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Human growth hormone level decreased in women aged <60 years but increased in men aged >50 years

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Abstract

To investigate the relationship amongst human growth hormone (HGH), sex, and age groups.

A cross-sectional study was conducted on a health check-up population from Wannan area of China from 2014 to 2016. The study involved 6843 individuals aged 23 to 85 years. Logistic regression analysis and smooth curve were applied to determine the relationship amongst age, sex, and HGH.

The average level of HGH in the population was 0.37 ± 0.59 ng/mL. There were significant differences in sex, age, body mass index (BMI), triglycerides (TG), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), and glucose (GLU) amongst different quartiles of HGH ($P < .001$). A U-shape relationship was established between HGH and age. After sex stratification, the results showed that the thresholds of age were 60 years in women, and 50 years in men, after adjusting for body mass index, triglycerides, total cholesterol, blood pressure, and blood glucose. Logistic regression showed that HGH level decreased in women aged <60 years (OR = 1.472, $P < .001$) and increased in men aged >50 years (OR = 0.711, $P < .001$). So the distributive characteristics of HGH concentration vary with sex and age group.

Abbreviations: BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, GH = growth hormone, GHD = growth hormone deficiency, GLU = glucose, HDL = high density lipoprotein, HGH = human growth hormone, IGF-1 = insulin-like growth factors-1, IR = ionizing radiation, LDL = low density lipoprotein, OR = odds ratio, SBP = systolic blood pressure, SE = standard error, TC = total cholesterol, TG = triglyceride, WHO = World Health Organization.

Keywords: age, sex, human growth hormone, U-shaped curve

1. Introduction

Human growth hormone (HGH) produces insulin-like growth factors-1 (IGF-1) through autocrine stimulation of liver or paracrine stimulation of various tissues.[1–3] Deficiency of HGH and IGF-1 may lead to depression in growth and weight gain, changes in body composition, and metabolic impairment.[4] Studies have established links between obesity and cardiovascular diseases such as hypertension, diabetes, and dyslipidemia,[5] So growth hormone deficiency (GHD) in adults is one of the causes of cardiovascular diseases and death.[6–8] Epidemiological and animal studies have shown that overexpression of IGF-1 or high levels of HGH promote the occurrence of liver cancer, rectal cancer, breast cancer, and other cancers.[9–12] High expression of HGH has been detected in clinical studies of colorectal cancer, in which the high expression of HGH is positively correlated with tumor size and rate of lymph node metastasis.[13] Large genome-wide association studies have confirmed that HGH signaling pathway is linked directly to breast cancer. Studies have also found that HGH reduces the sensitivity of breast cancer and endometrial cells to ionizing radiation (IR), leading to a reduction in radiotherapy efficacy.[14,15] Thus, HGH is often used as a biomarker for early diagnosis of these cancers.[16–18] However, HGH is affected by some factors. Animal studies have shown that HGH tends to increase with age, and may play a role in accelerating the aging process.[19] However, in other studies, although HGH level in adults was influenced by age and sex, HGH concentration decreased with age, even from middle age, with differences in changes between men and women (changes in HGH levels in women were not obvious after menopause, but in men were significant).[20–23]

Existing studies have unclear described the relationship between HGH and age in different sexes. This study was used a health check-up population to investigate the distribution and changes in HGH in different sex and age groups.

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2. Materials and methods

2.1. Study subjects

A cross-sectional study was conducted on 6843 health check-up participants aged 23 to 85 years in Health Management Center of the First Affiliated Hospital of Wannan Medical College in Wuhu, China from 2014 to 2016. This study was approved by the Ethics Committee of Southern Anhui Medical College. Before the survey, each participant provided verbal informed consent. In addition, data related to private information were deleted during the analysis process. The inclusion criteria included: subjects within the age range of 23 to 85 years; availability of data on age, sex,systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), glucose (GLU), low density lipoprotein (LDL) and high density lipoprotein (HDL), and HGH. All subjects completed physical examination, blood biochemical examination, and blood routine examination. The exclusion criteria were: subjects with incomplete clinical data, duplicated cases, and missing data; patients receiving drug intervention, and those with cancer, severe cardiovascular disease, or severe infections. The study involved a total of 6843 participants made up of 2595 women (37.92%) and 4248 men (62.08%) who underwent a health check upon their request. The mean ages of the female and male participants were 49.8 ± 12.3 and 51.7 ± 12.2 years, respectively.

2.2. Questionnaire

A questionnaire was used to collect information with respect to demographic and behavioral characteristics, disease history, and surgical history. The demographic characteristics included age, sex, occupation and educational background, while the behavioral characteristics included smoking and drinking. The other information were disease history, surgical history, and history of severe infections.

2.3. Physical examination

According to the guidelines of World Health Organization (WHO)/International Society of Hypertension,[24] unified trained professionals measured height, weight, blood pressure, and other variables using standard methods. Height measurement required subjects to stand barefooted on the floor of the height meter, with their trunks naturally straight, heads straight, eyes flat in front, upper limbs drooping naturally, and legs straight. The recorded data were accurate to 0.1 cm. Body weight measurement required barefooted subjects to wear shorts and stand naturally in the center of the weight pedal to keep their bodies stable. The recorded data were accurate to 0.1 kg. BMI was calculated by dividing body weight (kg) by height (cm) squared, with an accuracy of 0.01 kg/m^2. Blood pressure was measured with a mercury sphygmomanometer, and the subjects were advised to sit still for 5 minutes before the measurement. Systolic and diastolic blood pressures were measured.

2.4. Laboratory examination

Fasting venous blood (5 mL) was collected from each subject in the morning, and all samples were analyzed within 24 hours. The variable was measured by the Hitachi 7600 automatic biochemical analyser (Hitachi, Japan). The indicators included TG, TC, GLU, LDL, and HDL. The concentration of HGH was measured using the Access Automatic Immunoassay Analyzer from Beckman, USA.

2.5. Diagnostic criteria

Hypertension was defined as SBP exceeding 140 mmHg or DBP exceeding 90 mmHg or ongoing treatment with antihypertensive drugs.[24]

3. Statistical analysis

The participants were divided into 4 groups via 4 quartiles of HGH. The demographic characteristics are presented as mean ± standard deviation, or frequency (%). Chi-square test or variance of analysis was used to compare the differences in variables of demographic and behavioral characteristics, physical examination, blood biochemical examination, and blood routine examination among different quartiles of HGH. After adjusting for BMI, GLU, TC, TG, SBP, DBP, HDL, and LDL, analysis of a possible non-linear relationship amongst HGH, age and sex was done using generalized smoothing splines with knot locations generated automatically in generalized additive models with R package MGCV.[25] In addition, after adjusting for smoking, drinking and BMI, the relationship amongst HGH, sex and different age groups was determined with 2-piecewise logistic regression model analysis. All tests were two-sided and statistical significance was assumed at $P < .05$. Data management and all analyses were performed using R software program (V.3.4.2.).

4. Results

4.1. General characteristics of different HGH groups

Table 1 shows that sex, age, TG, TC, GLU, LDL, and HDL differed significantly amongst the 4 HGH groups ($P < .001$). The proportion of women increased at higher HGH concentrations, and HDL also increased at higher HGH concentrations, while BMI and TG decreased with increase in HGH concentration.

4.2. Relationship between HGH and age

Figure 1 shows a U-shaped curve relationship between HGH and age. The concentration of HGH decreased with age before 55 years of age, and increased with age after 55 years of age, before and after adjustment for BMI, GLU, TC, TG, SBP, DBP, HDL, and LDL. However, logistic regression analysis showed that there was no relationship between age and HGH (Table 2).

4.3. Relationship between HGH and age in different sexes

After adjusting for BMI, GLU, TC, TG, SBP, DBP, HDL, and LDL, the smooth curve showed a U-shape relationship between HGH and age in women and men. The age thresholds of 60 (in women) and 50 (in men) were observed between the age groups and HGH concentration (Fig. 2). Segmental logistic regression analysis with sex stratification showed that HGH levels decreased in women when aged <60 years (OR = 0.711, $P < .001$), but no significant trend was found when age was >60 years (Table 3 and Fig. 2A). In the men group, the curve changed significantly from upward trend to downward trend at ages >50 years (OR = 1.472, $P < .001$), but there was no statistical significance at ages <50 years ($P = .992$) (Table 3 and Fig. 2B).

Table 1

Comparison of demographic characteristics and biochemical indicators of different groups of human growth hormone.

Variable	HGH, ng/mL				χ^2/F	*P* value
	<0.08 (n=1670)	0.08–0.18 (n=1758)	0.18–0.43 (n=1691)	0.43~ (n=1724)		
Sex						
Female	548 (32.81%)	559 (31.80%)	627 (37.08%)	861 (49.94%)	152.81	<.001
Male	1122 (67.19%)	1199 (68.20%)	1064 (62.92%)	863 (50.06%)		
Age, y	50.35±11.46	51.36±11.96	51.77±12.50	50.29±13.09	18.11	<.001
BMI, kg/m^2	24.40±3.22	24.04±3.27	23.81±3.19	23.03±3.23	151.87	<.001
SBP, mmHg	118.95±16.66	118.63±16.82	118.22±16.86	116.59±17.39	25.50	<.001
DBP, mmHg	78.99±10.35	78.92±10.71	78.43±10.34	76.98±10.39	41.08	<.001
GLU, mmol/L	5.54±1.17	5.57±1.15	5.55±1.22	5.42±1.12	11.55	.009
TC, mmol/L	4.78±0.91	4.69±0.87	4.74±0.90	4.69±0.88	11.21	.011
TG, mmol/L	1.73±1.27	1.63±1.29	1.60±1.43	1.42±1.23	142.78	<.001
LDL, mmol/L	2.78±0.76	2.72±0.74	2.74±0.76	2.72±0.72	9.89	.020
HDL, mmol/L	1.24±0.35	1.26±0.36	1.31±0.38	1.35±0.39	92.86	<.001

Notes: Data are presented as mean±standard deviation, or number of subjects (%).

BMI=body mass index, DBP=diastolic blood pressure, GLU=glucose, HDL=high density lipoprotein, HGH=human growth hormone, LDL=low density lipoprotein, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides.

5. Discussion

It has been reported that insulin-like growth factor (IGF-1) secreted by HGH is related to hepatocellular carcinoma, because in mammals, besides energy metabolism, the pathway of IGF is involved in cell proliferation, migration, and malignant transformation.[26] Cardiovascular diseases caused by oversecretion of HGH seriously affect the quality of human life,[27,28] so the control of HGH plays a very important role in health and disease process.[29,30]

In this study, it was found that HGH was significantly correlated with sex and age (Table 3). Before sex stratification analysis, logistic regression model showed that there was no significant association between HGH with age, but from smooth curve analysis a U-shaped curve existed between these 2, with or without adjustment for influencing factors. Then, after sex stratification analysis, the results revealed different U-shaped curves between HGH and age in men and women. When women were under 60 years old, the concentration of HGH decreased with age, while it increased with age when men were over 50 years old.

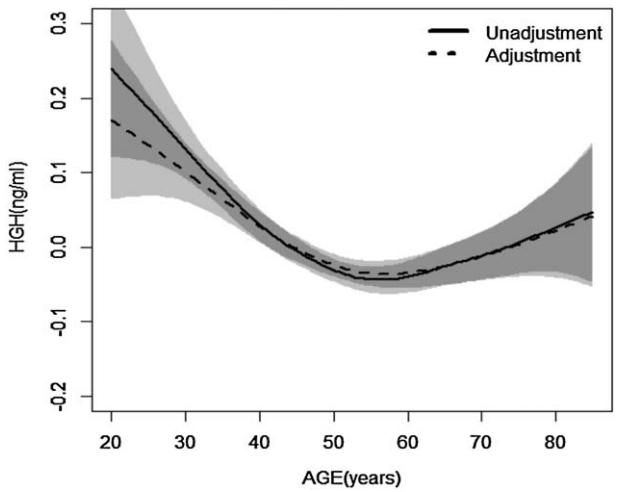

Figure 1. Smooth curve for human growth hormone and age. Notes: Horizontal coordinates represent different components, while vertical coordinates represent residuals of HGH. Solid line: no adjustment; dashed line: adjusted for body mass index, glucose, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, high density lipoprotein, low density lipoprotein. HGH=human growth hormone.

However, studies on the association of HGH levels with age in different sex groups are limited. Existing literature shows that changes in HGH peak value in adolescence are directly related to elevation in estrogen levels.[31] Estrogens may increase GH concentrations in women during aging,[19] HGH production begins to decline from middle age.[32] Women aged over 60 years are basically menopausal, with very low estrogen secretion.[33] Endogenous factors may protect the GH axis from age in postmenopausal women.[22] These are consistent with the results obtained in the present study, in which HGH level decreased with age before the age of 60, with no correlation between HGH and age at ages above 60 years. Compared with healthy premenopausal women, changes in HGH concentration were more obvious in men. Some studies show that age-related decreases in growth hormone (GH) release are due to weakening of the hypothalamic regulatory feedback.[34–36] At the age of 50, the serum HGH level of men showed a turning point. This is contrary to a previous report showing that HGH secretion in men was generally lower than that in women.[37] In the present study, it was also revealed that the overall HGH level of women was higher than that of men. Moreover, BMI was identified as a factor associated with HGH, those with high BMI have a high risk of acute renal insufficiency and other diseases. It has been widely reported in cohort and other studies that HGH significantly reduces fat mass.[38–40] Consistent with previous reports,[41,42] it was also found in this study that LDL and TG are linked to elevation of HGH concentration.

Table 2

Logistic regression analysis of human growth hormone and age.

Variable	Unadjusted			Adjusted*		
	β	SE	*P*	β	SE	*P*
Age	0.006	0.030	.836	0.019	0.031	.533

Notes: *Adjusted for BMI, GLU, TC, TG, SBP, DBP, HDL, LDL.

BMI=body mass index, DBP=diastolic blood pressure, GLU=glucose, HDL=high density lipoprotein, LDL=low density lipoprotein, SBP=systolic blood pressure, SE=standard error, TC=total cholesterol, TG=triglycerides.

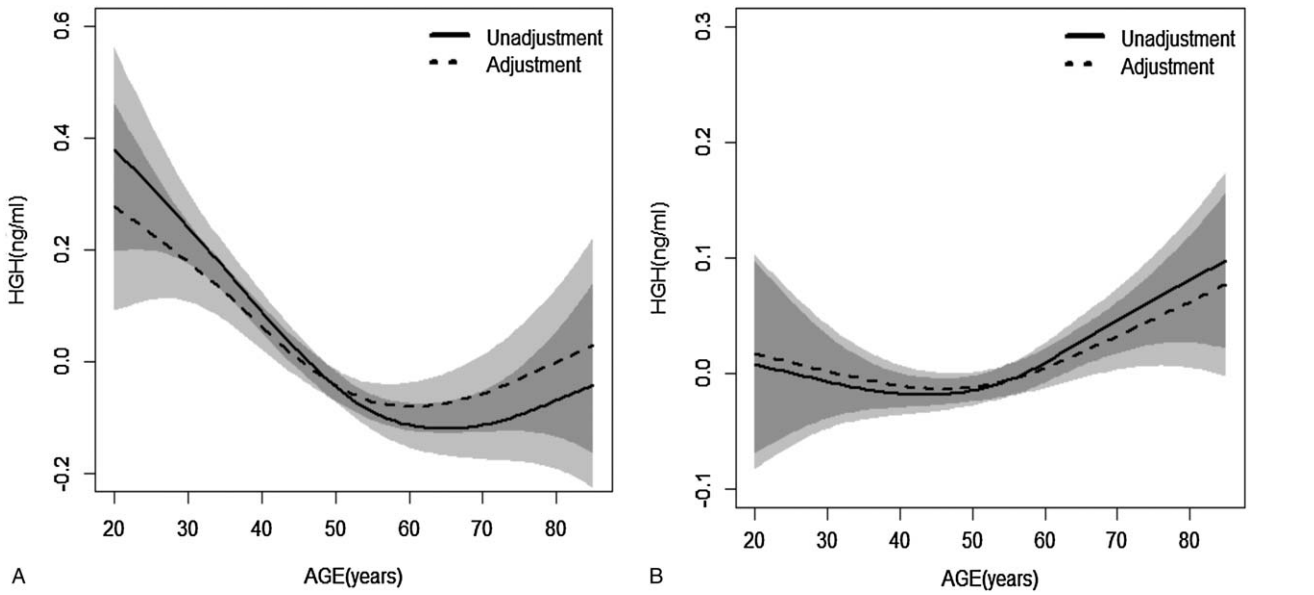

Figure 2. A. Smooth curve of human growth hormone and age in women group. Notes: Horizontal coordinates represent age, while vertical coordinates represent residuals of HGH. Solid line: no adjustment; dashed line: adjusted for body mass index, glucose, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, high density lipoprotein, low density lipoprotein. B. Smooth curve of human growth hormone and age in men group. Notes: Horizontal coordinates represent age, while vertical coordinates represent residuals of HGH. Solid line: no adjustment; dashed line: adjusted for body mass index, glucose, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, high density lipoprotein, low density lipoprotein. HGH = human growth hormone.

Table 3

Stratified logistic regression of human growth hormone and age in different sexes.

	Unadjusted				Adjusted*			
Age	**OR**	**CI95%**		***P***	**OR**	**CI95%**		***P***
Female								
Total	0.733	0.666	0.807	<.001	0.767	0.690	0.851	<.001
<60	0.623	0.528	0.735	<.001	0.682	0.574	0.810	<.001
≥60	1.022	0.675	1.548	.918	0.917	0.599	1.405	.692
Male								
Total	1.258	1.167	1.355	<.001	1.263	1.169	1.364	<.001
<50	0.883	0.720	1.084	.236	0.898	0.728	1.107	.314
≥50	1.407	1.254	1.578	<.001	1.424	1.263	1.606	<.001

Notes: *Adjusted for BMI, GLU, TC, TG, SBP, DBP, HDL, LDL.
BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, GLU = glucose, HDL = high density lipoprotein, LDL = low density lipoprotein, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

6. Study limitations

This study has several limitations. Firstly, because the study participants were all health check-up, the potential and early cancer patients were not excluded due to the simplicity of physical examination and the difficulty in obtaining follow-up diagnostic and follow-up data. Secondly, being a cross-sectional study, causal relationships were not determined. In future, the scope of the study should be expanded to include a prospective study focused on serum HGH changes in men and women in the middle and old age, so as to investigate the underlying mechanism.

7. Conclusion

This study has established U-shape relationships between HGH and age, with 2 thresholds of age (60 years in women and 50 years in men): HGH decreased in women aged <60 years, and increased in men aged >50 years. These results suggest that when using HGH as a biomarker for cancer screening, the influence factors such as age and sex should be taken into consideration.

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