GROWTH HORMONE REPLACEMENT THERAPY IN PATIENTS WITH CUSHING'S DISEASE

Milan Vrkljan, Tajana Zah, Josip Rešetić, Branka Vizner, Vilma Kosović and Davorka Herman

Department of Endocrinology, Diabetes and Metabolic Diseases, University Department of Medicine, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – In this retrospective study, the benefit of growth hormone in replacement therapy was assessed in comparison with standard hormone replacement therapy in patients with panhypopituitarism. The study included ten female patients aged 29-44 (mean age 37.6±8.6) years, who had undergone adenectomy for pituitary tumor and Cushing's disease. After adenectomy, the patients received conventional hormone replacement therapy for panhypopituitarism, consisting of hydrocortisol (Cortef), L-thyroxine (Euthyrox) and ovarian hormones, for 6 months. After 6 months of therapy, both subjective and objective recovery was quite poor, as indicated by the following parameters: cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, diastolic and systolic blood pressure at rest, and body mass index. The growth hormone basal and peak values as determined by insulin tolerance test (ITT) test, and insulin-like growth factor (IGF-I) were below the normal range. All patients were indicated TRH nonreactive on TRH testing. Then, growth hormone was added to their conventional therapy in a dose of 2 IU/day s.c., and the same parameters were determined after 6 months of therapy. The criteria for the introduction of growth hormone in therapy were as follows: subjectively and objectively inadequate recovery after adenectomy; growth hormone and IGF-I values below the normal range in basal conditions; and inappropriate growth hormone result on ITT test (patients were administered 0.1 IU insulin *per* kg body weight, whereafter peak growth hormone level was measured). On TRH testing, patients were administered 200 mg TRH, whereafter growth hormone levels were measured. After 6 months of therapy with Cortef, Euthyrox, ovarian hormones and growth hormone, all patients felt much better subjectively (three of them still reported ostealgia, whereas densitometry showed no improvement in only four of ten patients). Objective test results also improved (cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, diastolic and systolic blood pressure at rest, and body mass index). The mean plasma concentration of total cholesterol decreased from 6.95±1-05 to 4.9±1.8 mmol/L, plasma triglycerides from 4.39±1.61 to 1.94±0.76 mmol/L, plasma glucose from 7.83±3.17 to 5.12±1.22 mmol/L, mean body weight from 80.2±5.2 to 74.7±4.7 kg, mean body mass index from 29.1± 2.1 to 26.8±1.6 kg/m^2, waist circumference from 0.827±0.093 to 8.814±0.064 m, pulse from 82.2±7.8 to 71±11.0 *per* min, systolic blood pressure from 148.5±11.5 to 141±9.0 mm Hg, and diastolic blood pressure from 89±16.0 to 84.5±5.5 mm Hg. Osteoporosis was reduced, ostealgia and podagra disappeared in most patients. It was concluded that the introduction of growth hormone in standard hormone replacement therapy led to a considerably better patient recovery as compared with standard hormone replacement therapy alone.

Key words: *Cushing syndrome – therapy; Somatotropin – therapeutic use; Hormone replacement therapy; Follow up studies*

Correspondence to: *Milan Vrkljan, M.D., Ph.D.*, Department of Endocrinology, Diabetes and Metabolic Diseases, University Department of Medicine, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

Received February 17, 2003, accepted in revised form October 24, 2003

Introduction

Pituitary tumors which produce an excess of growth hormone (GH) lead to a clinical state known as Cushing's disease. Cushing's syndrome is characterized by an excesss of adrenocorticotropic hormone (ACTH). Cushing's disease usually affects adults aged 20 to 50 years, with a female predominance of over 70% of cases. The incidence of Cushing's disease in women is threefold that in men. Most ACTH secreting pituitary adenomas are microadenomas, which pose a diagnostic and therapeutic problem because of the biologic effect of cortisol. Cortisol hypersecretion causes irreversible damage to all organs and tissues, and manifests with a very impressive clinical picture. Typical symptoms and signs of Cushing's disease are facial rounding (moon face), truncal obesity, weight gain, buffalo hump, hypertension, purple skin striae, hirsutism, thin skin, abnormal glucose tolerance, impotence, amenorrhea, muscle weakness, osteoporosis, depression, and diabetes.

Tumors that have aggressive and invasive growth often lead to insufficiency of particular pituitary cells, thus provoking clinical features of panhypopituitarism and requiring replacement therapy. Replacement therapy is to be used for life, and includes thyroid, adrenal and gonadal hormones. It is known from clinical practice that some patients with Cushing's disease never achieve satisfactory clinical response, even though regular taking replacement therapy has been laboratory verified. The question is why it is so.

Growth hormone is a single-sequenced peptide produced by somatotroph cells of the anterior lobe of the pituitary gland located at the base of the brain. The secretion of GH is controlled by the hypothalamus through the hypothalamic-regulatory hormones released into the hypophyseal portal circulation. These hormones are somatocrinin (GHRH), which has a stimulatory effect on GH release, and somatostatin (SRIF), which has an opposite effect. Although they both regulate GH secretion, hypothalamic GHRH plays a major role in the pulsatile secretion of GH, whereas SRIF has only a modulatory role in the GH response to GHRH. Nutrition and metabolic milieu, endogenous sleep rhythms, stress, puberty, pregnancy, and exercise also modify spontaneous GH secretion.

GH influences the growth of all tissues in the body by enlarging the mass and number of cells, and is necessary for the longitudinal growth of the skeleton. This major peripheral growth-promoting effect of GH is mediated indirectly by the production of insulin-like growth factor (IGF-I). Besides its effect on the growth, GH influences many metabolic processes in the body. Therefore, GH enhances protein synthesis in all body cells. By modifying fatty acids from adipose tissue and increasing their energy empowering performance, it does not only expend deposited fat but also saves carbohydrates by decreasing glucose utilization.

The aim of this study was to show the conventional hormone replacement therapy consisting of L-thyroxine, hydrocortisol and gonadal hormones to be inadequate after adenectomy. Our intention was to show that better objective findings and subjective patient feeling concerning their health condition could be achieved by replacement therapy containing conventional hormones plus GH than with the conventional replacement therapy alone.

Patients and Methods

This retrospective study included ten female patients aged 29-44 (mean age 37.6±8.6) years, with biochemical (serum cortisol) and radiologic evidence of pituitary tumor and Cushing's disease. All patients underwent adenectomy, which resulted in panhypopituitarism, verified by the levels of T3, T4, TSH, ACTH (8 a.m. and 5 p.m.) and cortisol (8 a.m. and 5 p.m.) measured on day 3 postoperatively. The patients were administered hydrocortisol (Cortef), L-thyroxine (Euthyrox) and ovarian hormones as conventional replacement therapy. After 6 months of conventional replacement therapy, most patients reported they did not feel well. To substantiate their complaints, they underwent laboratory and other testing including cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, blood pressure and pulse, and body mass index (BMI). They were also administered a questionnaire on ostealgia and densitometry was performed for osteopenia. BMI was calculated according to the formula: BMI = body mass (kg)/body height (m^2). Laboratory test results revealed their replacement therapy was carried out successfully, however, testing for GH, IGF-I, insulin tolerance test (ITT) and TSH produced values below normal ranges in all study patients. On ITT test, the patients were administered 0.1 IU insulin *per* kg body weight, whereafter the peak growth hormone level was determined. On TRH test, the patients received 200 mg TRH, whereafter GH value was measured. Then, GH was added to their conventional replacement therapy at a dose of 2 IU/day s.c. After 6 months of this therapy, the same parameters were determined again (cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, blood pressure and pulse, and BMI). The same questionnaire on ostealgia was redistributed to the patients, and densitometry was performed. Also, the levels of IGF-I and cortisol (8 a.m. and 5 p.m.) were measured.

Results

This retrospective study included ten female patients aged 29 to 44 (mean age 37.6±8.6) years with biochemical (serum cortisol) and radiologic evidence of pituitary tumor – Cushing's disease. The patients underwent adenectomy, and the mean serum T3, T4 and TSH levels measured immediately postoperatively were below the normal ranges (Table 1).

Three days after adenectomy, serum levels of ACTH and cortisol were determined at 8 a.m. and 5 p.m. All patients had serum level of ACTH <2.0 pmol/L at both 8 a.m. and 5 p.m. Serum cortisol at 8 a.m. varied from 170 to 405 nmol/L, mean 245.8±159.2 nmol/L, and at 5 p.m. from 78 to 120 nmol/L, mean 99.7±21.7 nmol/L. All mean cortisol levels were quite low (Table 2).

Table 1. T3, T4 and TSH levels measured three days of adenectomy

Patient No.	T3 (nmol/L)	T4 (nmol/L)	TSH (mIU/L)
1	1.3	92	0.6
2	1.5	120	0.9
3	2.0	87	0.2
4	2.1	90	0.4
5	1.7	103	0.6
6	1.9	110	0.7
7	1.3	100	0.9
8	1.4	102	1.1
9	1.5	87	1.0
10	1.6	92	0.9
Mean	1.63±0.47	98.3±21.7	0.73±0.53

As all patients had low mean serum levels of T3, T4, TSH, ACTH (8 a.m. and 5 p.m.) and cortisol (8 a.m. and 5 p.m.), we concluded they had developed panhypopituitarism and prescribed conventional replacement therapy with hydrocortisol (Cortef 20, 0, 10), L-thyroxine (Euthyrox 50-100) and ovarian hormones. Six-month administration of this conventional hormone replacement therapy failed to result in satisfactory recovery, and all patients reported subjective discomforts (fatigue, ostealgia and osteopenia). These objective complaints were substantiated by laboratory and other testing, including cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, systolic and diastolic blood pressure, pulse, and BMI. The mean cholesterol level was 6.95±1.05 mmol/L, exceeding the normal level of <5.2 mmol/L. The mean triglyceride level was 4.39±1.61 mmol/L, exceeding the normal level of <1.8 mmol/L. The mean blood glucose level was 7.83±3.17, exceeding the normal range of 4.2-6.4 mmol/L. The mean body weight was 80.2±5.2 kg, and mean body height 1.663±0.083 m. The mean BMI was 29.1±3.0, also exceeding the normal value. The mean value of waist circumference was 0.877±0.077 m. The mean pulse *per* minute was 82.2±7.8 (normal 60-80/min) at rest. The mean systolic and diastolic pressure at rest was 148.5±11.5 mm Hg and 89.0±16.0 mm Hg, respectively (Table 3).

Table 2. ACTH (8 a.m.), ACTH (5 p.m.), cortisol (8 a.m.) and cortisol (5 p.m.) levels measured three days of adenectomy

Patient No.	ACTH 8 a.m. (pmol/L)	ACTH 5 p.m. (pmol/L)	Cortisol 8 a.m. (nmol/L)	Cortisol 5 p.m. (nmol/L)
1	<2.0	<2.0	171	85
2	<2.0	<2.0	170	78
3	<2.0	<2.0	266	100
4	<2.0	<2.0	290	120
5	<2.0	<2.0	190	85
6	<2.0	<2.0	266	100
7	<2.0	<2.0	311	97
8	<2.0	<2.0	405	120
9	<2.0	<2.0	190	120
10	<2.0	<2.0	199	92
Mean	<2.0	<2.0	245.8±159.2	99.7±21.7

As the conventional hormone replacement therapy failed to result in a satisfactory recovery in our patients, as judged from both subjective reports and objective findings, testing for GH and IGF-I levels was performed to see whether they were below the normal ranges. Therefore, basal GH, IGF-I, ITT (peak GH) and TRH test were determined. After 6 months of conventional replacement therapy, the mean basal GH level was 0.25 mg/L. On ITT test, the mean peak GH level was 2.275±1.875 mg/L, mean IGF-I 290.9±170.9 IU, and mean GH on TRH test 1.18±0.92 mg/L. All these mean levels were below normal ranges, thus the patients were designated as 'TRH nonresponders' (Table 4).

Therefore, we introduced GH in the replacement therapy, at a dose of 2 IU or 0.65 mg/day s.c. The criteria for the addition of GH in therapy were: 1) subjectively and objectively inadequate recovery after adenectomy; 2) basal GH and IGF-I levels below the normal range; and 3) inappropriate GH result on ITT test and 'TRH nonresponding' on

Table 3. Parameter values after 6 months of conventional hormone replacement therapy

Patient No.	Chol (mmol/L)	TG (mmol/L)	BG (mmol/L)	BW (kg)	BH (m)	BMI (kg/m^2)	WC (m)	Pulse (*per* min)	sBP (mm Hg)	dBP (mm Hg)
1	6.1	3.9	6.7	80	1.65	29.4	0.80	82	160	100
2	7.2	4.1	7.0	81	1.62	30.9	0.90	80	150	90
3	8.0	3.2	9.0	78	1.68	27.6	0.92	90	140	100
4	7.6	3.4	9.1	84	1.70	29.1	0.90	85	145	100
5	7.0	6.0	11.0	80	1.58	32.1	0.84	87	140	105
6	7.1	5.8	5.6	82	1.69	28.7	0.87	78	160	100
7	6.1	4.8	6.1	75	1.60	29.3	0.90	79	140	90
8	6.6	5.0	6.9	79	1.71	27.0	0.92	76	140	105
9	6.7	3.1	8.2	82	1.72	27.7	0.85	80	150	100
10	7.1	4.6	8.7	81	1.68	28.7	0.87	85	160	90
Mean	6.95±1.05	4.39±1.61	7.83±3.17	80.2±5.2	1.663±0.083	29.1±3.0	0.877±0.077	82.2±7.8	148.5±11.5	89.0±16.0

Chol=cholesterol, TG=triglycerides, BG=blood glucose, BW=body weight, BH=body height, BMI=body mass index, WC=waist circumference, sBP=systolic blood pressure, dBP=diastolic blood pressure

TRH test. Now, the patients were administered hydrocortisol, L-thyroxine, ovarian hormones and GH for another 6 months, and then the tests were repeated. After 6 months of this GH supplemented therapy, great improvement was recorded in the objective parameters as compared with the conventional replacement therapy alone. The mean plasma concentration of IGF-I increased from 290.9±170.9 to 533.6±221.6 IU/L, and mean plasma concentration of cortisol at 8 a.m. and 5 p.m. from 217.8±187.2 to 453.3±148.7 nmol/L and from 99.7±21.7 to 218.3±181.7 mmol/L, respectively (Table 5).

After 6 months of therapy with conventional replacement therapy plus GH, the parameters of cholesterol, triglycerides, blood glucose, body weight, body height, waist circumference, systolic and diastolic blood pressure, pulse, and BMI were determined again. The mean level of cholesterol was 4.9±1.8 mmol/L, which was within the normal range (<5.2 mmol/L). In comparison to the levels measured before the introduction of GH in therapy, the mean plasma total cholesterol decreased from 6.95±1.05 to 4.9±1.8 mmol/L. The mean level of triglycerides was 1.94±0.76 mmol/L, which was within the normal range (<1.8 mmol/L). The mean blood glucose level was 5.12±1.22 mmol/L, which was within the normal range (4.2-6.4 mmol/L). The mean body weight was 74.2±0.083 kg, and mean body height 1.663±0.083 m. The mean BMI was 26.8±1.6 kg/m^2 and

Table 4. Growth hormone (GH), insulin-like growth factor I (IGF-I), peak growth hormone and TSH levels after 6 months of conventional hormone replacement therapy

Patient No.	GH (mg/L)	IGF-I (IU/L)	ITT test (peak GH; mg/L)	TRH test (GH mg/L)
1	0.25	411	4.15	0.8
2	0.25	301	2.1	1.0
3	0.25	312	1.7	1.0
4	0.25	401	2.2	2.1
5	0.25	170	2.7	1.7
6	0.25	190	2.6	1.6
7	0.25	312	2.0	0.8
8	0.25	401	1.9	0.9
9	0.25	291	1.7	0.8
10	0.25	120	1.7	1.1
Mean	0.25±0.0	290.9±170.9	2.275±1.875	1.18±0.92

Table 5. Insulin-like growth factor I (IGF-I) and cortisol (8 a.m.and 5 p.m.) levels after 6 months of growth hormone plus conventional hormone replacement therapy

Patient No.	IGF-I (IU/L)	Cortisol 8 a.m. (nmol/L)	Cortisol 5 p.m. (nmol/L)
1	702	320	250
2	620	420	190
3	510	490	170
4	470	400	207
5	312	602	171
6	407	490	202
7	502	460	400
8	601	501	202
9	721	470	201
10	491	380	190
Mean	533.6±221.6	453.3±148.7	218.3±181.7

Table 6. Parameter values after 6 months of growth hormone plus conventional hormone replacement therapy

Patient No.	Chol (mmol/L)	TG (mmol/L)	BG (mmol/L)	BW (kg)	BH (m)	BMI (kg/m^2)	WC (m)	Pulse (*per* min)	BP (mm Hg)
1	4.7	1.2	3.9	75	1.65	27.5	0.75	70	140
2	5.6	1.7	6.0	70	1.62	26.7	0.87	60	140
3	4.2	1.9	4.0	72	1.68	25.5	0.87	70	140
4	4.1	1.6	5.2	77	1.70	26.6	0.80	70	149
5	6.7	2.1	6.0	71	1.58	28.4	0.77	70	140
6	6.0	2.4	4.7	79	1.69	27.7	0.77	70	140
7	5.8	1.7	6.0	71	1.60	27.7	0.87	68	150
8	4.2	2.7	5.7	75	1.71	25.7	0.85	75	140
9	3.1	1.9	5.0	75	1.72	25.4	0.79	77	140
10	4.6	2.2	4.7	77	1.68	27.3	0.80	80	140
Mean	4.9±1.8	1.94±0.76	5.12±1.22	74.2±0.083	1.663±0.078	26.8±1.6	0.814±0.064	71±11.0	141±9.0

Chol=cholesterol, TG=triglycerides, BG=blood glucose, BW=body weight, BH=body height, BMI=body mass index, WC=waist circumference, BP=systolic/diastolic blood pressure

mean waist circumference 0.814±0.064 m, showing improvement from the values calculated before the introduction of GH in therapy. The mean pulse at rest was 71±11.0 *per* minute, also indicating improvement from the initial values. The mean systolic and diastolic pressure at rest was 141±9.0 and 84.5±5.5 mm Hg, both showing improvement from the initial values (Table 6).

Upon the introduction of GH in hormone replacement therapy, the mean plasma cholesterol concentration decreased from 6.95±1.05 to 4.9±1.8 mmol/L, which was within the normal range (<5.2 mmol/L) (Fig. 1). The mean triglyceride level decreased from 4.39±1.61 to 1.94±0.76 mmol/L, which was within the normal range (<1.8 mmol/L) (Fig. 2). The mean blood glucose decreased from 7.83±3.17 to 5.12±1.22 mmol/L, which was within the normal range (4.2-6.4 mmol/L) (Fig. 3). The mean value of body weight decreased from 80.2±5.2 to 74.7±4.7 kg (Fig. 4). The mean body height was 1.663±0.083 m. The mean BMI was reduced from 29.1±2.1 to 26.8±1.6 kg/m^2 (Fig. 5). The mean value of waist circumference decreased from 0.827±0.093 to 0.814±0.064 m (Fig. 6). The mean value of pulse at rest decreased from 82.2±7.8 to 71±11.0 *per* minute (Fig. 7). The mean systolic and diastolic pressure at rest decreased from 148.5±11.5 to 141±9.0 mm Hg and from 89±16.0 to 84.5±5.5 mm Hg, respectively (Figs. 8 and 9).

After 6-month therapy with Euthyrox, Cortef, ovarian hormones and GH, all patients reported they felt much better (three of them still suffered ostealgia and four showed

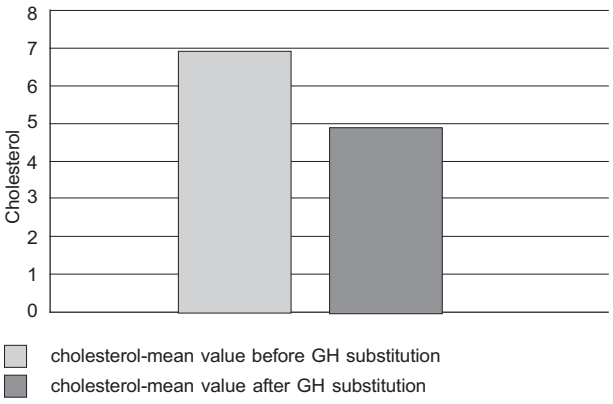

Fig. 1. Mean total plasma cholesterol levels before and 6 months of growth hormone introduction in hormone replacement therapy

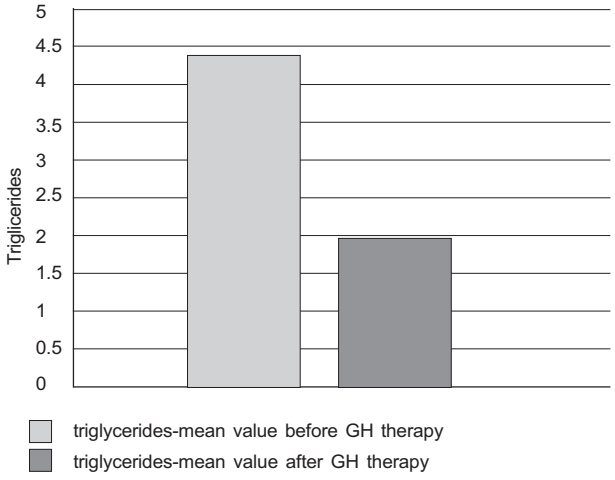

Fig. 2. Mean triglyceride levels before and 6 months of growth hormone introduction in hormone replacement therapy

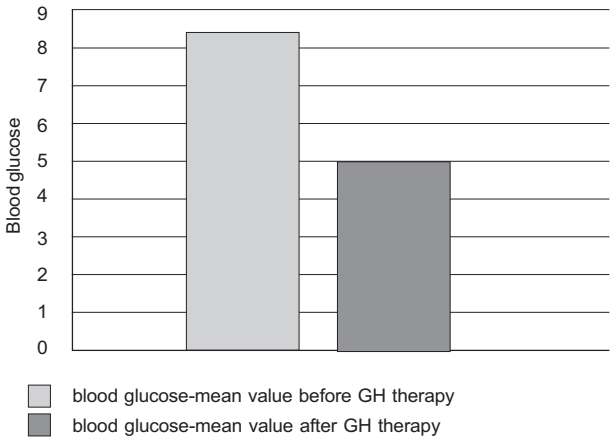

Fig. 3. Mean blood glucose levels before and 6 months of growth hormone introduction in hormone replacement therapy

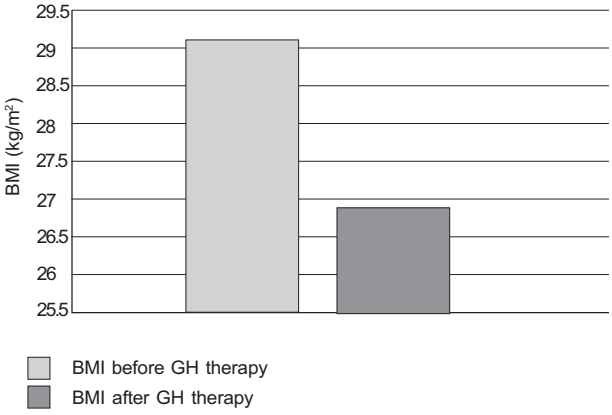

Fig. 5. Mean body mass index values before and 6 months of growth hormone introduction in hormone replacement therapy

no improvement on densitometry, however, osteoporosis was reduced).

It is concluded that the administration of GH in addition to standard hormone replacement therapy led to a considerably better patient recovery than the standard replacement therapy alone. Figures 10 and 11 show patients with Cushing's disease. The same patient before and after therapy is presented in Figs. 10 and 11, respectively, clearly illustrating the favorable therapeutic effect. Upon the addition of GH to standard hormone replacement therapy, the values of many risk factors for atherosclerosis such as total cholesterol, triglycerides, BMI, blood pressure, waist circumference and blood glucose were considerably reduced, and

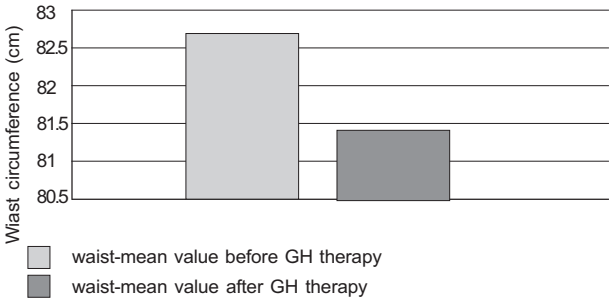

Fig. 6. Mean waist circumference values before and 6 months of growth hormone introduction in hormone replacement therapy

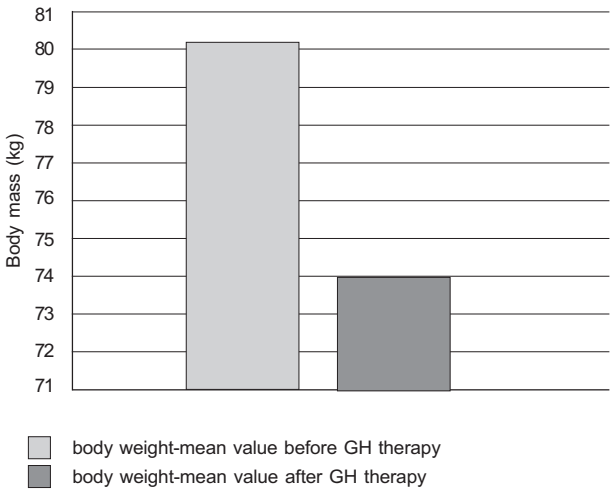

Fig. 4. Mean values of body weight before and 6 months of growth hormone introduction in hormone replacement therapy

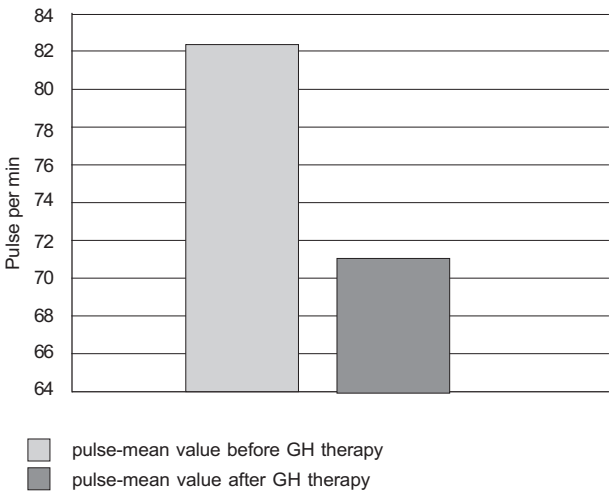

Fig. 7. Mean pulse values before and 6 months of growth hormone introduction in hormone replacement therapy

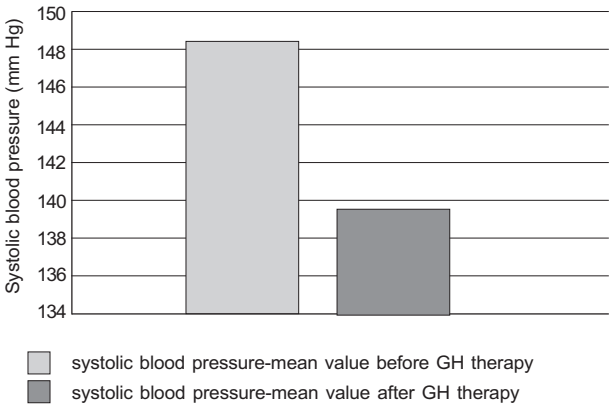

Fig. 8. Mean values of systolic blood pressure before and 6 months of growth hormone introduction in hormone replacement therapy

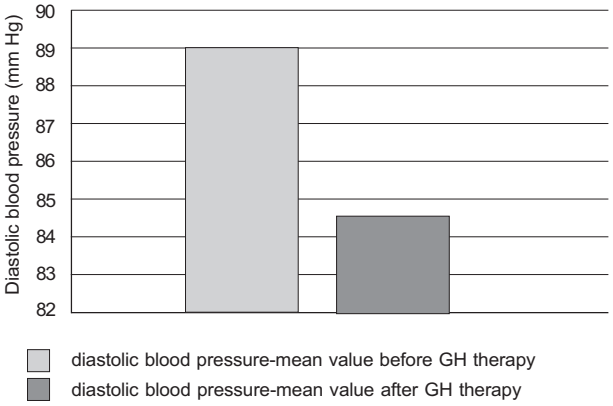

Fig. 9. Mean values of diastolic blood pressure before and 6 months of growth hormone introduction in hormone replacement therapy

patients reported improvement of their general condition on answering the questionnaire on subjective discomforts, as compared with standard hormone replacement therapy alone.

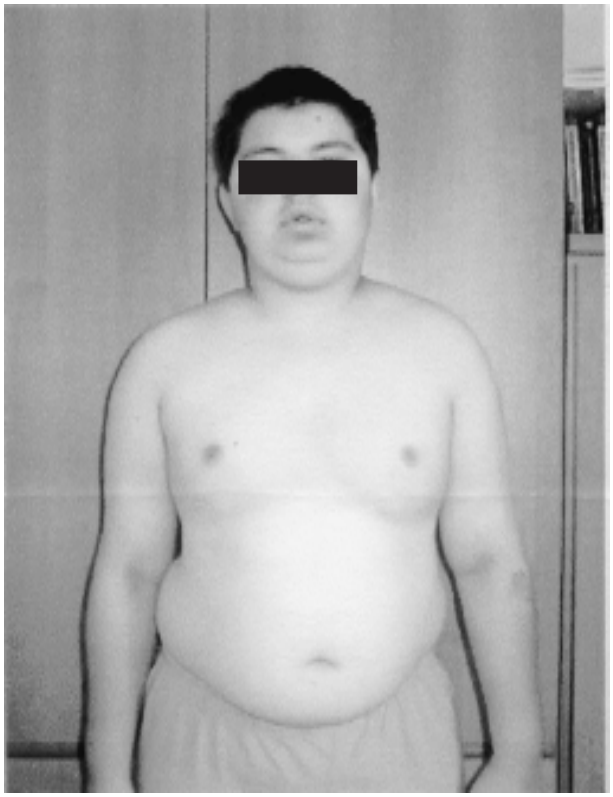

Fig. 10. A male patient with Cushing's disease before growth hormone plus conventional hormone replacement therapy.

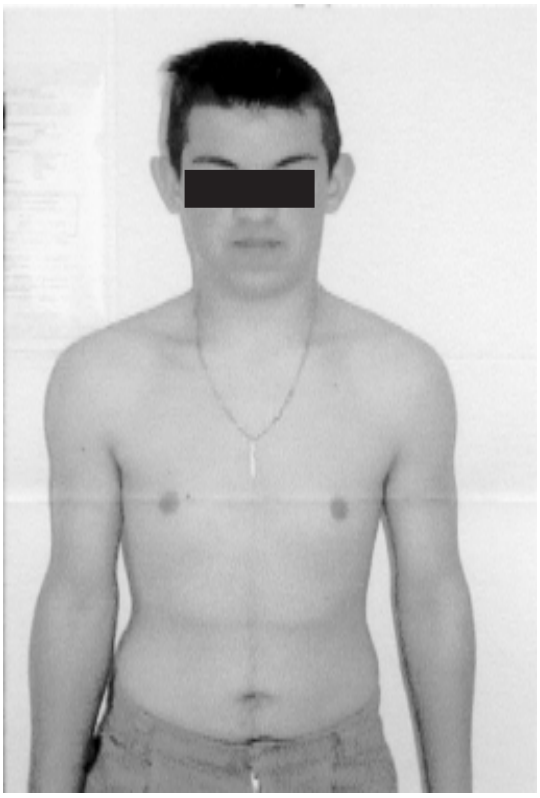

Fig. 11. The same patient after 6-month growth hormone plus conventional hormone replacement therapy.

Discussion

Growth hormone is a very important hormone, especially in patients submitted to adenectomy for pituitary tumor and Cushing's disease, followed by the development of panhypopituitarism. Our study results showed the patients administered conventional hormone replacement therapy with adrenal, thyroid and gonadal hormones to have inadequate recovery, whereas the introduction of GH in replacement therapy led to subjectively and objectively considerably better recovery.

Thus, it is concluded that the addition of GH at a dose of 2 IU *per* day to conventional hormone replacement therapy consisting of hydrocortisol (Cortef), L-thyroxine (Euthyrox) and ovarian hormone results in considerable subjective improvement (ostealgia reported by three *vs.* ten of ten patients before the introduction of GH in therapy, and better densitometry results recorded in six of ten patients). These favorable changes occurred due to the beneficial effect of GH on bone metabolism, as GH increases overall bone mass and its mineral content. Consequently, the risk of fractures is reduced and the patient quality of life improved. The benefit of GH was demonstrable through the reduced values of cholesterol, triglycerides, blood glucose, BMI, systolic and diastolic blood pressure, and waist circumference, which are all associated with the development of atherosclerosis. Through lowering these atherogenic risk factors, GH contributes to the reduction of the risk of atherosclerosis and premature cardiovascular diseases in this population.

In the present study, the individual variability in response to GH in replacement therapy may be perceived as reflecting the relatively small number of patients included. It remains to be determined in additional studies whether the period of 6 months of hormone replacement therapy is too short to demonstrate all the benefits of GH in longterm replacement therapy. Our patients will be followed up and tested again upon withdrawal of GH from therapy after 6 months. These results will then be reported. The results of this study also suggest that GH should be given due place in hormone replacement therapy for patients submitted to adenectomy and subsequent panhypopituitarism. We have not yet acquired experience in the use of replacement therapy with GH in patients with hypopituitarism, as these are our first cases ever.

References

1. De BOHER H, BLOK GJ, Van der VEEN EA. Clinical aspects of growth hormone deficiency in adults. Endocr Rev 1995;16:63.
2. VRKLJAN M, SKORIĆ B, VIZNER B, REŠETIĆ J, STANČIĆ V, THALLER V. Diagnostic problems related to hypercortisolism with special reference to major depressive disorder and Cushing's syndrome. Acta Clin Croat 1998;37:155-65.
3. CARROLLI PV, CHRIST ER, BENGTSSON BA, *et al.* Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab 1998;83:382.
4. BATES AS, HOFF W, VANT G, JONES PJ, *et al.* The effect of hypopituitarism on life expectancy. J Clin Endocrinol Metab 1996;81:1169.
5. BENGTSSON BA, EDEN S, LONN L, *et al.* Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 1993;76:309.
6. BINNERTS A, DEURENBERG P, SWART GR, *et al.* Body composition in growth hormone deficient adults. Am J Clin Nutr 1992;55:918.
7. De BOHER H, BLOK GJ, VOERMAN HJ, *et al.* Serum lipid levels in growth hormone deficient men. Metabolism 1994;43:199.
8. ROSEN T, HANSSON T, GRANHED H, *et al.* Reduced bone mineral content in adult patients with growth hormone deficiency. Acta Endocrinol 1993;129:201.
9. COLAO A, Di SOMMA C, CUOCULO A, *et al.* Improved cardiovascular risk factors and cardiac performance after 12 months of growth hormone (GH) replacement in young adult patients with GH deficiency. J Clin Endocrinol Metab 1994;78:669.
10. BJÖRK S, JÖNSSON B, WESTPHAL O, *et al.* Quality of life of adults with growth hormone deficiency: a controlled study. Acta Pediatr Scand Suppl 1989;356:55.
11. LANDON J, GREENWOOD FC, STAMP TC, *et al.* The plasma sugar, free fatty acids, cortisol and growth hormone response to insulin, and comparison of this procedure with other tests of pituitary and adrenal function. II. J Clin Invest 1966;45:437.
12. VRKLJAN M, VIZNER B, GNJIDIĆ Ž, BEDEK D, REŠETIĆ J, SEKSO M. Distribution of pituitary tumors in Croatia. Lijecn Vjesn 1999;121.
13. VRKLJAN M, STANČIĆ V, TOMAC A, LJUBIČIĆ N, ČABRIJAN T. Pathogenesis of pituitary adenomas. Acta Clin Croat 1997;36:173-7.
14. FAGLIA G, BECK-PECCOZ P, AMBROSI B, *et al.* Pituitary adenomas: new trends in basic and clinical research. Excerpta Med Int Contrib Ser 1991;961.

Sažetak

NADOMJESNA TERAPIJA HORMONOM RASTA U BOLESNIKA S CUSHINGOVOM BOLEŠĆU

M. Vrkljan, T. Zah, J. Rešetić, B. Vizner, V. Kosović i D. Herman

Deset bolesnica s tumorom hipofize i Cushingovom bolešću praćeno je u ovom retrospektivnom istraživanju. Sve bolesnice su operirane i imale su panhipopituitarizam nakon operacije. Kroz 6 mjeseci provođena je standardna hormonska nadomjesna terapija Cortefom, Euthyroxom i gonadnim hormonima. Nakon 6 mjeseci terapije provedene su pretrage i bolesnice su odgovorile na manji upitnik o subjektivnom osjećanju. Pretrage su uključile kolesterol, trigliceride i glukozu u krvi, tjelesnu težinu i tjelesnu visinu, opseg struka, indeks tjelesne mase, puls u mirovanju, sistolički i dijastolički tlak, denzitometriju i prisutnost kostobolje. Objektivni pregled, subjektivno osjećanje i nalazi laboratorijske obrade pokazali su kako nijedna bolesnica nije postigla zadovoljavajući poslijeoperacijski oporavak. U naknadnim pretragama mjerena je bazalna razina hormona rasta i vršna vrijednost dobivena testom ITT, te IGF-I. Nađene su niske vrijednosti u bazalnim uvjetima i u testu. Test TRH pokazao je nedostatan odgovor hormona rasta u svih bolesnica. Nakon analize dobivenih nalaza donešena je odluka o terapiji hormonom rasta uza standardnu nadomjesnu hormonsku terapiju (nadbubrežna žijezda, štitnjača i gonade), što je provedeno kroz slijedećih 6 mjeseci. Testiranje je ponovljeno nakon 6 mjeseci, kada su mjereni isti parametri kao i odmah nakon operacije, tj. kolesterol, trigliceridi, glukoza u krvi, tjelesna težina, tjelesna visina, opseg struka, indeks tjelesne mase, puls u mirovanju, sistolički i dijastolički tlak. Subjektivni upitnik sadržavao je pitanja o kostobolji, a napravljena je i denzitometrija. Analiza je pokazala kako su bolesnice koje su uzimale hormon rasta uza standardnu hormonsku nadomjesnu terapiju prema svim parametrima nakon 6 mjeseci terapije postigle puno bolje rezultate, te da se subjektivno bolje osjećaju. Rezultati su pokazali kako je pozitivan učinak hormona rasta nakon operacije tumora hipofize neosporan, te da se stupanj oporavka koji se postiže nakon uključivanja hormona rasta u terapiju ne može postići standardnom hormonskom nadomjesnom terapijom.

Ključne riječi: *Cushingov sindrom – terapija; Somatotropin – terapijska primjena; Hormonska nadomjesna terapija; Studije praćenja*