Introduction

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis is an important regulator of growth and development during childhood and adolescence, but it also regulates body composition, metabolism and aerobic capacity throughout life. With the introduction of recombinant DNA technology, availability of recombinant human GH (rhGH) allowed adult with severe GH deficiency (GHD) to receive replacement therapy, which has permitted an explosion of interest in understanding the role of this hormone throughout the human lifespan. rhGH replacement therapy in GHD adults has been shown to increase muscle mass, muscle strength and bone mass, to improve the quality of life and to have a beneficial effect on the lipid profile (Jørgensen et al., 1989; Salomon et al., 1989; Bengtsson et al., 1993). An important decrease in fat mass was also observed. These clinical observations subsequently led to the definition of the clinical syndrome of adult GHD (Cuneo et al., 1996), although their components were not sufficiently distinctive since they are normal accompaniment of ageing. Consequently, the diagnosis of adult GHD requires specific biochemical criteria (Shalet et al., 1998).
GH secretion status can be assessed by measurement of serum IGF-1, the most sensitive marker of GH action. Since 30–40% of patients with severe GHD have serum IGF-1 concentrations in the lower part of the normal age-related reference range, the reliability of IGF-1 measurement for the diagnosis of GHD has been questioned (Hoffman et al., 1994). A variety of serum GH cut-off points following GH-provocative stimuli have been proposed to define adult GHD (Thorner et al., 1995; Growth Hormone Research Society, 2000).

Circulating GH levels show a significant decline with ageing in both sexes (Finkelstein et al., 1972; Zadik et al., 1985). The age-dependent decline in GH secretion is paralleled by changes in body composition, with a decrease in lean body mass and an increase in total body fat (especially intra-abdominal fat) (Rudman, 1985). GH secretory patterns in humans are sexually dimorphic, and the effect of age on spontaneous GH secretion is less pronounced in premenopausal women, since it remains relatively stable until after the menopause, when GH levels significantly fall (Ho et al., 1987; Winer et al., 1990).

Clinical observations indicate that estrogens are involved in the determination of body fat distribution, with greater accumulation of subcutaneous fat in the gluteofemoral region and less visceral fat mass than in men. With the menopause, women tend to accumulate visceral fat. This phenomenon can be prevented by hormone replacement therapy (HRT). Estrogens are also important modulators of GH secretion, and estrogen deficiency may contribute, together with the ageing-related GH decline, to increase visceral fat deposition, with its metabolic consequences.

This article (i) provides a brief overview of the different regulators of GH secretion, (ii) reviews the mechanisms involved in age-related changes in GH concentrations, with particular emphasis on the inter-relationships between menopause and GH, and (iii) discusses the interventions aimed at the restoration of GH and IGF-1 circulating levels.

### Methods

We searched the PubMed database covering the period 1972–2008. The following key words were selected: ‘Growth Hormone’, ‘Somatopause’ and ‘Menopause’. Articles were limited to studies in humans and to reports published in English. We also included additional papers identified through hand searches. Meeting proceedings were not included. We selected 234 relevant citations from PubMed database. We also included three chapters from books from our personal library. Methods for selecting and synthesizing the data were based on our personal experience.

### Factors regulating GH secretion

#### Neuroendocrine control of GH

GH synthesis and its pulsatile release by the anterior pituitary gland are regulated by the hypothalamic neuropeptides GH-releasing hormone (GHRH), somatotropin release-inhibiting factor (somatostatin) and by the recently discovered gastric hormone ghrelin (Smith et al., 2005). These neurohormones are subject to modulation by a host of neurotransmitters, other hypothalamic neuropeptides and peripheral metabolic signals and are the final mediators of GH secretion (Delitala et al., 1988; Delitala, 1989; Giustina and Veldhuis, 1998).

GHRH, synthesized in the arcuate and ventromedial nuclei, stimulates both GH synthesis and release (Ling et al., 1984). Endogenous GHRH is the principal regulator of GH pulse. GH and GHRH pulses in the pituitary-portal blood in conscious experimental animals are directly correlated (Plotsky and Vale, 1985). In humans, competitive GHRH antagonists severely impair spontaneous pulsatile GH secretion (Jaffe et al., 1993) and inhibit acute GH response to a variety of pharmacological GH-releasing stimuli (Jaffe et al., 1996; Pandya et al., 1998).

Somatostatin, arising from the periventricular and paraventricular nuclei, blocks exocytotic release of GH without affecting its synthesis, but powerfully antagonizes the mitogenic effect of GHRH on somatotrophs via somatostatinergic receptor types 2 and 5 (Billestrup et al., 1986). Somatostatin modulates GH secretory burst frequency and mass (Calabresi et al., 1996) and suppresses GH release, both spontaneous and induced by all known GH secretagogues (GHSs). Several lines of evidence led to the hypothesis that a GH peak occurs when a GHRH peak coincides with a somatostatin nadir (Tannenbaum and Ling, 1984; Hindmarsh et al., 1991). Either the ending of an endogenous somatostatin pulse or the discontinuing of exogenous somatostatin administration elicits a rebound GH rise and significantly augments GH response to GHRH and, possibly, to endogenous GHRH pulse, thus modulating the amplitude of GH pulse (Dickerman et al., 1993).

Multiple negative feedback loops autoregulate the GH axis (Fig. 1). Somatostatin auto-inhibits its own release (Peterfreund and Vale, 1984), and GHRH inhibits its own release by increasing somatostatin release (Yamauchi et al., 1991). GH also auto-regulates its own ‘release’ by enhancing somatostatin synthesis and release (Berelowitz et al., 1981). Finally, IGF-1 inhibits GH synthesis and release (Yamashita and Melmed, 1986; Hartman et al., 1993).

Ghrelin, a 28 amino acid peptide of a primarily gastric origin, is present in the arcuate nuclei of the hypothalamus (Mozid et al., 2003) and in the anterior pituitary gland (somatotrophs, thyrotrophs and lactotrophs), where acts in a paracrine fashion (Smith et al., 2005). Ghrelin stimulates GH release directly from somatotrophs, although its action appears to be more potent when applied to the combined hypothalamic–pituitary units in vitro, thus suggesting the participation of an intact GHRH system in its action (Bowers et al., 1991). The production of ghrelin declines during ageing in both rodents and humans (Liu et al., 2002; Rigamonti et al., 2002). To date, the physiological role of ghrelin in human GH secretion is still unclear.

A number of central neurotransmitter and neuropeptides are involved in GH regulation. Data obtained in experimental animals and humans indicate that they act at the hypothalamic level via GHRH and somatostatinergic neurons.

Here, only a brief mention of the relevance of these compounds in the neuroendocrine control of human GH secretion is given. The importance of α-adrenergic mechanisms in GH secretion was substantiated by the finding that the α2-agonist clonidine given acutely induced a clear-cut rise in plasma GH (Gil-Ad et al., 1991). The drug is still widely used as a diagnostic test in pediatric endocrinology. In contrast, the role of α1-adrenoceptors seems to be an inhibitory one, since methoxamine, an α1-agonist, significantly suppresses basal GH levels in normal adults (‘personal data’). The inhibitory role of β-receptor activation on GH secretion has been known.
for many years. Whereas activation of β-adrenoreceptors inhibits GH secretion, β-blocking agents enhance the GH response to many GH-stimulating agents (Ghigo et al., 1990a). The potentiating effect of β-blockers is probably achieved through suppression of inhibitory influences mediated by β-adrenoreceptors, on which the synaptically released catecholamines act (Muller et al., 1999).

Dopaminergic pathways are also involved in the control of GH secretion, although their role appears to be largely ancillary. Direct dopamine agonists such as apomorphine, the ergot derivatives bromocriptine, lisuride and cabergoline, or indirect dopamine agonists such as amphetamine or methylphenidate all cause acute GH secretion (Vance et al., 1987).

Evidences that cholinergic transmission is involved in GH regulation accumulated from more recent human studies demonstrating that antagonists of cholinergic muscarinic receptors completely blocked basal as well stimulated GH secretion (Delitala et al., 1982; Delitala et al., 1983a, b). Moreover, pyridostigmine, a cholinesterase inhibitor, stimulated basal GH secretion and enhanced the GH response to many secretagogues. The available data suggest that cholinergic modulation on GH secretion is mediated by somatostatin, in keeping with experimental evidences obtained in rodents (Muller et al., 1999). The premedication with pyridostigmine (the drug inhibits somatostatin release through an enhanced hypothalamic cholinergic tone) is currently the most reliable test (together with GHRH) to assess the GH secretory status in man, since it reduces the wide inter- and intra-individual variability of GH secretion (Ghigo et al., 1996).

The role of serotonin and histamine pathways in GH regulation is less clear in man, where different drugs that either inhibit or potentiate the functional activity of these neurotransmitters gave conflicting results (Muller et al., 1999). Collectively, the available evidence suggests a stimulatory role of histamine and serotonin on GH secretion, although the physiological importance of these hypothalamic systems is not completely clear.

Opiates and endogenous opioids stimulate GH secretion in animals. In humans, the administration of an enkephalin analogue (an agonist of mu receptors) proved to be a strong GH releaser. The effect of this compound is specific, being completely abolished by a pretreatment with naloxone (Stubbs et al., 1978). With regard to the potential modulatory action of brain neurotransmitters, the GH secretion induced by the enkephalin analogue was abolished by muscarinic receptor antagonists, suggesting the participation of somatostatin in this mechanism (Delitala et al., 1982).

Galanin, a 29 amino acid neuropeptide, is highly concentrated in the hypothalamus, and partly co-localized with GHRH neurons in the median eminence (Muller et al., 1999). In addition to eliciting GH secretion when given alone, galanine enhanced the GH response to GHRH in healthy humans suggesting a somatostatin-mediated effect (Giustina et al., 1994). Arginine is the most striking stimulating hormone for GH.
amino acid for GH secretion. The action of arginine appears to be exerted via suppression of hypothalamic somatostatin tone, as suggested by neuropharmacological studies (Ghigo et al., 1991). Although the effect of arginine on GH secretion may depend on its conversion to nitric oxide (NO), a gaseous neurotransmitter, its effect does not appear to be linked to NO production, since other NO donors did not modify GH secretion in humans (Korbonits et al., 1996).

The effect of these substances on human GH secretion is summarized in Table I.

### Table I  Regulators of GH secretion in humans

<table>
<thead>
<tr>
<th>Effector</th>
<th>Increases GH</th>
<th>Reduces GH</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>α1-Adrenergic receptors</td>
<td>✓</td>
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<td>α2-Adrenergic receptors</td>
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<td>β-Adrenergic receptors</td>
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<td>Amino acids</td>
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<td>Bombesin</td>
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<td>Dopamine</td>
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<td>Muscarinic receptors</td>
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<td>Cortisol</td>
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<tr>
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<td>Increases amplitude</td>
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<td>Estrogen</td>
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<td>Exercise</td>
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<td>Neuropeptide Y</td>
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<td>Inversely correlated with GH</td>
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<tr>
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<td>Thyrotrpin</td>
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The GH–IGF-1 system

IGF-1 is the best-characterized GH-dependent peptide, and GH is the major hormonal determinant of its plasma concentrations (for a detailed review, see Clemmons, 2006), although nutrition, possibly the immune system, and other factors (i.e. thyroid hormones) play an additional role (Chenmasek et al., 1983). IGF-1 is produced by a multitude of cell types, which support the concept of a paracrine/autocrine mode of its action. Most IGF-1 results from hepatic ‘synthesis and release’, but the liver is not the target organ since it possesses few IGF-1 receptors.

IGF-1 circulates bound to high-affinity insulin-like growth factor-binding protein (IGFBP). There are six IGFBPs in serum, and their concentrations fluctuate in a variety of clinical conditions (see Clemmons, 2006 for review). In general, IGFBP-3 and -5 are regulated by GH in a manner similar to IGF-1. IGFBP-3 is by far the most abundant binding protein in the circulation. This glycoprotein binds IGF-1 and another GH-dependent glycoprotein, the so-called acid-labile subunit (ALS), which is synthesized almost exclusively in liver and fat (Boisclair et al., 2000). Within the intravascular space, ALS, IGFBP-3 and IGF-1 form a large (~140 kDa) ternary complex which prolongs IGF-1 half-life from 6 min to ~16 h. This ternary complex cannot freely cross capillary barriers and is therefore excluded from renal filtration (Kupfer et al., 1993). The most important functions of these binding proteins include transporting the IGF-1 in the vasculature, modulating its access to the extra-vascular space and regulating the access to receptor.

### Nutritional status

The nutritional status is an important determinant of serum IGF-1 concentrations. Fasting results in a significant reduction in serum IGF-1, and it blunts the IGF-1 response to GH administration (Underwood et al., 1994). During fasting and re-feeding, the change in IGF-1 levels correlates with the change in nitrogen balance (Clemmons and Underwood, 1991). Chronic malnutrition, in particular lack of carbohydrates and amino acids, causes a marked reduction of IGF-1 plasma levels (Phillips and Unterman, 1984). Catabolic conditions, such as hepatic failure, renal failure, inflammatory bowel disease and malabsorption syndromes, are associated with low plasma IGF-1 concentrations (Tönshoff et al., 1995; Mock, 1986). Similarly, patients with poorly controlled type 1 diabetes mellitus have low IGF-1 levels that normalize with adequate insulin therapy (Bereket et al., 1995). These changes are probably due to the action of insulin at the liver level, although nutritional improvements during insulin therapy likely contribute to the change in IGF-1 plasma levels.

Another variable that can affect plasma IGF-1 concentrations is the stress-induced resistance to GH. Cortisol attenuates GH stimulation of IGF-1 (Lang et al., 2002), and several cytokines such as interleukin (IL)-1 and tumour necrosis factor-α (TNF-α) inhibit GH-stimulated IGF-1 synthesis and GH receptor (GHR) mRNA levels in liver cells (Wolf et al., 1996).

### Sleep

In normal subjects, spontaneous GH secretion is maximal at night. GH secretion is associated with sleep, and the maximal GH levels occur at the onset or recurrence of Stages 3 and 4 of sleep (Holl et al., 1991). Mean GH secretion rates, calculated by deconvolution analysis, are 4-fold higher during Stages 3 and 4 of sleep compared with periods
of rapid eye movement sleep or Stages 0, 1 and 2. The neuroenдо-
crine mechanisms of nocturnal GH augmentation are not known, although hypothalamic GHRH release is likely a major contributing
component (Van Cauter et al., 1992).

**Sexual dimorphism**

The gender dimorphism of GH secretion suggests that androgens and
estrogens may play different roles in the regulation of somatotroph
axis. Young women have ~24-h integrated serum GH concentrations
50% higher than young men, due to higher incremental and maximal
GH peak amplitudes, but show no significant difference in GH half-life,
interpulse times or pulse frequency (Zadik et al., 1985; Van den Berg
et al., 1996). During the late follicular phase of the menstrual cycle,
GH pulse amplitude and integrated GH concentrations are approxi-
ately doubled compared with the early follicular and mid-luteal
phases (Faria et al., 1992; Ovesen et al., 1998). Human data suggest
that GHRH is tonically secreted during the daytime in women but
not in men. The female pattern of GHRH secretion is characterized
by GHRH pulses superimposed on tonically elevated GHRH levels
during the day, whereas the male pattern of GHRH consists of
acute periodic GHRH bursts arising from a near-zero GHRH back-
ground (Veldhuis, 1996; Jessup et al., 2003).

Such gender difference is an estrogen-related, but not androgen-
related, phenomenon, since only aromatizable androgens increase
GH pulse amplitude in boys (Veldhuis et al., 1997).

**Body composition**

The association between adiposity and diminished response to stimu-
lated GH secretion has been studied for many years. The GH
response to GHRH and other GHSs is reduced in obesity; either
fasting or weight loss tends to restore the GH response (Williams
et al., 1984; Kelijman and Frohman, 1988).

The mechanisms through which GH secretion is reduced in obesity
are not completely understood. The increased insulin concentrations
associated with obesity might inhibit GH secretion, perhaps by influen-
cing IGF-I and IGFBP concentrations, thereby allowing IGF-I levels to
rise and exert an inhibitory effect on GH secretion (Hartman
et al., 1993). Elevation of free fatty acid (FFA) levels, associated with
obesity, could suppress GH secretion (Imaki et al., 1985) possibly
acting at the pituitary level. Interestingly, the nicotinic acid analogue
acipimox, which reduces plasma FFA by blocking their secretion
from adipocytes, tends to normalize GH secretion in obese subjects
(Pontiroli et al., 1990; Cordido et al., 1996). The mechanism of
decreased GH concentrations in obesity has also been ascribed to
an increased hypothalamic somatostatinergic tone, since pyridostig-
mine, a cholinesterase inhibitor, is able to reverse this by suppressing
somatostatin release into portal circulation. However, this cannot be
the full explanation, as pyridostigmine and arginine (compounds that
decrease somatostatinergic tone) were not able to completely
reverse the reduced GH secretion of obesity, even when administered
together with GHRH and the GHS GH-releasing peptide (GHRP)-6
(His-γ-Trp-Ala-Trp-O-Phe-Lys-NH₂) (Ghigo et al., 1992; Ghigo et al.,
1994).

The relationship between measures of regional fat distribution and
the GH/IGF-I axis should be considered in this context. The degree
of GH attenuation correlates with the amount of total and visceral fat
(Rudman, 1985; Rasmussen et al., 1995; Vahl et al., 1997; Classy et al.,
2001). Intra-abdominal fat, as measured by computed tomography, is
inversely related to serum IGF-I concentrations in obesity, thus
suggesting that visceral fat may be inversely related to the 24-h GH
secretion in both sexes. Multiple linear regression analysis revealed
that intra-abdominal fat is the major determinant of GH secretion in
healthy obese adults. Also, intra-abdominal fat was more important
than sex in predicting GH secretion (Vahl et al., 1997).

Since GH replacement therapy has been shown to decrease visceral
fat in GHD patients (Jørgensen et al., 1989; Salomon et al., 1989;
Bengtsson et al., 1993; Attanasio et al., 2002), the reduced GH
output observed in patients with truncorial obesity might contribute to
the metabolic consequences of this clinical condition. Thus,
increased central adiposity can be a cause of reduced GH secretion
as well as its consequence.

**Physical exercise**

Acute physical exercise is a powerful stimulus to secretion of GH,
which occurs ~15 min from the start of exercise, peaks at the end
of the exercise (or shortly after) and remained elevated up to
120 min after exercise (Sutton and Lazarus, 1976). The GH rise
may vary between subjects depending on sex (Giannoulis et al.,
2005), age (Holt et al., 2001), body composition (Kanaley
et al., 1999), intensity and duration of acute exercise (Pritzlaff
et al., 1999; Wideman et al., 2006), muscle mass used during exercise and training
status (Hagberg et al., 1988; Holt et al., 2001). Anaerobic exercise
causes a larger secretion of GH than aerobic exercise of the same
duration (Vanhelder et al., 1984). A linear dose–response relationship
between exercise intensity and the increase in the mass of GH
secreted per pulse (with no change in pulse frequency or the half-life
of elimination) was demonstrated (Pritzlaff et al., 1999; Pritzlaff-Ray
et al., 2002). The absolute GH secretion is greater in premenopausal
women, but the increments from baseline were similar in men and
women. Interestingly, the GH response to exercise seems to be deter-
mined by age and physical fitness rather than by increased adiposity
(Holt et al., 2001). It is likely, therefore, that improving physical
fitness by exercise training can enhance GH secretion through the day.

**Ageing and the endocrine system**

The menopause

In women, the most dramatic change in the activity of the endocrine
system is the menopause. This decline in ovarian activity is
accompanied by vasomotor reactions, depression and changes in
body composition with a decrease in lean mass and an increase in
body fat. A high incidence of osteoporotic fractures, cardiovascular
diseases and cognitive impairment are other features of estrogen
deficiency (Santoro and Chervenak, 2004).

The adrenopause

The second endocrine system whose function declines and that
demonstrates an age-related change is the adrenal gland. After reaching
the intra-individual maximum levels during the third decade of life,
dehydroepiandrosterone sulphate (DHEAS) steadily decline down to
10–20% of its maximum level by around the age of 70 years
(Orentreich et al., 1984; Orentreich et al., 1992). This decline has
been termed adrenopause, in spite of the fact that cortisol secretion does not significantly change with age. There is a clear sex difference in DHEAS levels with lower concentrations in women compared with men (Orentreich et al., 1984). Adrenopause is independent of menopause and occurs in both sexes as a gradual process at similar age. The reduced DHEAS/cortisol ratio associated with ageing might contribute to the prevailing catabolic action of cortisol, although the available evidences do not justify dehydroepiandrosterone supplementation in all elderly subjects (Arlt, 2004).

The somatopause

The third endocrine axis that gradually declines during physiological ageing is the GH/IGF-1 axis. Shortly after birth GH secretion is high and rapidly falls during the neonatal period. During puberty, GH secretion increases up to 3-fold, and the mass of GH secreted per burst increases 2- to 10-fold (Martha et al., 1989, 1992). This phenomenon results in an important increase in serum IGF-1 levels, thereby modulating linear growth. However, genetic factors define final height since there is no difference in mean spontaneous or stimulated GH secretion between tall and short normal young adults. Serum IGF-1 also does not differ between the two groups (Trainor et al., 1999). Several studies have shown that human ageing is associated with declining activity of the GH/IGF-1 axis (Finkelstein et al., 1972; Rudman, 1985; Zadik et al., 1985). Together with the many catabolic changes observed in ageing, these biochemical evidences led to coin the term somatopause to indicate the potential link between age-related decline in GH and frailty in older subjects. The decline in GH secretion begins, in both sexes, during the third decade and reaches a plateau during the seventh decade (Ho and Hoffman, 1993). Deconvolution analysis of 24-h GH profiles showed, by using a highly sensitive assay, that GH secretion falls by 14% per decade of life (Iranmanesh et al., 1991). This phenomenon is determined by a reduction in GH secretory burst frequency and in the daily secretory rate. Body mass index was a major negative determinant of GH secretory burst amplitude (Giustina and Veldhuis, 1998). Following the fifth decade, a reduction of sleep-related GH secretion is also observed. This is probably related to changes in sleep pattern associated with increasing age (Kamel and Gammack, 2006). The negative impact of ageing on GH secretion is ~2-fold more evident in men than in premenopausal women of similar age (Weltman et al., 1999). Twenty-four hour mean serum GH concentrations in premenopausal women remain relatively stable until the menopause, when these gender differences disappear. The age-related decline of GH secretion is coupled with a reduction of both IGF-1 and its binding protein IGFBP-3 (Corpas et al., 1993).

The mechanisms underlying the reduced GH secretion are not clear, although an unbalanced secretion of hypothalamic GHRH and somatostatin into the portal circulation might be the cause. The pituitary remains responsive to direct stimulation by secretagogues, although some authors found a reduction in GH response to GHRH with increasing age (Lang et al., 1987; Russell-Aulet et al., 2001). In studies where some inhibitory influences on GH secretion were removed, the acute GH response to GHRH is well maintained in old age. Co-administration of compounds that are believed to suppress somatostatin, such as arginine, can restore the GH response in elderly subjects to levels similar to those observed in young adults (Ghigo et al., 1990b). An age-related decline in pituitary GH reserve cannot be totally excluded, since the normal GH peak observed in these studies might be inappropriate to the low level of circulating IGF-1. Thus, the available data suggest that the effect of age upon spontaneous and stimulated GH secretion probably include an increase in somatostatinergic tone, although a decline in GHRH (or other stimulating factors) may participate to this process. The former could be due to the hypothalamic cholinergic hypoactivity that has been described in ageing (Gibson et al., 1981).

Changes in body composition in the elderly

The age-dependent decrease in GH levels is paralleled by changes in body composition similar to those seen in people with GHD. Muscle mass falls by 1-1.5% from about age of 40 years onwards (Young, 1988; Janssen et al., 2000). Similarly, muscle fibres cross-sectional area and strength do not change significantly until around age 45 (Lexell et al., 1986; Tseng et al., 1995), whereas in healthy subjects aged 65–89 years strength falls by 1–2% per year (Skelton et al., 1994). The aetiology of the age-dependent loss of muscle mass and function includes a variety of factors: these include decreased level of physical activity (Westerterp, 2000), reduction in dietary protein and malnutrition (Young, 1990), and loss of α-motor neurons (Brown, 1972). An increase in catabolic cytokines (Roubenoff et al., 1998; Argilés et al., 2005), together with changes in Ca²⁺ and K⁺ ion channels, may also be involved in the age-related decline in muscle strength (Delbono, 2002). When reaching the eighth decade, men have lost ~7 kg and women have lost ~3.8 kg of muscle mass (Blum et al., 2003). The reduction in muscle mass which occurs in normal ageing is coupled with an increase in fat mass; this increase in fat mass (predominantly intra-abdominal) is associated with increased cardiovascular risk factors and is negatively correlated with 24-h GH secretion (Clasey et al., 2001).

Adipose tissue has long been considered to be an inert reservoir, storing calories as triglycerides. It then became apparent that white adipose tissue (adipocytes together with stromal vascular cells) is a highly active metabolic and endocrine organ, whose functions are not only to provide energy during food deprivation, but also to release many endocrine and paracrine factors (commonly referred as adipokines) (Kershaw and Flier, 2004; Trujillo and Scherer, 2006). So far, many adipocyte-derived signals have been identified, and significant progresses have been made in understanding their specific functions (Table II). The important endocrine function of adipocytes is emphasized by the adverse metabolic consequences of dysregulation of adipose tissue mass. It is now well accepted that adipose tissue excess, particularly in the visceral compartment, is associated with insulin resistance, diabetes, hypertension, prothrombotic and pro-inflammatory states, and cardiovascular diseases (Hotamisligil et al., 1993; Katsuki et al., 1998; Capaccio, 2001; Alhaud et al., 2002; Mertens and Van Gaal, 2002; Engeli et al., 2003; Fernández-Real and Ricart, 2003; Goossens et al., 2003; Juhan-Vague et al., 2003; Juge-Aubry et al., 2005) (Fig. 2). Even though each adipocyte produces a small quantity of adipokines, when adipose mass expands (as a result of increasing size of fat cells and proliferation of pre-adipocytes), the sum of adipokines impacts on multiple body functions. Adipokines act both locally and distally through autocrine, paracrine and endocrine effects. Thus, using adipokines as one of the major
**Table II** Metabolic effects of the principal cytokines and enzymatic activities in human adipocytes

<table>
<thead>
<tr>
<th>Cytokine/Enzyme</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>Improves insulin sensitivity. Anti-atherogenic properties</td>
</tr>
<tr>
<td>Adipsin</td>
<td>Stimulates triglyceride storage in adipose tissue, inhibits lipolysis</td>
</tr>
<tr>
<td>Aromatase</td>
<td>Mediates the conversion of androstenedione to estrone, and estrone to estradiol</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Inhibits adipogenesis, increases circulating FFA, decreases adiponectin secretion, increases hepatic synthesis of FFA and cholesterol, stimulates production of acute phase protein</td>
</tr>
<tr>
<td>Leptin</td>
<td>Starvation signal. Stimulates lipolysis, inhibits lipogenesis, improves insulin sensitivity. Angiogenic activity</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor (PAI)-1</td>
<td>Inhibits plasminogen activators and fibrinolytic activity</td>
</tr>
<tr>
<td>Renin–angiotensin system</td>
<td>Significantly correlates with blood pressure; stimulates differentiation of pre-adipocytes. Increases hepatic gluconeogenesis and glycogenolysis</td>
</tr>
<tr>
<td>Resistin</td>
<td>Controversial effects on glucose metabolism in humans</td>
</tr>
<tr>
<td>Tumour necrosis factor-α</td>
<td>Impairs insulin signalling, stimulates release of FFA by adipocytes, decreases adiponectin secretion</td>
</tr>
<tr>
<td>11β-HSD</td>
<td>Regenerates cortisol from cortisone</td>
</tr>
<tr>
<td>17β-HSD</td>
<td>Converts androstenedione to testosterone, and estrone to estradiol</td>
</tr>
</tbody>
</table>

FFA, free fatty acid.

**Figure 2** Highly expressed endocrine activities in adipocytes.
Adipokines mediate important crosstalk between insulin-sensitive tissues. Excessive production of ILs and TNF-α induces insulin resistance, whereas increased activity of renin–angiotensin system and plasminogen activator inhibitor (PAI)-1 favours endothelial dysfunction, hypertension and thrombosis. Leptin regulates energy balance and exerts an insulin-sensitizing effect. Adiponectin exerts an anti-atherogenic effect and increases insulin action at target tissues. The role of resistin on insulin resistance is not clear in humans. Adipose tissue mediates the conversion of androgens to estrogens and regenerates metabolically active cortisol from cortisone.
communication tool, adipocytes and stromal cells affect a large number of other tissues and organs, and participate in appetite control, energy balance, blood pressure regulation, lipid metabolism, angiogenesis and haemostasis. The implication of these findings is emphasized by the adverse metabolic consequence of dysregulation of adipose tissue mass in the pathogenesis of obesity-related disorders.

Adipose tissue also expresses a variety of enzymes for activation, interconversion and inactivation of steroid hormones. Cytochrome P450 aromatase mediates the conversion of androgens to estrogens (androstenedione to estrone, and testosterone to estradiol). 17β-Hydroxysteroid dehydrogenase (17β-HSD) converts weak androgens and estrogens to their more potent counterparts (androstenedione to testosterone, and estrone to estradiol). The ratio of 17β-HSD to P450 aromatase is positively correlated with central obesity, indicating an increased local androgen production in visceral adiposity (Bélanger et al., 2002; Meseguer et al., 2002). Given the mass of adipose tissue, the contribution of adipose tissue to the whole-body steroid metabolism is important, with adipose tissue contributing up to 100% of circulating estrogen in post-menopausal women and 50% of circulating testosterone in premenopausal women (Bélanger et al., 2002; Meseguer et al., 2002).

It is well known that sex steroid hormones are major determinants of body fat distribution. There is a gender dimorphism in body fat distribution, because normally menstruating women have a greater accumulation of subcutaneous fat in the gluteal and femoral regions, whereas men have about twice as much visceral adipose tissue than premenopausal women (Enzi et al., 1986). This is due to the higher lipoprotein lipase (LPL) activity in femoral than in abdominal fat (Arner et al., 1991), whereas the catecholamine-induced rate of FFA mobilization from visceral fat is lower in women than in men (Lönqvist et al., 1997). Omental adipocytes from post-menopausal women are larger and have higher LPL activity compared with those of premenopausal women (Tchernof et al., 2004), reflecting a shift towards visceral fat storage. It has been reported that in women visceral obesity is associated with elevated levels of testosterone and a reduction in sex hormone-binding globulin (Glass, 1989).

Visceral fat also shows a high density of androgen receptors. Estrogens down-regulate the density of this receptor, thereby protecting the visceral adipose tissue from androgenic effects (Haarbo et al., 1991; Björntorp, 1997). Therefore, when estrogen levels become sufficiently low, visceral fat accumulation may occur. It is also likely that hormones other than androgens and estrogens may contribute to the distribution of body fat to visceral adipose tissue. The elevated cortisol production in visceral obesity (see below) and the low GH level in that condition can increase visceral fat content. Since progesterone competes with cortisol binding to the glucocorticoid receptor, progesterone may therefore protect from the increased cortisol production by visceral adipocytes. This android pattern of body fat distribution, together with estrogen deficiency, appears to be related to the higher prevalence of dyslipidaemia, hypertension, diabetes and cardiovascular diseases in post-menopausal women compared with premenopausal women.

Adipose tissue is also involved in the regulation of glucocorticoid metabolism. This tissue-specific glucocorticoid metabolism is primarily determined by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), which catalyses the interconversion of active cortisol from inert cortisone. 11β-HSD-1 is highly expressed in adipose tissue, particularly in visceral adipose tissue, where regeneration of metabolically active cortisol from cortisone occurs (Paulsen et al., 2007). Several observations have associated 11β-HSD-1 dysregulation with a variety of medical conditions including obesity, diabetes hypertension, cardiovascular diseases and polycystic ovarian syndrome (Bujańska et al., 1997; Wake et al., 2003; Valsamakis et al., 2004).

GH plays an important role in the peripheral interconversion of cortisol and cortisone through its IGF-1-mediated inhibitory effect on 11β-HSD-1 expression and activity (Agha and Monson, 2007). These interactions may at least in part explain the phenotype of GHD and the effects of GH treatment of this condition on body composition.

Interventions aimed at the restoration of GH and IGF-1 circulating levels

GH supplementation in post-menopausal women

The rationale for the (potential) use of rhGH as intervention in ageing is based on the observation that there is an age-dependent decline in circulating GH and IGF-1, and that the senescent changes in body composition and metabolic parameters are similar to those observed in adult with GHD. The beneficial effects of GH replacement have been documented in GHD adults: redistribution of body mass, decrease in visceral fat, increase in lean body mass and exercise capacity, improvement in lipoprotein profile, increase in bone formation, improvement in quality of life and psychological well-being. All these effects are the expected beneficial results of rhGH treatment in post-menopausal women, as well as in elderly men (Johannsson, 2007).

Many studies have correlated cross-sectional data with serum IGF-1 levels in ageing populations, aiming to demonstrate that higher IGF-1 levels correlate with health status and a number of clinical variables including cognitive function (Kalmijn et al., 2000), carotid artery intima-media thickness (Van den Beld et al., 2003), incidence of stroke (Denti et al., 2004), muscle mass and muscle strength (Cappola et al., 2001; Payette et al., 2003). All these studies have led investigators to suggest that well-being and functional status were directly related to IGF-1 levels in elderly individuals. Therefore, these data seem to indicate that the use of rhGH to increase serum IGF-1 levels may provide a therapeutic option for the treatment of many of the consequences of ageing.

Rudman et al. (1990) published the first randomized controlled trial of rhGH supplementation in elderly subjects. Several changes occurred in the rhGH-treated group, including an increase in IGF-1, lean body mass, bone mineral density at the lumbar spine, skin thickness and a decrease in total fat mass.

Similar results were found by Papadakis et al. (1996) in subjects older than 69 years. Other clinical trials showed similar results in terms of changes in body composition (Holloway et al., 1994; Thompson et al., 1995; Welle et al., 1996; Yarasheski et al., 1997; Lange et al., 2000; Hennessey et al., 2001; Lange et al., 2001; Münzer et al., 2001; Blackman et al., 2002; Giannoulis et al., 2006). In post-menopausal women, the combination of exercise, diet and rhGH supplementation resulted in
an enhanced loss of truncal rather than peripheral fat compared with placebo (Taaffe et al., 2001). The decision on the final dose during drug titration is therefore dependent on clinical and biological response markers (Drake et al., 1998). Serum IGF-1 is still the most useful biological marker for dose titration, and it also allows the detection of rhGH over-replacement. In fact, an enhanced peripheral GH sensitivity in GH deprivation has been reported (Aimaretti et al., 2001).

The effect of the addition of sex hormone therapy to rhGH gave different results in men and women. Men replaced with testosterone and rhGH have an increase in total body strength and a greater decrease in fat mass than those on rhGH alone. These results were not seen in the group of women in the study who underwent rhGH and oral or transdermal estrogen replacement (Blackman et al., 2002). There is evidence indicating that estradiol is able to impair the post-receptor mechanism underlying the stimulatory effect of GH on IGF-1 synthesis. The lowest effective rhGH dose in stimulating IGF-1 plasma level is higher in women than in men (Ghigo et al., 1999).

The effects of physical activity and rhGH supplementation on body composition and muscle strength were also investigated in several studies. In both men and women over 60 years, rhGH treatment resulted in an increase in lean body mass and a reduction of fat mass. These changes were not observed in the cohort undertaking exercise and placebo (Taaffe et al., 1994; Lange et al., 2000). A 14-week exercise programme increased strength over the period of study in elderly men, but rhGH supplementation had no additional effect on this increase (Taaffe et al., 1994). rhGH treatment alone or in combination failed to demonstrate a significant increase in the proportion of type 2 fibres in muscles, or alterations in the breakdown and synthesis of myofibrillar protein (Taaffe et al., 1996; Welle et al., 1996; Hennessey et al., 2001).

The changes in body composition may be viewed as positive effects, particularly the reduction in visceral fat mass, since a decrease of this adipose compartment is likely to counteract the pathogenic mechanisms of the metabolic syndrome. The available data suggest that women may respond to rhGH therapy differently from men. Women may require higher doses of rhGH than men to achieve physiological GH profile, and a major non-physiological and prolonged elevation of circulating GH is constantly achieved with a subcutaneous injection (Jørgensen, 1991).

The use of oral GHSs, by enhancing endogenous pulsatile GH secretion, might represent a more physiological approach to increase GH concentrations. Following the synthesis of the GHRP-6, a potent GHS (Momany et al., 1981), the non-peptidyl GHS MK-0677 was synthesized (Smith et al., 1993) and used to characterize an orphan receptor involved in pulsatile GH secretion (Smith et al., 1999; Smith et al., 2004). The GHS receptor (GHSR) is expressed, as well as in the neurons of the arcuate nucleus, in areas that affect appetite, mood, biological rhythms, cognition and memory (Guan et al., 1997). Following cloning and characterization of the GHSR, an endogenous ligand, ghrelin, was isolated and identified (Kojima et al., 1999). Hence, GHSR ligands might be ideal agents to stimulate the GH/IGF-1 axis. Since these compounds act at the pituitary and hypothalamic levels, the functional integrity of the hypothalamic–pituitary axis is required. In contrast to GH injections, these GHSs produce a GH secretion that is subject to a physiological feedback, thus preventing hyperstimulation of the system. The GH-releasing effect of GHSs is independent of gender, but undergoes marked age-related variations (Arvat et al., 1997). This evidence supports the hypothesis that a hypoactivity of the natural ligand of GHSR, together with somatostatinergic hyperactivity, could play a major role in the age-related decline of GH secretion.

There are few studies on the effects of these compounds in the elderly. The administration of the orally active MK-0677 (once daily up to 4 weeks) resulted in a significant increase in IGF-1 (Chapman et al., 1997). Another study reported that 6 months’ treatment with MK-0677 increased IGF-1 and was associated with some improvement in physical function in elderly patients with hip fracture (Bach et al., 2004). One-year treatment with MK-0677 resulted in an increase in fat-free mass by 1.6 kg compared with placebo (Thorner, 1997). Interestingly, this gain in fat-free mass was maintained in the second year of the study. The effects of long-term administration of the GHS hexarelin in healthy elderly subjects were also studied (Rahim et al., 1998). However, hexarelin administration (twice daily subcutaneously in a dose of 1.5 μg/kg) did not affect IGF-1 and several other biological end-points of GH action.
The available preliminary data, taken together, suggest that oral GHSs may provide significant therapeutic advantages over rhGH administration in elderly subjects, who are protected from an overtreatment by an intact feedback mechanism. Clearly, more extensive well-controlled clinical studies are required to assess the real benefits of GHSs.

GH has been widely promoted as an anti-ageing agent. However, given (i) the lack of conclusive data (in non-GHD patients) on GH-induced favourable modifications, (ii) the high prevalence of side effects observed and (iii) the lack of data on the long-term safety of rhGH, GH supplementation cannot be routinely recommended for use among post-menopausal women.

Ageing is probably a state of relative GHD compared with younger adults (Sherlock and Toogood, 2007); however, the question whether the age-related decline in GH is a maladaptive process or an appropriate adaptation to this stage of life is still unanswered (Nass et al., 2007).

Physical fitness

It is well established that habitual physical exercise is associated with greater insulin sensitivity, less atherogenic lipid profile, increased lean body mass, reduced body fat as well to an improvement in quality of life in older subjects. GH secreted in response to exercise could contribute to the post-exercise protein anabolic effect directly or indirectly through increased lipolysis (Gibney et al., 2007). Twenty-four-hour GH secretion rates and plasma IGF-1 correlate positively with physical activity (Poehlman and Copeland, 1990), and endurance training significantly amplifies the pulsatile secretion of GH (Weltman et al., 1994), whereas serum IGF-1 levels are increased and maintained in long-term training (Koziris et al., 1999). Although some available data suggest that exercise may represent an adequate stimulus for GH secretion in elderly, other observations indicate that the GH response to exercise is greatly reduced in ageing in comparison to younger subjects (Hagberg et al., 1988; Marcell et al., 1999; Holt et al., 2001; de Vries et al., 2004). More recently, an attenuation of GH response to graded exercise intensities from below to above the individual lactate threshold was demonstrated in older adults (Weltman et al., 2006), implicating that higher exercise intensities are required to stimulate GH secretion in older adults. Moreover, exercise per se has protective effects on bone metabolism: in fact, aerobic exercises, as well as weight exercises, can help to maintain bone mineral density in post-menopausal women (Engelke et al., 2006; Zehnacker and Bernis-Dougherty, 2007; Bergström et al., 2008).

Generally, older people tend to reduce physical activity, and this lifestyle factor together with concurrent multiple variables that accompany ageing (nutritional state, changes in body composition, altered pattern of sleep and varying sex steroid hormone concentrations) are contributory factors to the age-related decline in the GH/IGF-1 axis. Since abdominal adiposity and/or physical fitness are primary determinants in age-associated decline in GH secretion in healthy adults, and reduced GH secretion might contribute for accumulation of visceral adipose tissue (Vahl et al., 1996; Vahl et al., 1997; Holt et al., 2001; Weltman et al., 2003), an optimal (in terms of both intensity and duration) aerobic exercise should be reasonably prescribed to older adults in order to increase GH secretion and to reduce accumulation of visceral adipose tissue.

Estrogen replacement therapy

Estrogens regulate the metabolic effects of GH at many levels (Leung et al., 2004). The liver represents a major site of regulatory interaction at which estrogens inhibit GH biological effects in a dose-dependent fashion. This evidence came from clinical observation showing that the route of administration was a major determinant of the effect of estrogens in impairing the metabolic actions of GH, and that estrogens influence the responsiveness to GH replacement therapy in GHD adults (Span et al., 2000). Data reporting estrogen effects on GH/IGF-1 in women demonstrate that estrogen treatment enhances GH secretion, but this action was accompanied by variable and even suppressive effects on circulating IGF-1 (Moll et al., 1986; Liu et al., 1987; Mauras et al., 1990). When administered orally, the liver is exposed to supraphysiological estrogen concentrations that inhibit IGF-1 production, an effect that was not observed after administration via parenteral route (De Lignieres et al., 1986; Weissberger et al., 1991). Since estrogens are actively metabolized by the hepatic cytochrome enzymatic system, an adequate systemic effect of estrogens can be achieved only by an amount several fold in excess of daily production rates. This so-called first-pass effect tends to suppress the production of IGF-1 from the liver by inhibiting IGF-1 mRNA expression (Leung et al., 2004). Moreover, the liver is a major source of GH-binding protein (GHBP) which binds circulating GH. This binding alters the distribution and pharmacokinetics of GH and modulates GH biological action (Baumann, 2001).

Thus, oral estrogen treatment in post-menopausal women lowers circulating IGF-1 by acting directly at the liver level and, indirectly, by increasing GHBP which blunts GH action at the tissue level (Lim et al., 1990; Weissberger et al., 1991). Estrogens also attenuate GH action by inhibiting GH-R signalling via up-regulation of suppressor of cytokine signalling-2 (Leung et al., 2003). The increase in GH secretion induced by oral estrogen might also be due to a reduction of IGF-1 feedback inhibition. These estrogen-mediated effects on the GH/IGF-1 axis are absent with physiological replacement doses administered transdermally, whereas supraphysiologic doses administered transdermally increase mean 24-h GH secretion and reduce IGF-1 levels in post-menopausal women (Fried et al., 1996). Thus, the available data indicate that it is the high estrogen concentration that alters hepatic IGF-1 synthesis, regardless of the route of administration. The changes in IGF-1 are accompanied by a parallel change in IGFBP-3 and ALS levels.

The complex interrelationships between GH action and the route of estrogen administration have practical implications in post-menopausal women during the age-related decline of GH secretion. Several studies support the existence of a gender difference in GH ‘secretion’ (Giustina and Veldhuis, 1998). Interestingly, the difference in levels of GH and IGF-1 between men and women is lost after menopause (Ho et al., 1987). In this context, estrogens are believed to play a primary role in driving GH secretion in both sexes (Veldhuis et al., 2006). Hence, estrogen deficiency probably mediates some aspects of the age-related decline in the activity of the GH/IGF-1 axis, particularly in the post-menopausal setting. If so, the restoration of the GH/IGF-1 axis in a way that resembles the normal physiology (estrogens administration) might provide functional benefits, especially considering that women now live at least one-third of their lifetime in the post-menopausal period. Previous studies evaluating the effect of...
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estrogen replacement on the somatotropic axis have produced mixed results. Transdermal estrogen replacement to a mid-follicular level did not increase GH secretion, GH pulse frequency and amplitude, IGF-1 and its binding proteins in post-menopausal women as well as in women with idiopathic premature ovarian failure (Bellantoni et al., 1991; Bellantoni et al., 1996; Lieman et al., 2001). In the latter study, age and body composition appeared to be the predominant influences on GH activity in women. Acute and long-term estrogen supplementation to post-menopausal women (17β-estradiol, 1 mg twice daily orally) elevated GH concentrations by 1.8- to 3.3-fold through an amplification of GH secretory mass (Shah et al., 1999). The multi-site actions of estradiol supplementation in post-menopausal women on GH secretion have recently been reviewed (Veldhuis et al., 2005). The collective evidence is in agreement with the hypothesis that estrogens augment GH pulse amplitude by enhancing the release of endogenous GHRH and/or by increasing the pituitary accumulation of releasable GH stores. Since plasma IGF-1, IGFBP-1 and IGFBP-3 concentrations are not influenced by standard transdermal estrogen supplementation, the blood-borne-negative IGF-1 feedback on GH secretion is not altered by transdermal estrogen administration.

During controlled estradiol repletion in women given a GnRH agonist—to down-regulate the pituitary—ovarian axis—post-menopausal women, compared with premenopausal women, maintained lower IGF-1, IGFBP-3, as well as basal, GHRH- and GHRP-stimulated GH concentrations (Veldhuis et al., 2007). Thus, the multiple pathway impairments in GH secretion observed in post-menopausal women seem to be related to estrogen-independent factors like concomitant visceral adiposity and low IGF-1 concentrations. However, HRT with continuous estrogen progestin treatment (EPT) in post-menopausal women returns their 24-h GH levels towards those of middle-aged premenopausal women (Kalleinen et al., 2008). The data would support the hypothesis that EPT therapy, although not reflecting the action of endogenously secreted sex hormones during premenopause, might represent a valid pharmacological option to rejuvenate the GH/IGF-1 axis in women.

The majority of interventional studies support the notion that HRT attenuates the accumulation of central fat in post-menopausal women compared with placebo-treated women. Retrospective comparison of hormone users and non-users also supports a protective effect of hormone replacement on fat distribution (Haarbo et al., 1991; Manolio et al., 1993; The Writing Group for the PEPI Trial, 1995; Gambacciani et al., 1997; Thernmoef et al., 1998; Sumino et al., 2003). A more favourable body composition and fat distribution was also observed in obese post-menopausal women using HRT (Sites et al., 2001), although other studies performed in obese post-menopausal women showed no effect (Ryan et al., 2002).

The differences observed may reflect differences in type and dosage of HRT, number of subjects, lengths of observation period or methods used to estimate the adipose tissue. Improvement in the distribution of abdominal fat and fasting lipid level, together with the agonistic effect of estrogen on GH secretion, may represent beneficial effects of HRT against cardiovascular diseases in post-menopausal women.

The impact of progestogen (co-administered with estrogens to oppose the stimulatory effect of estrogens on the endometrium) on the GH/IGF-1 axis revealed little impact on the effects of estrogen on IGF-1, although different types of progestogens showed dissimilar effects on IGF-1 levels (Campagnoli et al., 2003; Nugent et al., 2003), these effects being related to the androgenic properties of the drugs. In contrast, progestins devoid of androgenic properties did not interfere with IGF-1 hepatic synthesis (Sonnet et al., 2007). Moreover, a standard estroprogestin post-menopausal therapy with a non-androgenic progestogen still enhanced the GH response to provocative stimuli (Villa et al., 2008).

Recent publications including the Women’s Health Initiative (WHI) (Rossouw et al., 2002) and other studies were reviewed by Turgeon et al. (2006) who posed the thesis that ovarian steroids exert important protective actions on cardiovascular diseases, neurodegenerative diseases, immune dysfunction, osteoporosis, as well as quality of life in post-menopausal women when interpreted in the context of the study design. The improved distribution of abdominal fat, together with the agonistic action of HRT on GH secretion, might contribute in this process.

Conclusions

A gradual and progressive decline in spontaneous GH secretion occurs in ageing and is reflected in a parallel fall in circulating IGF-I levels. Normal ageing and organic GHD share a clinical phenotype of relative visceral adiposity, sarcopenia, reduced bone mass, dyslipidaemia, reduced aerobic capacity, increased cardiovascular mortality and diminished quality of life. Menopause is associated with weight gain and with an increase in body fat. Post-menopausal women generally develop an android pattern of fat distribution (visceral adiposity), which has been attributed to the diminished estrogen secretion. This concomitant visceral adiposity, together with estrogen deficiency, appears to be related to the higher prevalence of dyslipidaemia, hypertension and insulin resistance in post-menopausal women, compared with fertile women. When combined, these factors are associated with a high risk of cardiovascular diseases and diabetes.

Obesity and GH secretion are inversely related. In relation to the increased adiposity in ageing people, a vicious cycle may ensue, given that visceral adiposity is the major determinant of GH secretion in healthy adults. Thus, increased central adiposity can be a cause of reduced GH secretion as well as its consequence.

The beneficial effects of GH replacement have been documented in adults with GHD. Since a number of the clinical features of the menopause are shared with those of the adult GHD, the use of rhGH to increased serum IGF-I levels was proposed in elderly subjects. A review of the literature reveals that favourable modifications in body composition were frequently noted. However, several studies failed to confirm the data. Side effects after rhGH administration showed a high prevalence. The treatment with natural and synthetic GHSs could represent a more physiological approach to rejuvenate the GH/IGF-1 axis, but additional well-controlled clinical studies are required to assess the real benefits of this therapy.

The improved distribution of abdominal fat and the decreased fasting lipid levels, which have been reported during HRT in post-menopausal women, may represent beneficial effects with respect to cardiovascular disease (Sumino et al., 2003). A selective reduction in visceral fat in post-menopausal women treated with oral estrogens plus cyclic medroxyprogesterone acetate has been reported (Mattiasen et al., 2002; Kanaya et al., 2003; Margolis et al., 2004). These changes, together with the agonistic effect of estrogen on GH.
secretion, might represent a valid alternative to rhGH administration in post-menopausal women. However, the recent release of large-scale randomized controlled trials (Hulley et al., 1998; Rossouw et al., 2002; Manson et al., 2003; Anderson et al., 2004) questioned the enthusiasm for widespread HRT use and led the researchers to re-evaluate the benefits and risks of this therapy in older women (Turgeon et al. 2006). Therefore, the routine clinical application of HRT to rejuvenate GH neurosecretion is not advisable.

Sleep and exercise are the two major stimuli for secretion of GH in normal people. There is also evidence that adults who continue to exercise tend to maintain lean body mass, physiological GH secretion (which is essential for maintaining physical fitness) and possibly the quality of sleep. If so, regular physical exercise still represents a safe intervention, able to improve metabolic parameters, overall fitness, quality of life and to rejuvenate the GH/IGF-1 axis in post-menopausal women. Going to the gym is beneficial and certainly cheaper than GH supplementation (Vance, 2003).

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