

Supplementary table 1. Anthropometric measures and cardiovascular risk factors after 4 years of GHRT in male patients and controls

Age cohort (y)	28-37		38-47		48-57		58-67		≥ 68	
	patients	controls	patients	controls	patients	controls	patients	controls	patients	controls
<i>Number</i>	59	185	92	300	185	249	113	184	39	90
<i>Body composition</i>										
BMI (kg/m ²)	29.2 ± 5.8***	25.6 ± 3.9	29.7 ± 5.4***	26.1 ± 3.4	29.0 ± 4.0***	27.0 ± 3.4	28.9 ± 4.5***	27.2 ± 3.6	28.1 ± 3.1	27.0 ± 2.9
Waist (cm)	97.5 ± 11.7**	91.6 ± 11.3	101.3 ± 13.6***	94.4 ± 9.6	100.4 ± 10.1**	97.7 ± 10.1	100.8 ± 12.3	100.1 ± 9.8	101.7 ± 10.6	101.5 ± 8.7
<i>Blood pressure and hypertension</i>										
Systolic BP (mmHg)	124 ± 12	122 ± 11	129 ± 16*	125 ± 13	134 ± 17**	129 ± 16	141 ± 20**	135 ± 19	143 ± 17	142 ± 21
Diastolic BP (mmHg)	78 ± 9***	70 ± 6	80 ± 11***	75 ± 8	83 ± 11***	78 ± 8	83 ± 10***	77 ± 8	80 ± 9*	77 ± 9
Hypertension - JCN 7 criteria (%)	17	9.7	29**	17	45.4*	33.7	62.8	52.7	61.5*	75.6
Treatment of Hypertension (%)	6.8	4.3	8.7	7.7	22.2	18.5	36.3	32.8	28.2*	52.2
<i>Glucose and diabetes</i>										
Fasting plasma glucose (mmol/L)	5.00 ± 0.98	4.76 ± 0.65	5.37 ± 1.8	4.90 ± 0.9	5.12 ± 1.06	5.29 ± 1.50	5.50 ± 1.24	5.33 ± 1.31	4.78 ± 1.01	5.38 ± 1.83
Diabetes Mellitus - IDF criteria (%)	6.8**	0.55	4.4	2.7	6.5	8.3	10.6	8.8	5.1	13.8
Treatment of Diabetes Mellitus (%)	3.4*	0	3.3	1	4.9	2.8	6.2	2.7	2.6	6.7
<i>Lipids and treatment of dyslipidemia</i>										
Total cholesterol (mmol/L)	5.32 ± 1.18	5.30 ± 1.15	5.34 ± 1.10*	5.67 ± 1.07	5.37 ± 1.07	5.52 ± 0.99	5.10 ± 1.11*	5.47 ± 1.08	4.94 ± 0.90	5.11 ± 0.92
HDL-cholesterol (mmol/L)	1.12 ± 0.25		1.16 ± 0.25		1.16 ± 0.31		1.25 ± 0.36		1.07 ± 0.27	
Triglycerides (mmol/L)	2.26 ± 1.14***		2.23 ± 1.18		2.09 ± 1.08		1.94 ± 1.06		1.71 ± 0.52*	
LDL-cholesterol (mmol/L)	3.26 ± 1.09		3.20 ± 1.09		3.31 ± 0.96		3.04 ± 0.99		3.11 ± 0.82	
Treatment of Dyslipidemia (%)	13.6***	2.2	13.0***	3.7	18.9**	10.0	26.6	18.6	15.3	25.6

Data are given as mean ± SD. *P< 0.05, **P<0.01, ***P<0.001 (patients vs. controls of similar age cohorts). BP: Blood Pressure

Supplementary table 2. Anthropometric measures and cardiovascular risk factors after 4 years of GHRT in female patients and controls

Age cohort (y)	28-37		38-47		48-57		58-67		≥ 68	
	patients	controls	patients	controls	patients	controls	patients	controls	patients	controls
Number	87	244	134	401	142	327	92	209	21	112
<i>Body composition</i>										
BMI (kg/m ²)	29.1 ± 6.7***	24.9 ± 4.6	29.3 ± 5.4***	25.7 ± 4.5	29.3 ± 6.3***	27.0 ± 4.4	29.6 ± 5.7*	28.0 ± 4.2	28.0 ± 5.0	28.3 ± 4.6
Waist (cm)	91.5 ± 14.9***	81.5 ± 10.7	92.9 ± 13.4***	84.8 ± 12.5	93.9 ± 13.7***	88.2 ± 11.0	93.8 ± 13.4	91.4 ± 11.2	92.4 ± 10.4	93.4 ± 12.2
<i>Blood pressure and hypertension</i>										
Systolic BP (mmHg)	123 ± 17***	112 ± 11	125 ± 18***	114 ± 13	132 ± 19***	121 ± 16	136 ± 17*	132 ± 21	148 ± 24	140 ± 20
Diastolic BP (mmHg)	79 ± 11***	66 ± 7	79 ± 12***	69 ± 8	80 ± 11***	71 ± 7	79 ± 10***	72 ± 9	79 ± 10***	71 ± 8
Hypertension - JCN 7 criteria (%)	19.5***	4.5	21.6**	11.2	41.6**	27.5	58.7	47.8	85.7*	62.5
Treatment of Hypertension (%)	11.5**	2.9	12.7	7.7	22.5	18.0	38	34.0	61.9	36.6
<i>Glucose and diabetes</i>										
Fasting plasma glucose (mmol/L)	5.41 ± 1.95***	4.52 ± 0.51	5.30 ± 1.43**	4.73 ± 0.76	5.55 ± 1.87**	4.88 ± 0.80	5.45 ± 1.39	5.26 ± 1.49	5.04 ± 0.70	5.27 ± 1.41
Diabetes Mellitus-IDF criteria (%)	8***	0	4.5	2.3	10.6**	3.4	16.3	10.2	4.8	11
Treatment of Diabetes Mellitus (%)	5.8**	0	2.2	1.2	7.8**	1.5	12.0*	4.8	4.8	7.1
<i>Lipids and treatment of dyslipidemia</i>										
Total cholesterol (mmol/L)	5.39 ± 1.17***	4.85 ± 0.92	5.67 ± 0.9***	5.16 ± 0.99	5.52 ± 1.15**	5.89 ± 0.99	5.54 ± 1.16*	5.91 ± 0.95	5.08 ± 1.36*	5.87 ± 0.88
HDL-cholesterol (mmol/L)	1.46 ± 0.44		1.33 ± 0.34		1.43 ± 0.44		1.44 ± 0.36		1.24 ± 0.45	
Triglycerides (mmol/L)	1.80 ± 1.02		1.93 ± 0.93		1.72 ± 0.86		1.85 ± 0.91		2.12 ± 1.12	
LDL-cholesterol (mmol/L)	3.12 ± 1		3.46 ± 0.87		3.32 ± 1.01		3.31 ± 0.97		2.97 ± 1.32	
Treatment of Dyslipidemia (%)	12.6***	1.2	14.9***	3.0	14.0**	5.8	30.4**	14.8	19.0	17.9

Data are given as mean ± SD. *P< 0.05, **P<0.01, ***P<0.001 (patients vs. controls of similar age cohorts). BP: Blood Pressure

Supplementary table 3. Changes in anthropometric measures and cardiovascular risk factors after 4 years in patients and controls

Age cohort (y)	28-37		38-47		48-57		58-67		>68	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Males	59	185	92	300	185	249	113	184	39	90
Δ BMI (kg/m ²)	1.02 ± 2.27	0.93 ± 1.4	0.9 ± 2.05	0.82 ± 1.27	0.23 ± 1.72**	0.72 ± 1.34	0.11 ± 1.7*	0.55 ± 1.49	0.22 ± 1.14	0.22 ± 1.1
Δ Waist (cm)	-0.97 ± 6.82***	4.92 ± 6.19	0.24 ± 6.16***	3.73 ± 5.16	-0.67 ± 5.96***	3.94 ± 5.5	-1.96 ± 9.05***	3.42 ± 5.73	0.34 ± 4.39*	3.04 ± 5.59
Δ Systolic BP (mmHg)	1 ± 14*	-3 ± 8	3 ± 16**	-2 ± 9	2 ± 19*	-2 ± 11	1 ± 20	-2 ± 14	-1 ± 17	-1 ± 14
Δ Diastolic BP (mmHg)	1 ± 10	0 ± 5	-1 ± 11	1 ± 5	-0 ± 12	0 ± 6	-1 ± 11	-2 ± 7	-1 ± 10	-2 ± 7
Δ Fasting glucose (mmol/l)	0.44 ± 0.95	0.24 ± 0.69	0.63 ± 1.81	0.32 ± 0.85	0.25 ± 1.20	0.38 ± 1.15	0.31 ± 0.99	0.26 ± 1.27	-0.1 ± 0.76	0.23 ± 1.99
Δ Total cholesterol (mmol/l)	-0.29 ± 1.16*	0.14 ± 0.9	-0.36 ± 1.43	-0.12 ± 1.05	-0.7 ± 1**	-0.36 ± 0.91	-0.58 ± 0.95	-0.36 ± 1	0 ± 0.65	-0.48 ± 0.96
Females	87	244	134	401	142	327	92	209	21	112
Δ BMI (kg/m ²)	0.62 ± 3	0.75 ± 1.79	0.52 ± 2.54	0.92 ± 1.85	0.15 ± 2.32***	0.99 ± 1.72	-0.05 ± 1.97**	0.71 ± 1.56	-0.37 ± 2.77	0.57 ± 1.66
Δ Waist (cm)	0.16 ± 8.44***	3.9 ± 7.01	-0.78 ± 7.47***	4.89 ± 9	-0.19 ± 6.68***	5.09 ± 7.25	-1.94 ± 8.65***	4.61 ± 7.29	0.79 ± 7.57	3.71 ± 7.45
Δ Systolic BP (mmHg)	2 ± 17*	-2 ± 9	1 ± 17	0 ± 10	2 ± 19	0 ± 11	-2 ± 23	0 ± 14	4 ± 17*	-5 ± 17
Δ Diastolic BP (mmHg)	0 ± 12	0 ± 5	0 ± 12	1 ± 5	-2 ± 11*	0 ± 5	-2 ± 12	-1 ± 6	1 ± 11	-3 ± 7
Δ Fasting glucose (mmol/l)	0.61 ± 1.38	0.26 ± 0.6	0.40 ± 1.09	0.31 ± 0.82	0.36 ± 1.53	0.24 ± 0.74	0.37 ± 0.73	0.33 ± 1.22	0.29 ± 0.63	0.31 ± 1.51
Δ Total cholesterol (mmol/l)	-0.89 ± 1.78**	-0.14 ± 0.68	-0.4 ± 0.86***	0.01 ± 0.74	-0.58 ± 1.02***	-0.02 ± 0.93	-1.05 ± 1.36***	-0.31 ± 1	-0.81 ± 1.40	-0.39 ± 0.99

Data are given as mean ± SD. *P< 0.05, **P<0.01, ***P<0.001 (patients vs. controls of similar age cohorts).

BP: Blood Pressure. Δ: delta.

Supplementary table 4. Patient characteristics in GHRT patients, in unsubstituted GHD patients from KIMS and in unsubstituted GHD patients from the Dutch NR

	GHRT patients	Unsubstituted GHD (KIMS)	Unsubstituted GHD (Dutch NR)
Number	964	60	18
Age (y)	51 ± 11.0	57.4 ± 13.0	59.1 ± 14.5
Females (%)	49.4	43.3	55.6
Diagnosis of GHD			
Pituitary Adenoma (%)	69.4	72.9	66.7
Other causes of acquired Pituitary Disease (%)	15.5	18.6	27.8
Idiopathic GHD (%)	6.4	1.7	5.6
Isolated GHD (%)	8.2	5.6	22.2
Multiple hormonal deficiencies (%)	91.8	94.4	77.8
Duration of Pituitary Disease before GH start (y)	7.77 ± 8.0	10.3 ± 8.6	na
Duration of GHD before GH start (y)	2.03 ± 3.4	5.4 ± 5.6	na
Previous therapy			
Surgical treatment (%)	67.4	61.7	72.2
Radiotherapy (%)	32.8	30.0	27.8
Pituitary hormone deficiencies			
TSH deficiency (%)	69.4	76.5 (n=51)	72.2
ACTH deficiency (%)	65.7	68.6 (n=51)	61.1
LH/FSH deficiency (%)	81.4	75.9 (n=54)	61.1
ADH deficiency (%)	21.4	14.9 (n=47)	0
GH treatment			
IGF-I SDS baseline	-1.73 ± 1.69	-1.13 ± 1.17 (n=34)	na
IGF-I SDS at 4 years	0.68 ± 1.22	-1.19 ± 1.50 (n=21)	na
Normal IGF-1 (SDS -2 to 2) at 4 years (%)	86.0	57.1 (n=21)	na
Normal IGF-1 (SDS -1 to 1) at 4 years (%)	49.1	38.1 (n=21)	na
GH dose at 4 years	0.42 ± 0.25	0	na

Data are given as absolute numbers or percentages and mean ± standard deviation.
GHD: growth hormone deficiency. na: not available.

Supplementary table 5. Changes in anthropometric measures and cardiovascular risk factors in GHRT patients, in unsubstituted GHD patients from KIMS, in unsubstituted GHD patients from the Dutch NR and in healthy controls (4 years vs. baseline)

	GHRT patients	Unsubstituted GHD (KIMS)	Unsubstituted GHD (Dutch NR)	Healthy controls
<i>Number</i>	964	60	18	2301
<i>Body composition</i>				
BMI (kg/m ²)	0.35 ± 2.19	0.05 ± 2.52 (n=52)	0.87 ± 2.08 (n=7)	0.78 ± 1.59
Waist (cm)	-0.65 ± 7.27 (n=859)	1.67 ± 8.17 (n=46)	na	4.29 ± 6.95
<i>Blood pressure and hypertension</i>				
Systolic BP (mmHg)	1.4 ± 18 (n=937)	-5.5 ± 22.5 (n=50)	7.1 ± 22.4 (n=15)	-1.4 ± 11 (n=2300)
Diastolic BP (mmHg)	-0.7 ± 11 (n=937)	-2.9 ± 11.5 (n=50)	2.7 ± 6.7 (n=15)	-0.2 ± 5.7 (n=2300)
<i>Glucose and diabetes</i>				
Fasting plasma glucose (mmol/L)	0.37 ± 1.25 (n=471)	0.02 ± 0.84 (n=24)	na	0.30 ± 1.02 (n=2244)
<i>Lipids and treatment of dyslipidemia</i>				
Total cholesterol (mmol/L)	-0.62 ± 1.16 (n=514)	0.48 ± 0.92 (n=6)	0.04 ± 0.61 (n=4)	-0.15 ± 0.92 (n=2266)
HDL-cholesterol (mmol/L)	0.06 ± 0.29	0.21 ± 0.07 (n=6)	0.12 ± 0.24 (n=3)	na
Triglycerides (mmol/L)	-0.22 ± 1.62	0.02 ± 0.75 (n=6)	-0.09 ± 1.69 (n=3)	na
LDL-cholesterol (mmol/L)	-0.60 ± 0.98 (N=484)	0.26 ± 0.78 (n=6)	-0.23 ± 0.31 (n=2)	na

Data are given as mean ± SD. BP: Blood Pressure. na: not available.