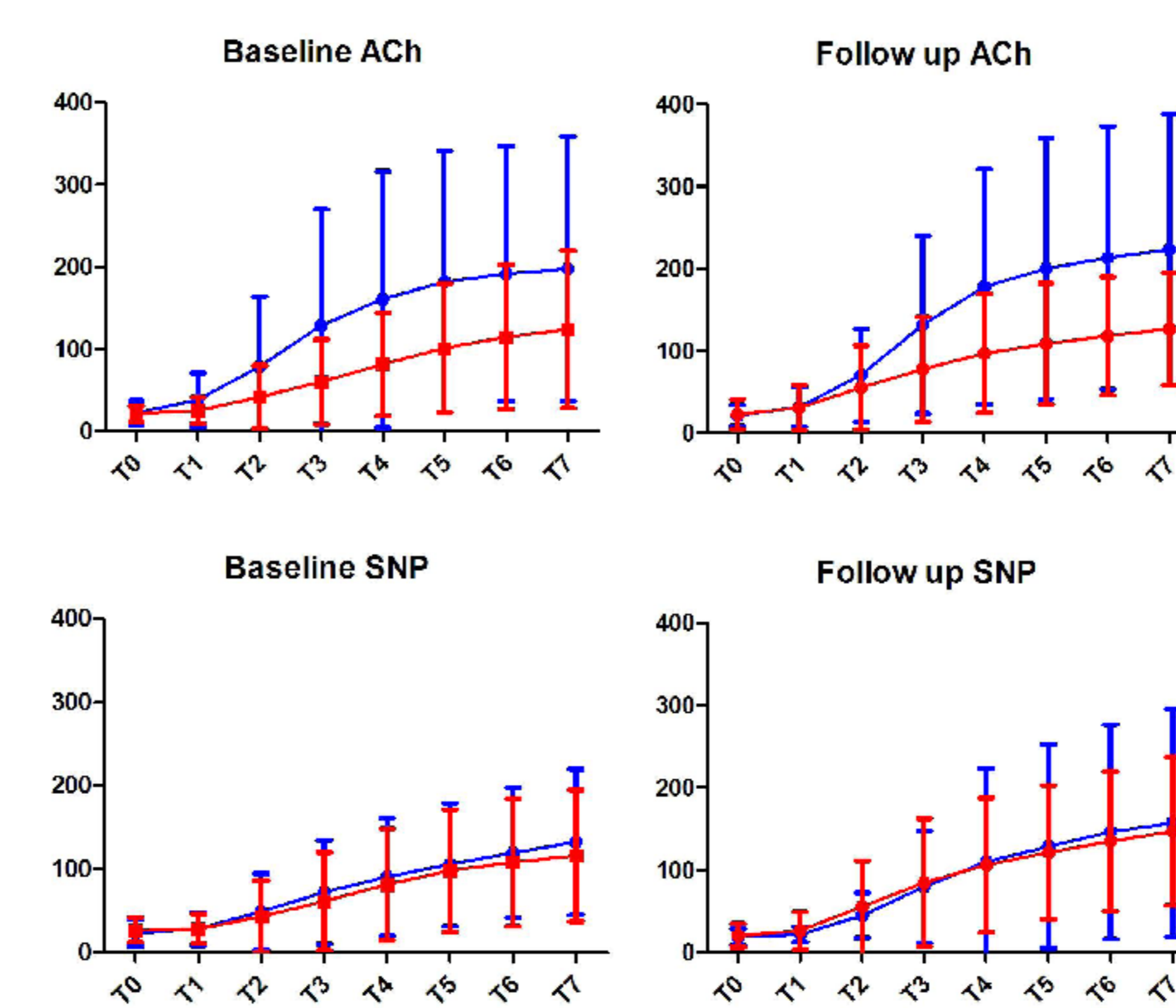
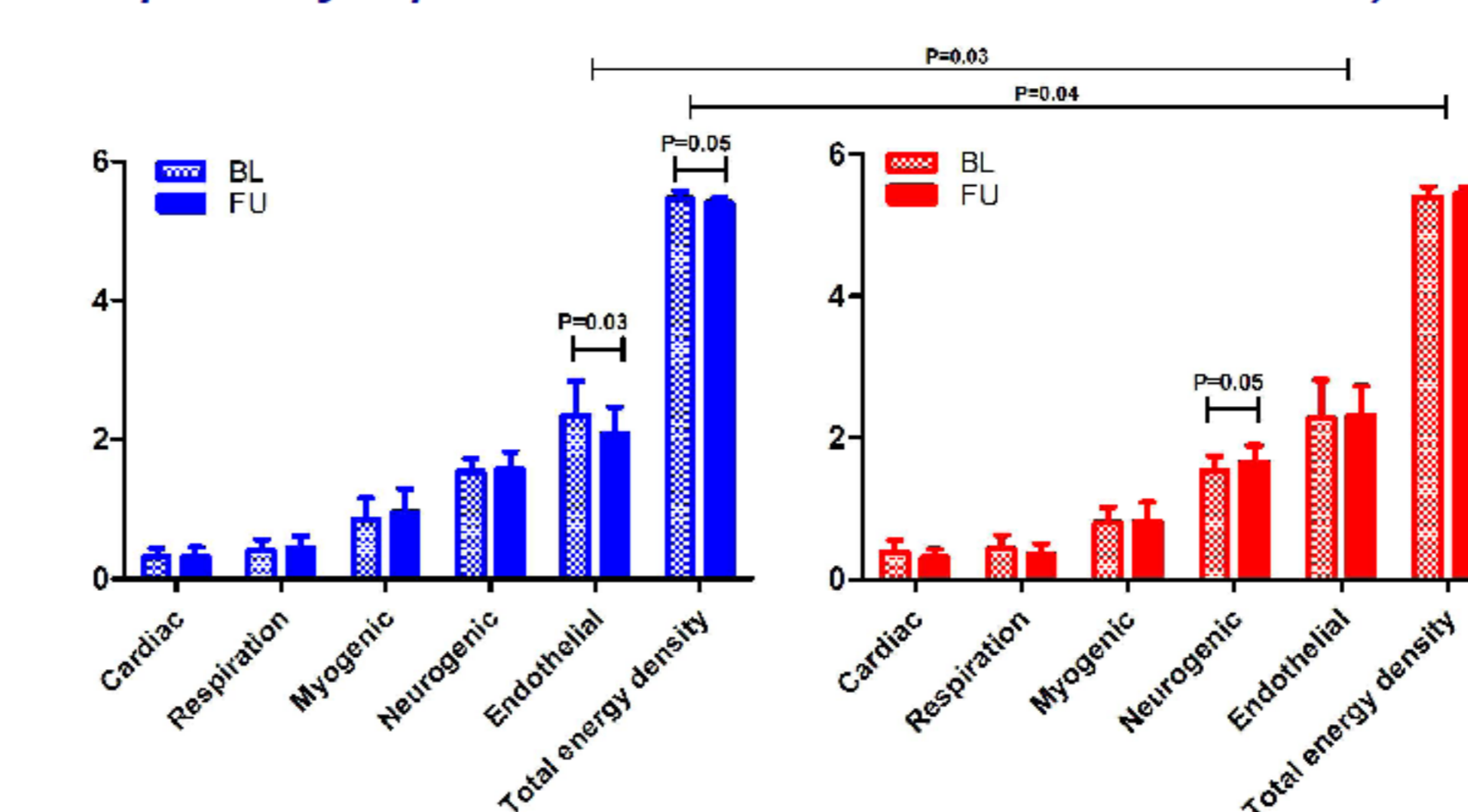


Figure 3. Vasomotion (in energy density) by laser Doppler of skin microvascular blood flow (wavelet analysis was used to assess the frequency spectrum between 0.01-1.6 Hz)



Summary

- Decreasing IGF-1 level for six months leads to a significant deterioration of local endothelial activity in vasomotion of the skin blood flow, and an increase in hsCRP.
- Increasing IGF-1 level leads to a significant increase in HOMA-IR.
- An increase in IGF-1 level may improve augmentation index during pulse wave analysis.

Conclusion

In this exploratory analysis on the possible underlying mechanisms of the link between IGF-1 and CV disease, IGF-1 level within the reference range in GH treated adults seems associated with microvascular endothelial activity, inflammation, and metabolic insulin resistance.

Contact:
 c.vanbunderen@vumc.nl