Endocrine (2014) 47:679–689
DOI 10.1007/s12020-014-0276-0

REVIEW

Unusual effects of GH deficiency in adults: a review about the effects of GH on skin, sleep, and coagulation

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Received: 27 January 2014 / Accepted: 18 April 2014 / Published online: 11 May 2014

Abstract Based on the literature data in the last two decades, growth hormone deficiency (GHD) in adults has been accepted as a clinical entity. Due to the presence of GH and IGF-I receptors throughout the body, the physiological effects of the GH-IGF-I axis are still under investigation. The effects of GH on skin, sleep, and coagulation parameters in adults have only been investigated in detail only in the recent years. In this review, our aim was to summarize the literature regarding the effects of GHD and GH replacement treatment on the skin, sleep, and coagulation parameters in adults.

Keywords GH deficiency · GH replacement · Skin · Sweating · Sleep · Coagulation · Fibrinolysis · Pituitary · Hemostasis

Introduction

Since growth hormone deficiency (GHD) in adults has been accepted as a clinical entity, some of the effects of GHD have been studied extensively [1]. GHD in adults is associated with abnormal body composition [2, 3], increased cardiovascular risk factors [4–7] such as altered lipid profile [8, 9], and cardiac function including cardiac autonomic tone [10]. Impaired cognitive functions, osteoporosis, increased fracture rate, and altered bone metabolism are also associated with GHD [2, 9, 11–14]. Improvements in most of these parameters have been demonstrated in previous short- and long-term studies [2, 9, 10, 15].

Due to the presence of GH and IGF-I receptors throughout the body, the physiological effects of the GH–IGF-I axis are still under investigation. The effects of GH on skin, sleep, and coagulation system in adults have started to be investigated more in detail in the recent years. Although we described these effects as unusual; they may be clinically relevant. In this review, we aimed to summarize the studies regarding the effects of GHD and GH replacement treatment (GHRT) on the skin, sleep, and coagulation parameters in adults. A literature search was performed using PubMed combining the key words:growth hormone, growth hormone deficiency, growth hormone therapy, skin, sweating, sleep, coagulation, and cardiovascular risk factors (last search: February 2014).

GH deficiency and skin changes

Endocrine abnormalities, including hypopituitarism, may be responsible for many changes in the skin. Dry, thin, and pale skin is described in panhypopituitarism, although the responsible hormones are not clearly identified [16]. Moreover, in patients with postpartum pituitary necrosis (Sheehan's syndrome), well-characterized skin changes are described, such as early aging of the skin and typical facial appearance with fine wrinkling [17, 18]. GH is one of the most commonly encountered deficient hormones in adults with hypopituitarism, regardless of the etiology [9, 19, 20]. The immunohistochemical and mRNA localizations of GH receptors in human skin and its appendages suggest a direct role of GH on skin function and characteristics [21, 22]. Moreover, the IGF-1 protein and mRNA expression, and IGF binding protein mRNA (which may mediate local

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actions of GH) have also been shown in human skin [23, 24]. GH may, therefore, affect the skin physiology directly or perhaps through the autocrine or paracrine actions of IGF-1.

Classically, it is known that patients with acromegaly have thick and greasy skin, and the excessive sweating occurs in 50–88 % of active acromegaly patients [25–27]. Although it has been suggested that reduced sweat secretion is part of adult GHD syndrome [28], few studies have investigated the effects of GHD and GHRT on sweating. Adult patients with childhood onset (CO)-GHD exhibit reduced sweating, and 4 months of GHRT significantly increased sweat secretion rate (SSR), but it could not be normalized [29]. Additionally, by using the pilocarpine iontophoresis method, it has been previously reported that SSR is significantly decreased in patients with CO-GHD and GH insensitivity syndromes [30, 31]. Sweating is important for the continuation of constant body temperature, particularly during heat stress and physical activity. The decreased sweating ability in GH-deficient adult patients does not commonly cause hyperthermia at rest. However, clinical experiences show that heat waves may cause discomfort to adult patients with GHD. Juul et al. demonstrated that during physiological provocation of sweat secretion by ergometer bicycling, or following heat stress, patients with GHD had a lower SSR and a steeper rise in core temperature than both trained and untrained healthy adults. Based on their findings, the authors concluded that impaired thermoregulation is a part of adult GHD, and patients with GHD are at risk for developing hyperthermia during exercise in hot environments [32, 33].Current studies revealed that sports-related repetitive head trauma may cause GHD in athletes including boxers, kick boxers, and soccer players [34–36].Thus, these athletes with GHD may be at risk of hyperthermia because they are generally exposed to extensive exercise. Future well-designed studies are warranted to reveal the effects of head trauma-induced GHD on SSR and thermoregulation in athletes.

Sneppen et al. reported reduced SSR in male but not in female GHD patients without any significant changes after 36 months of GHRT. The gender difference in SSR was attributed to androgen deficiency as a co-factor for reduced sweating in males [37]. In previous studies on CO-GHD [29, 32, 33], it was shown that severe impairment in SSR can be due to long-standing GHD and/or to lack of pubertal development at diagnosis of pituitary disease. SSR was measured only by the pilocarpine iontophoresis method in a limited number of patients with GHD in Sneppen et al.'s [37] study. This may also have contributed to the irrelevant findings, but it is tempting to speculate that sweat gland development seems to be more susceptible to hormonal deficiencies in childhood and adolescence than in adulthood. Additionally, in SSR regulation, GH seems to be the only factor in combination with sex steroids. Previous immunohistochemical studies demonstrated the presence of both androgen receptors [38] and GH receptors in the eccrine sweat glands [21, 22]. However, it is difficult to comment on sweat gland development and function with only SSR data measured by using the pilocarpine iontophoresis method.

Pituitary and/or local hormones are not the only factors in sweat gland development and sweating function. The innervations of sweat glands are also important for effective thermoregulation. The main neurotransmitter in the sympathetic innervations of sweat glands is acetylcholine, and acetylcholinesterase (AChE) is the enzyme responsible for the hydrolysis of acetylcholine at nerve terminals [39]. The neuropeptide vasoactive intestinal polypeptide (VIP) is also co-localized in the cholinergic nerve terminals, which enhances the secretory response of acetylcholine [40]. Hasan et al. [41] conducted a detailed study investigating the morphology (by punch skin biopsies from the forearm), function, and innervations of sweat glands in patients with AO-GHD. They clearly demonstrated that SSR was significantly reduced by around 45 % in 21 male and female untreated GH-deficient patients compared to controls. The skin biopsies revealed that both AChE and VIP stained nerves were significantly reduced in the GH-deficient patients; this situation was reversed by GHRT [41]. It has been previously suggested that GHD may result in atrophy of the sweat glands [33], but the histomorphological findings in Hasan et al.'s [41] study did not support this hypothesis. They have demonstrated no difference in acinar size between controls and patients with GHD. In another study investigating skin morphological changes in adults with GHD, skin biopsies were obtained from 17 patients with treated CO-GHD, 5 patients with untreated CO-GHD, and 13 age/sex-matched healthy controls [42]. The SSR, epidermal thickness, and area of eccrine sweat gland glomeruli were significantly decreased in patients with GHD. Although these parameters improved after GHRT, they were not completely normalized [42].These findings suggest that skin histomorphological changes are more prominent and more resistant to GHRT in adults with CO-GHD than in those with AO-GHD. Head to head comparisons between AO- and CO-GHD are necessary to be assured.

The above-mentioned studies clearly demonstrated decreased skin thickness and decreased sweating in patients with GHD. However, there are not enough data regarding the impact of GH and/or IGF-I on skin characteristics including pilosebaceous unit function [43]. Lange et al. [42] did not find any structural changes in the sebaceous glands of patients with GHD when compared with the controls. However, they did not investigate the

functional aspects of the sebaceous glands including the sebum content. The appearance of the skin is closely related to skin characteristics including hydration, PH, and sebum content. We investigated the skin characteristics including sebum content, skin capacitance (hydration), transepidermal water loss (TEWL), pH, and skin temperature by using a non-invasive measurement technique in 21 patients with Sheehan's syndrome. Severe GHD is a well-established feature of Sheehan's syndrome and these patients have a typical facial appearance with fine wrinkling, dry skin, and early aging of the skin [17, 44]. Skin capacitance was found to be significantly decreased on the forehead and forearm, and the sebum content was found to be decreased on the forehead of patients with Sheehan's syndrome when compared with age/sex-matched control subjects. The pH, temperature, and TEWL of the skin of the patients were not statistically different from those of the controls [45]. After 6 months of GHRT, there was a significant increase in sebum content on the forehead without a significant change in skin capacitance [46]. These findings clearly demonstrated, for the first time, that GHD is also responsible for the skin changes seen in Sheehan's syndrome in addition to secondary hypogonadism. Consistent with this clinical finding, GH was shown to directly act on sebocyte differentiation in a cell culture model [47]. In recent years, GHRT has been discussed as an antiaging agent due to its effects on skin and systemic effects. The amount of human GH decreases significantly after the age of 30. This decrease has been implicated as one of the causes of signs of aging, such as thinning (decreased epidermal thickness) of the skin [48]. Many women notice a sudden onset of the signs and symptoms of skin aging during the menopause, such as an increase in skin dryness, loss of firmness, decrease in elasticity, and increase in skin looseness [49]. More controversial is the non-licensed use of GH as an antiaging treatment for rejuvenating the skin. Although GH treatment may enhance dermal collagen content thus increasing skin thickness, GH is not approved as an antiaging agent and there are no data on the safety of GH use in this setting [50, 51].

The current literature data clearly demonstrate that GH and/or IGF-I have an important role in skin physiology. GHD in adults causes functional and structural changes in the skin and its appendages. The effects of adult GHD on the skin are summarized in Table 1. Although the data are controversial and not sufficient, GHRT could not fully normalize all the changes due to GHD. In daily clinical practice, we have to keep in mind that the patients with severe and long-term GHD may have sweating problems, and rarely may be at risk of hyperthermia after extensive exercise or heat exposure. Despite the above-mentioned data, the impact of GH on skin physiology still needs further investigation, and to understand the effects of GHRT on skin changes and characteristics, more placebo-controlled long-term studies are warranted.

Table 1 Changes in skin structure and function in adult patients with AO and/or CO-GHD

Decreased sweat secretion rate
Impaired thermoregulation during exercise especially in hot environments
Reduced innervation (AChE and VIP stained nerves were reduced)
Decreased epidermal thickness
Decreased area of eccrine sweat gland glomeruli
Decrease skin capacitance (hydration) on forehead and forearm
Decreased sebum content on forehead

AO adult onset, *CO* childhood onset

GH deficiency and sleep disturbances

Human sleep is characterized by cyclic occurrence of periods of non-rapid eye movement (NREM) sleep {Stage 1, Stage 2, Stage 3, and Stage 4 [Stage 3 +Stage 4 are accepted as slow-wave sleep (SWS)]} and rapid eye movement (REM) sleep [52]. A large body of evidence showed bidirectional interactions between the somatotropic axis and sleep regulation [52, 53]. GH was found to be preferentially secreted during sleep, especially during SWS [54–57]. While the association between sleep and GH release has been well documented, the effects of the GH–IGF-I axis on sleep regulation have not been uncovered yet. Therefore, in this review, we will focus on the effects of the somatotropic axis, particularly GHD and GHRT, on sleep parameters in adults.

Growth hormone releasing hormone (GHRH) promotes NREM sleep in various species. Animal [58] and human [59, 60] studies have shown that GHRH has a hypnotic action and mainly increases the duration and/or intensity of NREM sleep, in particular SWS, even in the absence of GH [58]. However, gender differences exist in the sleep-EEG effects of GHRH. In male rats, GHRH enhances NREM sleep when injected intracerebroventricularly [61], intravenously [58], or directly in the preoptic area [62]. In healthy young men, the sleep-promoting effects of GHRH were also confirmed by different studies [59, 60, 63, 64], whereas in one previous study, an opposite effect in healthy young women was reported [65]. However, more human studies with healthy and GH-deficient adults are warranted to clarify the role of gender difference in the GHRH effect on sleep.

The above-mentioned data imply that excessive hypothalamic GHRH may result in increased daytime sleepiness and fatigue in patients with GHD. In untreated GHD of pituitary origin, due to lack of negative feedback inhibition

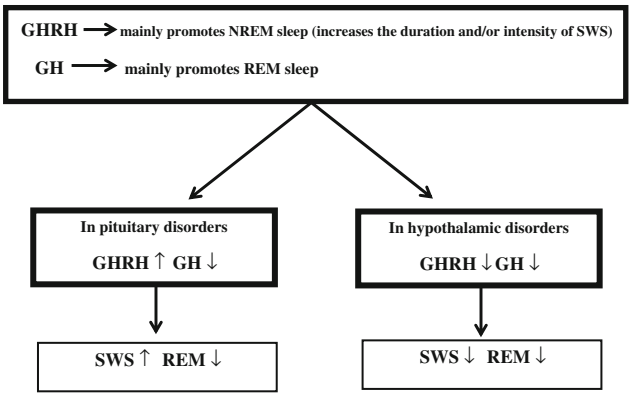

Fig. 1 Regulatory effects of GHRH and GH on sleep phases (*NREM* non-rapid eye movement, *SWS* slow-wave sleep, *REM* rapid eye movement)

by GH, overactivity of the hypothalamic GHRH system may occur [66]. Supporting this hypothesis, it was shown in transgenic mice that GHRH was decreased, NREM sleep was significantly suppressed during both the light and the dark period, although REM sleep was not altered [67]. However, preliminary findings in rodents [58, 61] and humans [68, 69] indicate that GH itself may stimulate rapid eye movement (REM) sleep. The effects of GHRH and GH on sleep regulation are summarized in Figure 1. To understand the role of GH in human sleep physiology, the findings of patients with GHD due to hypothalamic and/or pituitary causes are crucial. However, very few studies have objectively characterized sleep in GH-deficient patients and, to our knowledge, in the literature, only 6 studies have been published investigating the effects of GHRT on sleep in adult patients with GHD [70–75] (Table 2).

Recently Copinschi et al. investigated sleep disturbances in 30 untreated adult patients with GHD (primary pituitary defects in 26 and hypothalamic defect in 4 patients) and 30 gender-, age-, and body mass index-matched healthy controls. Although the total duration of NREM sleep was not altered, duration of SWS (Stage 3 and Stage 4) was found to be significantly increased when compared to controls. However, the duration of REM sleep was not altered. Among these 26 patients, the older group (*n*: 13, mean age: 60 ± 3 years) had decreased total sleep time and increased sleep fragmentation when compared to younger patients and controls. The reduction in total sleep time in older GH-deficient patients was associated with shortened REM sleep. In contrast to pituitary GHD, the 4 patients with hypothalamic GHD had lower intensity of SWS than the controls, suggesting reduced GHRH activity in these patients [66]. This study is well designed and a cornerstone study demonstrating the effects of GHD on sleep stages of either pituitary or hypothalamic origin on sleep stages. Later on, the reversibility of the sleep disturbances due to GHD after GHRT was achieved. In the first study evaluating the sleep effects of GHRT, a small group of adult patients with isolated CO-GHD was evaluated with PSG before and after 6 months of GHRT. Total sleep time was decreased and REM sleep time was increased significantly, but SWS duration (stage 3 + 4) did not change after GHRT [70]. In another study in five male patients with AO-GHD (postoperative pituitary insufficiency), PSG was performed after 1 year of GHRT and after 6 months of withdrawal. During GHRT, duration of sleep stages in NREM sleep was normal, but in contrast to the first study [68], REM sleep was decreased. After cessation of treatment, a significant decrease in SWS was reported. According to the findings of the study by Copinschi et al., it may be expected that SWS may be increased during the GH-free period due to possible increase in GHRH. Nevertheless, the number of patients was too low to draw a clear conclusion. Moreover, the authors did not mention whether the GHD was of pituitary or hypothalamic origin. This study at least showed that GHRT may influence sleep reaction in a complex way in middle-aged men; cessation of treatment was associated with a significant decrease in SWS [73]. Schneider et al. evaluated sleep characteristics before and after 6 months of GHD in 18 patients (14 men, 4 women) with CO-GHD. The authors reported that the group's baseline sleep parameters were comparable to those of healthy control groups from the literature. GHRT affected neither total sleep time nor time spent in different sleep stages. However, GHRT was found to have no sleep disturbing effect [75]. The most important limitations of this study were the lack of a control group from the same population and short duration of GHRT. In another similar study evaluating sleep architecture by PSG, 19 AO-GHD patients (11 men, 8 women) were investigated in terms of sleep parameter changes before and after 6 months of GHRT. Mean total sleep time, durations of SWS, and REM sleep were not significantly altered [74]. In a study from our clinic, we investigated sleep architecture by using PSG in patients with Sheehan's syndrome before and after 6 months of GHRT for the first time in the literature. Because the primary pathology in Sheehan's syndrome is in the pituitary gland, these patients are appropriate models for neuro-endocrinological evaluations, since all the cases are homogenous regarding etiology and the site of the lesion. We included 22 women with Sheehan's syndrome (mean age; 49.1 ± 2.2) and 12 age/sex-matched healthy controls. After baseline evaluation, patients were randomized to GHRT (*n*: 12) and placebo (*n*: 8) groups. GH-deficient patients had more NREM sleep, particularly in stage 4 sleep (SWS), less REM sleep, and also less sleep efficiency when compared to healthy controls. After

Table 2 Review of the studies investigating the effects of GHRT on sleep in adults with GHD

Studies	Patient number and diagnosis	Methods and study design	Effects of GHRT on sleep parameters
Astrom et al. [68]	8 patients (age range 20–30 years)	PSG analysis before and after 6 months of GHRT	Decreased total sleep time
	Isolated CO-GHD	No placebo control	Increased REM sleep
			No change in SWS duration
Nolte et al. [73]	5 patients (median age: 55 years)	PSG analysis after 12 months of GHRT and after 6 months of withdrawal period	During treatment period no changes in stages I,II and SWS duration
	AO-GHD due to pituitary disease	No placebo control	Decreased SWS duration after withdrawal period
Schneider et al. [75]	18 patients (mean age: 48.5 years)	PSG and spectral analysis before and after 6 months of GHRT	Sleep parameters did not change
	CO-GHD	No placebo control	
Peker et al. [74]	19 patients (mean age: 53 years)	PSG analysis before and after 6 months of GHRT	Sleep parameters did not change in the whole group
	AO-GHD	No placebo control	A marginal increase in REM sleep duration in GHD patients with OSA
Ismailogullari et al. [71]	20 patients (mean age: 51 years)	PSG analysis before and after 6 months of GHRT	Sleep disturbances before treatment (increased SWS and decreased REM sleep durations when compared to healthy controls) did not normalize
	Sheehan's syndrome	Parallel group design (12 patients GHRT, 8 patients placebo)	
Morselli et al. [72]	13 patients (mean age: 46.5 years)	PSG and spectral analysis after 4 months of GHRT and placebo periods	Decreased sleep period time
	9 patients AO-GHD, 4 patients CO-GHD	Randomized cross-over design	Decreased SWS intensity (delta activity)

6 months of GHRT, there was no significant difference in sleep parameters [71]. The main cause of unresponsiveness to GHRT could have been the short duration of the treatment and long duration/severity of the GHD in patients with Sheehan's syndrome. When we performed subgroup analysis, interestingly, one of the patients with severe obstructive sleep apnea (OSA) at baseline, dramatically improved in terms of apnea—hypopnea index (AHI): 91.1 at baseline, 6.8 at the sixth month of GHRT [71]. One previous study suggested that GHRT may induce OSA in GH-deficient adults [73]. However, in a recent study consisting of 19 GH-deficient adults, 12 patients were found to have OSA at baseline; the mean AHI was high, and remained unchanged after GHRT. In that study, a mild but significant increase in REM sleep time was observed in the GH-deficient patients with OSA after 6 months of GHRT [74]. In a very recent study by Morselli et al., 13 patients (12 men, 1 woman) with GHD due to pituitary origin (9 patients with AO-GHD and 4 patients with CO-GHD) were included in a randomized cross-over treatment study investigating sleep characteristics by PSG and spectral analysis, and the patients were treated with GH or placebo for 4 month periods [72]. The baseline sleep characteristics data of these patients before GHRT were previously published as the details above mentioned [66]. This study clearly demonstrated that, at the end of the GHRT period, patients had a shorter sleep period time than in the placebo period, mainly due to an earlier wake-up time. Additionally, there was a significant decrease in the intensity of SWS (delta activity) after the GHRT period when compared to the placebo period. Therefore, this is the first placebo-controlled study showing that 4 months of GHRT therapy may partly reverse the sleep disturbances previously observed in untreated patients [72]. Another important finding of this recent study is the decrease in delta activity associated with GHRT. This adds further evidence to the hypothesis that the excess of high-intensity SWS observed in untreated pituitary GHD patients is probably due to overactivity of the hypothalamic GHRH system because of the lack of negative feedback inhibition by GH. The results of studies regarding GHRT on sleep parameters are summarized in Table 2.

In conclusion, based on the experimental and clinical data in the literature, the GH-IGF-I axis seems to have an important role in sleep physiology. In adult patients with GHD due to pituitary origin, the current data suggest increased NREM sleep (mainly SWS) and decreased REM sleep durations when compared to age/sex-matched controls. These changes in sleep quality and characteristics

may be partly responsible for increased memory problems, increased daytime tiredness, and decreased quality of life in adults with GHD. Although the GHRT results are inconclusive due to lack of large scale placebo-controlled studies, it seems that short-term (6 months) GHRT could not fully reverse the disturbances in sleep parameters. However, it is clear that GHRT has no sleep disturbing effects and does not induce or aggravate OSA. Further long-term, larger studies with homogenous patient groups in both genders are warranted to clarify the effects of GHD and GHRT on sleep architecture.

GH deficiency and coagulation

Cardiovascular and cerebrovascular mortalities have been shown to be increased in patients with hypopituitarism, who were treated with hormones other than GH [76–79]. Alterations in the coagulation and fibrinolytic system may be one of the mechanisms responsible for the increased thromboembolic events associated with GHD [80]. However, longevity has proven to be normal in isolated GHD or GH resistance [81, 82]. Hemostasis is a complex system including many integrated steps. Normal platelet number and function, coagulation, and fibrinolysis are essential components of normal hemostasis. There are both antithrombotic factors: (i) anticoagulants such as antithrombin, protein C/protein S/thrombomodulin system, tissue factor pathway inhibitor, (ii) profibrinolytics such as tissue type plasminogen activator (t-PA), urokinase type plasminogen activator (u-PA); and thrombotic factors: (i) procoagulants such as tissue factor (TF), clotting factors, and von Willebrand factor (vWF), (ii) antifibrinolytic agents such as plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin, thrombin fibrinolysis activatable inhibitor (TAFI), in plasma. There is a mild to moderate prothrombotic state in adults with GHD [83]. We previously reported a patient with Sheehan's syndrome with panhypopituitarism including severe GHD presenting with massive cardiac thrombosis [84]. Therefore, the mild changes in hemostasis may be clinically important, especially if there is an associated genetic defect or acquired defects leading to thrombotic tendency.

The first animal studies revealed alterations in both coagulation and fibrinolytic systems in GHD. In rats, GHD was shown to impair blood clotting and decrease factor VII and factor IX, and the effects were found to be reversible with GHRT [85]. GHRT was shown to decrease the plasma levels of fibrinogen and increase plasminogen activator activity in rat heart [86].

Human studies in adults with GHD which investigates its effects on hemostasis are summarized in Table 3. Hyperfibrinogenemia and increased PAI-1 levels are well-known risk factors for cardiovascular or cerebrovascular disorders [87–89]. In most studies, fibrinogen and PAI-1 levels were found to be increased in patients with GHD and found to be related to increased waist hip ratio, body mass index, or insulin levels [80, 90–92]. PAI-1 levels were shown to be correlated with triglyceride, glucose, and insulin levels, but not with IGF-1 levels [91]. PAI-1 inhibition rises with increase in t-PA antigen (ag) indicating that high levels of either factor reflect an impaired fibrinolytic state [93]. Devin et al. demonstrated decreased t-PA levels in adult patients with GHD besides endothelial dysfunction and elevated PAI-1 ag levels [90]. Therefore, fibrinogen and PAI-1 are elevated, and t-PA levels are decreased in patients with GHD, explaining the thrombotic tendency.

Growth hormone replacement for 18 months or 2 years was shown to have favorable effects on fibrinogen [92, 94, 95], although some studies, in which GHRT periods were shorter [96, 97], did not confirm the findings. Besides decreased fibrinogen levels, GHRT resulted in significant decreases in PAI-1 activity, PAI-1 ag, and t-PA ag [95]. The authors suggested that these effects could be directly related to GH itself or to the favorable effects of GH on body composition [95].

Elhadd et al. showed increased levels of vWF, thrombomodulin, and some endothelial adhesion molecules, such as ICAM-1 and E-selectin, in 52 GH-deficient adults [98]. Patients under GHRT were found to have comparable levels of fibrinolytic markers, adhesion molecules, and endothelial functions to healthy controls, but E-selectin levels were still higher in GHD patients who were on GHRT [99, 100]. Although GHRT improves the prothrombotic state, patients on stabilized GH treatment for a median duration of 19 months were demonstrated to still have increased fibrinogen, F VIII, and vWF ag levels [101].

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are commonly used tests showing the integrity of the intrinsic and extrinsic pathways of coagulation. PT and aPTT levels were found to be in the normal range and did not change after 6 months of GHRT [96]. However, in the study by Mijic et al., PT was found to be increased after GHRT; it was pronounced in females and aPTT was found to be increased only in males [97]. The clinical relevance of these changes in PT and aPTT levels only after GHRT needs to be further investigated.

The platelet number was found to be affected neither by GHD nor by GHRT [96, 102]. Although collagen-ADP closure time was found to be normal and unchanged by GHRT, collagen epinephrine closure time was found to be higher than normal. Six months of GHRT resulted in normalization of these values, but the decrease was not found to be significantly different [96].

In summary, platelet number and function do not seem to be affected by GHD, but both coagulation and

Table 3 Review of the studies investigating the effects of GHD and GHRT on hemostasis in adults with GHD

Studies	Study population	GHD compared to control	GHRT
Johansson et al. [91]	20 GHD adults	Higher PAI-1 Higher fibrinogen	
Johansson et al. [95]	17 GHD adults 2 years of GHRT		Decreased PAI-1 act and PAI-1 ag Decreased tPA Decreased α2 antiplasmin Unchanged plasminogen Mildly decreased fibrinogen Unchanged F VII, F VIII Unchanged antithrombin III Decreased protein C Transient decrease in vWF levels
Sartorio et al. [80]	24 GHD adults 8 CO, 16 AO-GHD	Higher PAI-1 Higher fibrinogen Higher TAT concentrations	
Kvasnicka et al. [92]	11 GHD adults 12 months of GHRT	Higher PAI-1 Higher fibrinogen Higher adhesion molecules	Decreased fibrinogen Decreased adhesion molecules
Elhadd et al. [98]	52 GHD adults	Higher vWF Higher thrombomodulin Higher adhesion molecules	
Smith et al. [101]	30 GHD adults on GHRT for a median period of 19 months compared to controls		Higher fibrinogen Higher FVIII Higher vWF ag
Gomez et al. [99]	10 GHD adults 12 months of GHRT	Similar fibrinogen Similar TAT concentrations Higher E-selectin Other soluble adhesion molecules and inflammatory cytokines are similar	Unchanged fibrinogen Unchanged TAT Unchanged soluble adhesion molecules and inflammatory cytokines
Miljic et al. [97]	21 GHD adults	Similar fibrinogen Similar PT and aPTT	Unchanged fibrinogen Increased PT prominent in females Increased aPTT in males
Devin et al. [90]	12 GHD adults	Higher PAI-1 ag Lower tPA activity Sustained PAI-1 activity after venous occlusion	
Di Minno et al. [94]	60 GHD adults 6 months of GHRT		Only in patients with insulin reductions: Decreased PAI-1 Decreased tPA ag Decreased protein C Decreased protein S Decreased F VII a
Cakir et al. [96]	19 GHD adults with Sheehan's syndrome 6 months of GHRT in 12 patients, placebo in 7 patients	Higher incidence of protein S deficiency	Unchanged platelet number Unchanged PT, aPTT Decreased antithrombin 3 activity Decreased protein C activity Normalization of protein S activity in patients with protein S deficiency

fibrinolysis may be affected adversely by GHD in favor of thrombosis. GHRT may at least partially reverse these abnormalities. However, more detailed and experimental studies would be valuable to clarify the direct role of GH on these effects rather than on secondary changes in body composition or insulin levels.

Conclusions

Decreased sweating and decreased skin sebum content leading to dry skin are seen in patients with GHD. These may result in early aging of the skin and risk of hyperthermia in susceptible populations. GHD causes a decrease in REM sleep and an increase in SWS which may be associated with disturbed memory functions. Coagulation and fibrinolysis may also be adversely affected by GHD in favor of thrombosis. GHRT is able to reverse abnormalities in the skin, sleep pattern, and coagulation system at least partially. Longer, placebo-controlled studies in larger groups of patients with GHD regarding the effects of GHRT on these systems would be valuable.

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