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Diagnosis and Treatment of Hypopituitarism: An Update

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Abstract. **Diagnosis and treatment of patients with hypopituitarism needs careful clinical evaluation and individual optimization. Symptoms of hypopituitarism are variable, often insidious in onset and dependent on the degree of hormone deficiency. Diagnosis of hypopituitarism can be straightforward by measuring reduced basal hormone levels. Frequently, dynamic stimulation tests are indicated in equivocal basal hormone levels or to diagnose partial hormone deficiencies. Knowledge of the use and limitations of these dynamic tests is mandatory for proper interpretation.**

Hormone replacement therapy should be individualized, taking into account possible interactions. Persisting symptoms and reduced quality of life are frequently reported, explained by, at least in part, intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion.

In the present overview, the principles of diagnosis and treatment of hypopituitarism are discussed.

Key words. **Hypopituitarism, pituitary, diagnosis, hormone replacement therapy, quality of life**

Introduction

Hypopituitarism is the in general permanent state of partial or complete insufficiency of anterior pituitary hormone secretion [1]. Many diseases occurring in the region of the pituitary or hypothalamus can lead to hypopituitarism, occurring both in childhood as in adult life (Table 1). The identification of pituitary hormone deficiencies can be of vital importance, especially to prevent adrenal crises. Treatment of hypopituitarism consists of one or more hormonal replacement therapies. Despite conventional hormone replacement, several studies have reported an increased incidence of (cerebro)vascular disease and increased mortality. Moreover, many patients treated for endocrine insufficiencies still suffer from more or less vague complaints and a decreased quality of life.

In the present overview, diagnosis and treatment of hypopituitarism is discussed. The use and limitations of specific tests will be addressed as well as issues regarding the optimization of hormone replacement therapy.

Clinical Features of Hypopituitarism

The clinical manifestations of hypopituitarism are variable, often insidious in onset and dependent on the degree of hormone deficiency (Table 2). In secondary hormone deficiencies, for example thyrotropin deficiency, some basal hormone secretion can be preserved, resulting in a less severe clinical phenotype compared with primary hypothyroidism. Corticotropin deficiency is less evident than primary adrenal deficiency, since in most cases mineralocorticoid secretion remains intact. During an intercurrent illness or surgery, however, corticotropin secretion may not increase appropriately, in which case life-threatening adrenal crisis may develop.

In men with recent onset hypogonadism, physical examination is usually normal, while diminished facial and body hair, gynaecomastia and small, soft testes are features of longstanding hypogonadism. Anemia can also occur due to diminished erythropoiesis associated with hypogonadism. In premenopausal women, secondary amenorrhoea is a common feature.

Growth hormone deficiency is associated with diminished exercise tolerance, an increased (central) body fat and premature atherosclerosis. These physical limitations, in combination with decreased social functioning, lead to a decreased quality of life in patients with severe growth hormone deficiency. In partial growth hormone deficiency, however, these features are often less severe.

Hyperprolactinaemia is common in patients with hypopituitarism, due to the interference of a pituitary mass with dopaminergic inhibition of prolactin secretion or due to a macroprolactinoma. Galactorrhoea may occur, but more frequently hypogonadism is observed, due to the effect of raised prolactin levels on normal pulsatile gonadotropin secretion.

Diagnosis and Treatment of Hypopituitarism

As an initial investigation, basal serum hormone measurements may be all that is needed to confirm pituitary insufficiency. Table 3 summarizes the use and limitations of basal hormone levels. Preferably, a blood sample should be drawn early morning, when diurnal cortisol secretion is at its maximum. Both the

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Table 1. *Causes of hypopituitarism*

Childhood onset
Genetic disorderders, including familial hypopituitarism and familial isolated or multiple hormone deficiencies
Perinatal insults (abnormal delivery, asphyxia), pituitary hypoplasia or aplasia
Craniopharyngeoma's and other (peri)pituitary tumours
Craniospinal radiation
Trauma
Adult onset
Pituitary tumours, surgery, irradiation, infarction (apoplexia)
Peripituitary tumours, including meningioma's, glioma's, metastases
Lymphocytic hypophysitis
Postpartum hemorrhage (Sheehan's syndrome)
Internal carotid artery aneurysm, subarachnoid hemorrhage
Trauma, infection, abscesses
Haemochromatosis, granulomatous diseases, histiocytosis X

Table 2. *Clinical symptoms of hypopituitarism*

Corticotroph deficiency
Acute: fatigue, weakness, dizziness, nausea, vomiting, circulatory collaps
Chronic: tiredness, pallor, anorexia, weight loss, hypoglycaemia
Children: failure to thrive
Thyrotropin deficiency
Tiredness, cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, slowed mental processing
Gonadotropin deficiency
Children: delayed puberty
Women: amenorrhea, oligomenorrhea, infertility, loss of libido, dyspareunia (short-term); osteoporosis, premature atherosclerosis (long-term)
Men: loss of libido, impaired sexual function, decreased muscle mass, bone mass, erythropoiesis and hair growth
Growth Hormone deficiency
Children: growth retardation
Adults: decreased muscle mass and strength, increased (central) obesity, fatigue, premature atherosclerosis, decreased quality of life

target hormone concentration and the pituitary hormone concentration should be measured to assess the appropriateness of both values. In addition, a pituitary mass can lead to the secretion of biologically inactive pituitary hormones. In these cases, a normal pituitary hormone concentration is found, with a decreased target hormone concentration.

Dynamic stimulation tests are indicated in equivocal basal hormone levels or to diagnose partial hormone deficiencies. Every dynamic test has its specific limitations and the test of choice partly depends on local experience and practical considerations.

The goals of hormone replacement therapy are to raise circulating hormone concentrations within the normal range, taking into account the normal diurnal variation, to ameliorate the symptoms of hormone deficiency and to prevent long term sequelae of hormone deficits. However, the pharmacological and pharmacokinetic properties of currently available hormone preparations do not meet these goals.

Corticotropin deficiency

A morning cortisol value below 100 nmol/l indicates adrenal insufficiency, whereas a serum cortisol greater than 500 nmol/l is consistent with an intact hypothalamic-pituitary-adrenal axis [2]. If basal cortisol levels are between 100 and 500 nmol/l, as is often the case, corticotrophin deficiency is not unequivocally excluded and a dynamic test should be performed in patients with a reasonable risk of corticotropin deficiency.

Sustained secondary adrenal insufficiency leads to adrenal atrophy and also to reduced ACTH receptor expression in the adrenal gland, since ACTH upregulates its own receptor [2]. Thus the standard 250 μgr cosyntropin test can be used to establish secondary adrenal insufficiency, in which peak cortisol levels do not exceed 500 nmol/l. However, some patients do pass the cosyntropin test but not the insulin tolerance test [3]. The use of a cut-off value higher than 600 nmol/l probably reduces the risk of overlooking secondary adrenal insufficiency. There has been much debate whether a low dose (1 μgr) cosyntropin test would represent a more physiological stimulus for maximal adrenal stimulation compared to the 250 μgr corticotropin dose. Some reports have suggested a superior sensitivity for the 1 μg ACTH test [2]. However, a recent meta-analysis on this subject found similar operating characteristics of the 250 μg and 1 μg test for the diagnosis of secondary adrenal insufficiency [4]. Disadvantages of the low dose test are the impractical dilution of the commercially available 250 μgr ACTH ampoule to obtain the appropriate test concentration and the potential binding of the hormone to the surface of injection devices. In subjects with recent onset corticotropin deficiency, a normal increase of serum cortisol can be observed, since adrenal atrophy develops gradually after onset of ACTH release. For this reason, in patients who have undergone pituitary surgery, a cosyntropin test should only be carried out 4 to 6 weeks after the operation.

The insulin tolerance test (ITT) assesses the integrity of the complete hypothalamic-pituitary-adrenal axis and has the advantage of testing growth hormone reserve at the same time. Insulin (0.05–0.2 U/kg) given intravenously induces substantial transient hypoglycaemia, which is a powerful stressor that results in rapid activation of the HPA (and GH) axis. The test is valid only when a glucose level below 2.2 mmol/l is obtained. Cortisol levels above 500 nmol/l are indicative of an intact HPA-axis, although some advocate a higher cut-off level of 550 nmol/l [5,6]. The risk of severe hypoglycaemia necessitates supervision of a physician and the ITT is contraindicated in patients with signs of

Table 3. *Tests for the diagnosis of hypopituitarism*

	Hormone test	Reference range*	Diagnostic for hormone insufficiency*	Precautions/Limitations
Corticotroph function	Cortisol	165–680 nmol/l	Cortisol: <100 nmol/l: hypocortisolism 100–500 nmol/l: dynamic test >500 nmol/l: intact HPA-axis	Should be measured early morning
	ACTH	1.1–11.0 pmol/l	ACTH normal (<11 pmol/l)/undetectable : secondary adrenal insuff ACTH high (usually >45 pmol/l): primary adrenal insuff	Serum storage on ice
	Standard short synacthen test (250 μgr)		Peak cortisol <500 nmol/l (or 600 nmol/l)	
	Insulin tolerance test		Cortisol <500 nmol/l (or 550 nmol/l)	Contraindicated in subjects with a history of seizures, cerebrovascular and cardiovascular disease
	Metyrapone test (overnight or multiple dose)		Overnight test 11-DOC <200 nmol/l Multiple dose test 11-DOC < 350 nmol/l	
Thyrotrope function	FT4	11–25 pmol/l	<11 pmol/l	
	TSH	0.4–4.3 mU/l	Normal or low	Occasionally high (biological inactive hormone)
Gonadotroph function	LH	2–8 U/l	Low	
	FSH	1–8 U/l	Low	
	Oestradiol	>100 pmol/l	<100 pmol/l	
	Testosterone	10–30 nmol/l	<10 nmol/l	
Somatotrope function	IGF-I	15–43 nmol/l (age-dependent)	Normal or low	Reference range according to age. Can also occur in under nutrition, chronic illness, liver disease
	Insulin tolerance test		GH <3 μg/l	
	GHRH-Arginine test		GH <9 μg/l	
	GHRH-GHRP-6 test		GH <15 μg/l	
Lactotroph function	Prolactin	<0.36 U/l	Often slightly elevated (pituitary stalk compression)	Should be measured in every subject with a sellar mass, in order to exclude a prolactinoma. Exclude "high dose hook effect"

*Reference ranges vary dependent on laboratory and assay.

myocardial ischaemia and seizures. In children, acute hypokalaemia, induced by insulin and catecholamine excess, is a frequent finding in the ITT, which could serve as trigger of cardiac arrhythmias [7]. For this reason, the ITT has been abandoned in the diagnosis of childhood growth hormone deficiency.

Another diagnostic test uses metyrapone, an inhibitor of 11b-hydroxylase, preventing the conversion of 11-deoxycortisol (11-DOC) to cortisol. In healthy subjects this will lead to an accumulation of 11-DOC. Metyrapone can be administered as a single dose at midnight, or as multiple doses during one day, resulting in different cut-off levels [8] (Table 3). Compared to the ITT, the metyrapone test is less cumbersome for the patient and appears to be safely carried out on an outpatient basis [9].

There is no universal agreement on appropriate doses, timing and monitoring of glucocorticoid replacement therapy. The normal daily cortisol production rate of 5 to 10 mg/m^2 is equivalent to the oral administration of 15 to 25 mg hydrocortisone or 25 to 37.5 mg cortison acetate [10]. Treatment regimens use two or three doses per day (e.g. hydrocortisone 10–5 –5 mg), in order to mimic the normal diurnal pattern of cortisol secretion. However, several studies have shown that with these conventional regimens, a substantial proportion of patients is overreplaced, which can lead to substantial morbidity, including osteoporosis, obesity and impaired glucose tolerance [11,12]. This might particularly apply to patients with partial corticotropin deficiency. A recent study suggests that in these patients, replacement with hydrocortisone 5 mg twice daily results in a cortisol day curve similar to healthy controls [13]. Monitoring of glucocorticoid replacement therapy is mainly based on clinical grounds because no reliable objective parameters are available. Some have suggested the assessment of a cortisol day curve in patients on glucocorticoids. The inconvenience of serial blood sampling could be circumvented by the use of salivary cortisol measurement or bloodspot sampling [14]. However, the currently available exogenous glucocorticoids do not have the pharmacokinetic properties to mimic the diurnal cortisol pattern noted in healthy individuals [15]. In particular, despite replacement of hydrocortisone, cortisol concentrations remain low between 0400 and 0730 h, during which time cortisol concentration starts to increase in normal people [16].

Patients with corticotropin deficiency do not respond with increased cortisol secretion in case of infections, illness, trauma or surgery. All patients and their partners should be instructed regularly on increasing the oral dose two or three times during minor disease. For major surgery, trauma and severe diseases, intravenous administration of hydrocortisone (100 to 150 mg per day) is mandatory. In addition, all patients should carry a steroid emergency card or bracelet with information about their steroid dependence and instructions on stress-related dose adjustements.

The value of dehydroepiandrosterone sulphate (DHEA-S) measurement and DHEA suppletion in subjects with secondary adrenal insufficiency has received increasing attention. Two studies have addressed the question whether low DHEA-S levels are diagnostic for hypopituitarism, with discrepant results. One study found low DHEA-S levels in all 35 patients with hypopituitarism, implying that a DHEA-S concentration above 53.5 ug/dl (1.4 umol/l) makes the diagnosis of corticotropin deficiency extremely unlikely [17]. However, in the second study, some overlap of DHEA-S concentration in corticotropin deficient patients and those in normal subjects was found [18]. Partial corticotropin deficiency in some patients might explain these discrepant results.

Replacement of DHEA was shown to have positive effects on wellbeing and mood in patients with primary and secondary adrenal failure in several studies, although two recent studies did not find any effect of DHEA suppletion [19–23]. At present the diagnostic criteria for DHEA-insufficiency are unclear and treatment is hampered by pharmaceutically controlled preparations. Doses of 25–50 mg DHEA should be taken as one dose in the morning, aiming at the middle normal range for healthy young people. Until larger studies are completed, DHEA should be reserved for patients whose wellbeing is greatly impaired despite optimal glucocorticoid replacement.

Thyrotropin deficiency

Modern assays for TSH and for free thyroid hormones have significantly reduced the need for dynamic testing of the hypothalamo-pituitary-thyroid axis in patients with central hypopituitarism [24]. The diagnosis of thyrotropin deficiency should be made by serial free T4 measurements [25]. Not unusually, lowered free T4 levels with TSH concentrations within the reference range can be found. However, these serum TSH levels are "inappropriately" low in the presence of low free T4 levels and sometimes reflect secretion of biological inactive TSH.

Thyroxine replacement therapy is highly effective and safe. Importantly, corticotropin deficiency should be excluded before thyroxin therapy is started, in order not to provoke an addisonian crisis due to increased cortisol clearance. The thyroxin dose should be titrated aiming at restoration of FT4 levels in the upper part of the reference range, with usual doses of 1.5 μg/kg body weight. For the evaluation of the adequacy of thyroxin replacement therapy, several other clinical and biochemical indexes of thyroid hormone action have been evaluated, including heart rate, lipid profile, sex hormone-binding protein (SHBG), serum soluble interleukin-2 receptors and markers of bone turnover [26]. None of these parameters added much to the FT4 measurement. In primary hypothyroidism, a subgroup of patients reports persisting physical and mental complaints despite adequate thyroxine replacement. Adding T3 to the replacement therapy in these pa-

tients is not effective in improving physical functioning according to most studies [27,28]. In secondary hypothyroidism, no studies with T3 therapy have been performed yet, but a benefit seems unlikely in the light of the fore-mentioned studies in primary hypothyroidism.

There is some concern that long term iatrogenic hyperthyroidism, caused by oversupplementation, might have adverse effects on the cardiovascular system, in particular atrial fibrillation and bone mineral density, which can already be compromised in patients with coexisting hypogonadism and growth hormone deficiency [29].

Gonadotropin deficiency

Hypogonadism in premenopausal women is easy to diagnose because it leads to menstrual disturbances. Serum LH, FSH and estradiol concentrations can all be in the normal or low range, depending on the degree of deficiency. Hyperprolactinaemia also causes hypogonadism and must be excluded. Dynamic tests are of limited value and seldom used.

Estrogen deficiency requires replacement for the relief of symptoms (loss of libido, dyspareunia) and for the prevention of osteoporosis and premature cardiovascular disease. In premenopausal women, an oral contraceptive, containing 20–35 μg ethinyl oestradiol is an effective and often preferred form of replacement therapy. Alternatively, oral estrogen preparations (oestradiol valerate 2 mg or conjugated equine oestrogens 0.625–1.250 mg daily) given cyclically or continuously with a progestagen can be administered. Transdermal oestrogen supplementation has the advantage of reducing the dosage of GH therapy, explained by the first-pass effect.

Hypogonadotropic hypogonadism in male patients is shown by low testosterone concentrations with low or normal LH and FSH levels. Again, hyperprolactinaemia should be excluded, as well as low sex hormone binding globulin concentrations.

Testosterone substitution is necessary in all hypogonadal patients, because androgen deficiency causes slight anemia, changes in coagulation parameters, decreased bone density, muscle atrophy, regression of sexual function and alterations in mood and cognitive abilities. Androgen replacement comprises injectable forms of testosterone as well as implants, transdermal systems, sublingual, buccal and oral preparations. Transdermal systems provide the pharmacokinetic modality closest to natural diurnal variations in testosterone levels [30]. There is no universal agreement regarding target levels of replacement therapy, but most physicians aim for the mid — to upper normal range [31]. During treatment monitoring of testosterone levels, PSA and hematocrit is advised.

If fertility is desired, spermatogenesis can be initiated and maintained by gonadotropin therapy, conventionally in the form of human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG) or, more recently, purified or recombinant follicle stimulating hormone (FSH) [30]. Apart from this option, patients with disorders at the hypothalamic level can be stimulated with pulsatile gonadotropin-releasing hormone (GnRH). Both treatment modalities have to be administered on average for 7–10 months until pregnancy is achieved. In individual cases, treatment may be necessary for up to 46 months.

Growth Hormone deficiency

A number of criteria have been proposed for documentation of growth hormone deficiency using a variety of tests. A normal IGF-I concentration does not exclude the diagnosis of GH deficiency, as IGF-I levels are in the normal range in about one third of patients with GH deficiency, proven by GH provocative testing. Conversely, in a cohort of patients with 2 or 3 three other pituitary hormone deficiencies, growth hormone deficiency can be expected in more than 90 % of patients [32]. Therefore it has been argued that patients with an appropriate clinical history and either the presence of multiple pituitary hormone deficiencies or low serum IGF-I concentration do not require GH stimulation testing for the diagnosis of adult GHD [33]. However, in a substantial percentage of patients, and also demanded by many health care authorities, a GH stimulation test remains necessary. Patients should be receiving stable and adequate hormone replacement for other hormonal deficits before testing.

The insulin tolerance test (ITT) and the combination of growth-hormone-releasing hormone (GHRH, 1 μg/kg intravenously) and Arginine (0.5 g/kg intravenously) are reliable tests. Cut-off levels for severe GH deficiency are GH less than 3 μg/l for the ITT and GH less than 9 μg/l for the GHRH/Arginine test [34,35]. The ITT has been criticised for poor reproducibility and inconvenience, but currently remains the favourite test for the diagnosis of GH deficiency. Extravasation of arginine can cause full-thickness skin necrosis that requires serious surgical intervention with aesthetic and functional sequellea [36].

Recently, the GHRH/GHRP-6 stimulation test was validated for the diagnosis of adult GH deficiency. In this test, 1 μg/kg GHRH and 1 μg/kg GHRP-6 is given intravenously, with subsequent blood sampling at regular intervals for 120 minutes. An evoked GH concentration of larger than 15 ug/l accurately distinguishes between healthy and GH-deficient adults [37].

It is well known that obese subjects have a blunted GH response to any provocative stimulus. Therefore, body mass index should be considered when defining the diagnostic cut-off points in the assessment of GH deficiency [38].

All patients with documented severe growth hormone deficiency are eligible for GH replacement [39]. Several other factors can be taken into account in the decision to start GH therapy. Objective signs of GH deficiency are alterations in body composition such as an increased fat mass (mainly around the waist), low

muscle mass and strength and lowered bone mineral density. Subjective factors are an impaired sense of well-being mainly manifested by a lack of energy, fatigue, decreased physical mobility and a tendency towards social isolation.

Growth hormone therapy is started with a low dose (0.15–0.30 mg/day). The wide variation of the response to GH therapy (in terms of IGF-I generation) emphasises the need to titrate GH therapy individually. The dosage should be increased gradually on the basis of IGF-I levels and/or body composition measurements, over a period of several months [40]. Serum IGF-I reference ranges should be age and gender specific. Some have recommended targeting serum IGF-I to between the median and upper end of the reference range, while others prefer aiming at the lower end of the reference range, a more conservative and possibly safer approach [41]. Gender differences in the response to GH therapy have been well documented, with men showing a greater response in terms of IGF-I generation, especially compared to premenopausal, estrogen replete women [42]. This is also reflected by the observation that, with a starting dose of 0.27 mg/day, men reached serum IGF-I target values more rapidly (median 4 weeks) than women (median 8 weeks) [43]. Long-acting GH preparations are currently being developed, possibly requiring GH administration once every two weeks [44,45].

Several other parameters, apart from IGF-I and body composition measurement, have been assessed as an index for adequacy of GH treatment. Candidate biochemical markers include IGF-BP3, acid-labile subunit (ALS) and markers of bone turnover, but none of these parameters seem to be of additional value [40]. Free IGF-1 is another possible biochemical marker that needs further evaluation. Finally, the recognition of polymorphisms in the IGF-1 gene, and the impact of these polymorphisms on GH-mediated regulation of IGF-1 secretion might increase the understanding of individual GH responsiveness and optimal replacement therapy [46].

Data on the long-term effects of GH replacement therapy in adults have become available during the last years [47]. From these surveillance studies, it appears that GH therapy has significant, lasting effects on body composition and lipid profiles. No increase morbidity/mortality has been observed due to an increase of malignancies. However, safety issues concerning possible stimulation of tumour formation have not been resolved yet and survey studies are being continued.

Other Issues in the Management of Patients with Hypopituitarism

Interactions

There are several possible interactions of replacement therapy with multiple hormone preparations, of which some have clinical relevance. Oral but not transdermal administration of estrogen impairs the metabolic action of GH in the liver, causing a fall in IGF-I production and fat oxidation. This results in a loss of lean tissue and a gain of body fat in postmenopausal women and an impairment of GH effect in hypopituitary women on GH replacement. Estrogen affects GH action at the level of receptor expression and signalling, and the molecular basis has recently been elucidated. Practically, GH dose should be reduced in perimenopausal women after cessation of oestrogen replacement therapy. Conversely, testosterone has a tendency to increase IGF-I levels. Male patients should receive stable testosterone therapy before assessing GH status or starting GH therapy.

Estrogen therapy was also shown to increase the need for thyroxine in hypothyroid patients, explained by a rise in thyroxin- binding hormone globulin concentration [48].

Another interaction is the effect of GH therapy which reduces the availability of administered cortisone acetate [49]. GH has been shown to inhibit the activity of 11ß-hydroxysteroid dehydrogenase type 1, the enzyme converting inactive cortisone to cortisol [50]. Therefore, in patients taking cortisone acetate, serum cortisol assessments should be done after the institution of GH therapy to ensure that glucocorticoid therapy remains adequate.

Finally, GH activates thyroxine deiodination, resulting in a slight decrease in free thyroxin concentration and a simultaneous increase in tri-iodothyronine [51]. However, these mild and transient changes generally do not require adjustment of the thyroxin replacement dose.

Pregnancy

In women with hypopituitarism, pregnancy needs specific adjustments of hormone replacement therapy. During pregnancy, a physiological gradual rise of cortisol binding globulin level and free cortisol concentration occurs [52]. Therefore, during the third trimester, hydrocortisone replacement should be increased by 50%. Peripartum a stress-dose of hydrocortisone should be administered. With increasing thyroid binding hormone levels, thyroid hormone supplementation should also be increased by approximately 30%.

Metabolic syndrome

Patients with hypopituitarism develop a phenotype similar to the metabolic syndrome with central obesity and diabetes. Hypopituitarism may even be accompanied by progressive non-alcoholic fatty liver disease [53].

The high prevalence of obesity and cardiovascular risk factors in hypopituitarism affirms the need for effective treatment of hypertension, lipid disorders and weight loss intervention in these patients. A recent study evaluated the combined effect of sibutramine, diet, and exercise in obese hypopituitary patients [54]. In this study, almost all patients achieved at least 5% weight loss, and 60% lost more than 10% weight within 11 months. However, the long-term effects on cardio-

vascular disease as well as on mortality need to be established.

Reassessment of pituitary function

In patients on dopaminergic therapy for a prolactinoma, recovery of pituitary function is observed in approximately two-thirds of cases [55,56]. Therefore, reassessment of pituitary function in these patients is mandatory to prevent unnecessary replacement therapy.

Hypopituitarism in patients presenting with a pituitary adenoma is generally considered to be permanent. However, is has been suggested that in a significant number of patients, pituitary function recovers after transsphenoidal adenomectomy [57]. Restoring normal intrasellar pressure and subsequently normalisation of portal blood flow might explain this potential recovery of pituitary function [58]. In practice it seems prudent to reassess pituitary function 2 to 3 months after transsphenoidal surgery.

Many children with isolated idiopathic growth hormone deficiency will produce normal GH responses if retested at adult height [59]. Even in patients with severe growth hormone deficiency in childhood secondary to irradiation, about one third of patients will not fulfill the biochemical criteria for GH replacement in adulthood [60]. Patients with multiple pituitary hormone deficits are more likely to have ongoing growth hormone deficiency [61]. According to a recent guideline, all patients with childhood growth hormone deficiency should be reassessed at final height. After discontinuing growth hormone therapy for at least one month, IGF-I measurement and/or a GH stimulation test should be performed in order to assess the need for adult growth hormone replacement therapy [59].

Quality of life

Several studies have documented a reduced quality of life in patients treated for hypopituitarism, due to persisting psychological and physical impairments [62,63]. It is likely that these complaints are, at least in part, caused by intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion [64]. Most studies have focussed on the beneficial effect of growth hormone replacement therapy on quality of life. However, even with long term growth hormone thrapy, residual impairments are present [65].

Hypopituitarism has also important socioeconomic effects, with double annual health costs compared to the normal population [66].

Conclusions

Diagnosis and treatment of patients with hypopituitarism needs careful clinical evaluation and individual optimization. There are several outstanding questions, including the effects of DHEA-supplementation and the long term effects of GH therapy. Future efforts should aim at further development of tools to assess the optimal hormone replacement therapy for every patient. An individualized, physiological approach could possibly help to reach the ultimate goal: a normal quantity and quality of a healthy life for these patients.

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