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ASSESSING THE INVERSE CORRELATION OF SPONTANEOUS GROWTH HORMONE RELEASE TO INTERMUSCULAR THIGH FAT IN POSTMENOPAUSAL FEMALES WITH ABDOMINAL OBESITY: A CROSS-SECTIONAL CLINICAL STUDY

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ABSTRACT

Background: Decreased growth hormone secretion and accelerated visceral fat deposition are seen in subjects with metabolic syndrome. However, scarce literature data focused on the association of decreased growth hormone secretion and increased fate in liver and muscle previously.

Aims: The present cross-sectional clinical study was conducted to assess the association of growth hormone secretion with adipose tissue deposition in regional body parts

Materials and Methods: In 22 females, CT, body weight, Growth hormone profile, and OGTT (oral glucose tolerance test) were done followed by Growth hormone levels. Growth hormone concentration, IGF-1 levels, growth hormone-binding protein, estradiol levels, free fatty acid levels, HbA1c, and serum insulin levels were also assessed. The collected data were subjected to statistical evaluation and results were formed.

Results: Negative correlation between pulsatile and basal GH secretions with respective p-values of <0.001 and <0.01, but not with liver fat content and mean muscle attenuation (thigh) with p-values of 0.8. Glucose disposal rate correlated positively with pulsatile and basal growth hormone secretions. A negative correlation was seen with other parameters like triglycerides, fasting glucose, and insulin with a p-value <0.05 for all variables. A clear inverse relationship was seen between thigh IMAT and muscle attenuation with p of <0.002. A significant inverse relation was seen between pulsatile GH secretion and IMAT thigh (p <0.001).

Conclusion: Within its limitations, the present study concludes that in postmenopausal females with abdominal obesity, pulsatile GH secretion was inversely related with thigh IMAT, whereas basal GH secretion was associated with VAT, and no association of GH secretion was seen with liver fat.

Keywords: Abdominal obesity, abdominal visceral fat, growth hormone, metabolic disorder, post-menopausal females, thigh intermuscular mass

INTRODUCTION

Metabolic syndrome is strongly associated with excess deposition of adipose tissue in the viscera. Also excessive visceral fat is the main feature seen in metabolic syndrome. Metabolic syndrome is associated with an increased risk of developing diabetes and cardiovascular diseases. Metabolic syndrome is also associated with the fatty liver of non-alcoholic etiology, which a disease with varied and wide presentations from steatosis to steatohepatitis secondary to decreased growth hormone secretion which further leads to hyposomatotrophism in affected subjects.[1] The pathophysiology of visceral fat deposition in metabolic syndrome is poorly understood, however, it can be attributed to cumulative multiple endocrine disturbances and alterations affecting the sympathetic nervous system, and somatotropic, gonadal, and hypothalamic-adrenal axes, leading to visceral fat deposition.[2]

Various similarities are seen between adults with growth hormone deficiency and subjects with metabolic syndrome including high serum triglycerides, insulin resistance, low serum HDL cholesterol, and increased abdominal fats. Decreased GH secretion in adults with abdominal obesity relates strongly and inversely to visceral adipose tissue amount, with similar occurrence in males and females.[3] Replacement of growth hormone via exogenous therapy results in improved lipid profile, decreased risk for cardiovascular disease, and decreased visceral fat. The inverse relationship between decreased growth hormone (GH) release and increased visceral adipose tissues (VAT) in all age groups and both genders have been confirmed previously by approximate entropy and deconvolution analysis along with GH assays.[4]

The effect of GH release on regional fat has also been studied using magnetic resonance imaging (MRI) and CT (computed tomography) assessed body compositions. Fat deposition as seen in visceral adipose tissues is associated with metabolic syndrome and related metabolic alterations including insulin resistance.[5] Scarce data is literature is available concerning growth hormone secretion and adipose tissue regional distribution in areas like liver, muscles, and abdomen. Hence, the present clinical study was conducted to assess the correlation of spontaneous growth hormone release to regional adipose tissue distribution in the liver, muscles, and abdomen. The present study also assessed the association between metabolic risk factors and growth hormone secretion.

MATERIALS AND METHODS

The present cross-sectional clinical study was conducted at MBBS, Junior Resident, Department Of General Medicine, Rama Medical College Hospital & Research Centre, Kanpur, Uttar Pradesh, after obtaining clearance from the concerned Ethical committee. The study included 22 females with abdominal obesity and in the post-menopause phase. The study subjects were within the age group of 50 years to 70 years with a mean age of 54.6 years. The subjects were recruited from the patients visiting the Outpatient Department, Department of Obstetrics and Gynaecology of the institute.

The inclusion criteria for the study were post-menopausal females for at least past 1 year, within the age of 50-70 years, IGF (Insulin-like Growth Factor-1) value between K1 and K2, BMI (body mass index) between 25-35 kg/m^2, sagittal diameter >21 cm, waist-hip ratio >0.85, and subjects with no hormonal therapy (estrogen) post-menopause. The exclusion criteria were females with claudicatio intermittens, malignancy, stroke, hormone replacement therapy, diabetes mellitus, and subjects who were not willing to participate in the study.

After the final inclusion of 22 subjects, informed consent was taken. The subjects were advised to visit the Outpatient department 3 times a month with at least one week gap. At visit 1, body composition was assessed using measurements via CT and body weight followed by insulin sensitivity evaluation after overnight fast using hyperinsulinaemic glucose clamp. At visit 2, the Growth hormone profile was monitored at 20 minutes intervals for 12 hours. At visit 3, OGTT (oral glucose tolerance test) was done after an overnight fast using the standard method, where diabetes mellitus and impaired glucose tolerance were assessed following American Diabetes Association criteria.

Growth hormone secretory levels were assessed using approximate entropy and regional fat depots assessment was also done. CT was used to assess regional fat deposition. Regions assessed were visceral adipose tissues in L4 vertebrae, intermuscular adipose tissue and subcutaneous adipose tissue in the thigh, and abdominal subcutaneous adipose tissue. Intermuscular adipose tissue is the adipose tissue within muscle fascia between muscle bundles. 3 CT scans were done for each subject with scan 1 1cm below the gluteal fold in the thigh, scan 2 at L4, and scan 3 at the liver level. Liver attenuation was also noted to evaluate the fat content of the liver using the liver spleen attenuation ratio. Using biochemical and histomorphometric analysis methods, the liver spleen attenuation ratio showed an inverse relation to the fat content in the liver. Liver spleen ratio of <1 and liver attenuation of ≤30 HU (Hounsfield unit) was considered the cut-off for fatty liver. Mean muscle attenuation was determined in the right thigh showing an inverse association of muscle lipid content to skeletal muscle attenuation on CT.

Biochemical methods were adopted to assess growth hormone concentration, IGF-1 levels, growth hormone-binding protein, estradiol levels, free fatty acid levels, HbA1c, and serum insulin levels.

The collected data were subjected to the statistical evaluation using SPSS software version 21.0, 2012, Armonk, NY, ANOVA, and t-test. The results were formulated keeping the level of significance at $p<0.05$.

RESULTS

The present cross-sectional study was conducted on 22 post-menopausal females to assess the correlation of spontaneous growth hormone release to regional adipose tissue distribution in the liver, muscles, and abdomen. The present study also assessed the association between metabolic risk factors and growth hormone secretion. The study subjects were within the age group of 50 years to 70 years with the mean age of 54.6 years, IGF (Insulin-like Growth Factor-1) value between K1 and K2, BMI (body mass index) between 25-35 kg/m^2, sagittal

diameter >21 cm, and waist-hip ratio >0.85. In all the females, HbA1c values and fasting glucose levels were within the normal limits. One female had type 2 Diabetes and was excluded from the trial leaving 21 as the final sample size.

Concerning the correlation between regional fat deposition and growth hormone secretion, it was seen that there was a negative correlation between pulsatile and basal GH secretions with respective p-values of <0.001 and <0.01, but not with liver fat content and mean muscle attenuation (thigh) with p-values of 0.8 as shown in Table 1. Also, no relation was seen between regional fat deposition and approximate entropy with p-values of <0.6, <0.3, <0.2, <0.8, <0.2, and <0.3 for liver attenuation, VAT, SAT, mean muscle attenuation, IMAT, and thigh SAT respectively.

On assessing the correlation of metabolic parameters and regional fat deposition in the study subjects, it was observed that glucose disposal rate correlated positively with pulsatile and basal growth hormone secretions (Table 2) with p-values of <0.1, <0.002, <0.02, <0.001, and <0.02 for muscle attenuation, liver attenuation, VAT, SAT, and IMAT respectively. However, a negative correlation was seen with other parameters like triglycerides, fasting glucose, and insulin with a p-value <0.05 for all variables. Also, a positive correlation was seen in growth hormone-binding protein and thigh SAT, abdominal SAT, and VAT with respective p-values of <0.05, <0.01, and 0.03 respectively (Table 2). A clear inverse relationship was seen between thigh IMAT and muscle attenuation with p of <0.002.

The present study also assessed the correlation of metabolic parameters, regional fat deposition, and GH secretion in the study females, a negative relation was seen with visceral adipose tissue (p-value <0.05), but no relation was seen with IMAT thigh. A similar significant inverse relation was seen between pulsatile GH secretion and IMAT thigh (p <0.001), whereas a non-significant relationship was seen with visceral adipose tissue (Table 3) and basal GH secretion. Concerning basal GH secretion, a significant relation was seen with VAT only (p=0.01), whereas triglycerides and IGF binding protein 1 was associated non-significantly (0.14 and 0.2 respectively). For pulsatile GH secretion, IMAT thigh was only related significantly (p=0.01), whereas triglycerides, VAT, fasting glucose, fasting insulin, and IGF- binding protein 1 had a non-significant relationship with respective p-values of 0.3, 0.2, 0.1, 0.2, and 0.07.

DISCUSSION

The results of the present study suggest that in postmenopausal females with abdominal obesity, pulsatile GH secretion was inversely related with thigh IMAT (p<0.001), whereas basal GH secretion was associated with VAT (p<0.001), no association of GH secretion was seen with liver fat.

There was a negative correlation between pulsatile and basal GH secretions with respective p-values of <0.001 and <0.01, but not with liver fat content and mean muscle attenuation (thigh) with p-values of 0.8. Also, no relation was seen between regional fat deposition and approximate entropy with p-values of <0.6, <0.3, <0.2, <0.8, <0.2, and <0.3 for liver attenuation, VAT, SAT, mean muscle attenuation, IMAT, and thigh SAT respectively. Pijl H et al[7] and Miller KK et al[8] in 2005 reported similar findings between GH secretion and regional fat deposition.

In the present study, glucose disposal rate correlated positively with pulsatile and basal growth hormone secretions (Table 2) with p-values of <0.1, <0.002, <0.02, <0.001, and <0.02 for muscle attenuation, liver attenuation, VAT, SAT, and IMAT respectively. However, a negative correlation was seen with other parameters like triglycerides, fasting glucose, and insulin with a p-value <0.05 for all variables. Also, a positive correlation was seen in growth hormone-binding protein and thigh SAT, abdominal SAT, and VAT with respective p-values of <0.05, <0.01, and 0.03 respectively. A clear inverse relationship was seen between thigh IMAT and muscle attenuation with p of <0.002. These findings were in agreement with the studies of Gallagher D et al[9] in 2005 and Goodpaster BH et al[10] in 2000 where adipose tissue and glucose-related factors were assessed.

The study also showed a negative relation was seen with visceral adipose tissue (p-value <0.05), but no relation was seen with IMAT thigh. A similar significant inverse relation was seen between pulsatile GH secretion and IMAT thigh (p <0.001), whereas a non-significant relationship was seen with visceral adipose tissue and basal GH secretion. Concerning basal GH secretion, a significant relation was seen with VAT only (p=0.01), whereas triglycerides and IGF binding protein 1 was associated non-significantly (0.14 and 0.2 respectively). For pulsatile GH secretion, IMAT thigh was only related significantly (p=0.01), whereas triglycerides, VAT, fasting glucose, fasting insulin, and IGF- binding protein 1 had a non-significant relationship with respective p-values of 0.3, 0.2, 0.1, 0.2, and 0.07. These findings were consistent with the studies by Starck G et al[11] in 2002 and

Buijs MM et al[12] in 2003 where intermuscular adipose tissue and growth hormone secretions have comparable results.

CONCLUSION

Within its limitations, the present study concludes that in postmenopausal females with abdominal obesity, pulsatile GH secretion was inversely related with thigh IMAT, whereas basal GH secretion was associated with VAT, and no association of GH secretion was seen with liver fat. These study results-focused that the mechanism behind this correlation is fat deposition dependent interaction between the somatotrophic axis and fat mass in the body, where intermuscular thigh tissues play a vital role. However, the present study had few limitations including smaller sample size, shorter monitoring period, geographical area biases, and single-institutional nature. Hence, further longitudinal studies with a larger sample size and longer monitoring period are required to reach a definitive conclusion.

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TABLE

GH parameters	Liver attenuation		Visceral adipose tissue (VAT)		Abdominal sc adipose tissue (SAT)		Mean Muscle attenuation		Thigh intermuscular adipose tissue (IMAT)		Thigh sc adipose tissue	
	Value	p	Value	p	Value	p	Value	p	Value	p	Value	p
Approximate entropy	0.1	<0.6	0.2	<0.3	0.3	<0.2	0.1	<0.8	0.2	<0.2	0.3	<0.2
Basal GH secretion rate (µg/l/min)	-0.0002	<0.6	-0.8	<0.001	-0.6	<0.05	0.5	<0.05	-0.7	<0.01	-0.2	<0.3
Mean area	-0.1	<0.5	-0.4	<0.05	-0.3	<0.1	0.4	<0.1	-0.6	<0.001	-0.02	<0.8
Mean Interval (min)	0.1	<0.7	-0.1	<0.7	-0.1	<0.3	-0.1	<0.7	-0.3	<0.1	0.003	<0.8

No. of Peaks	0.1	<0.4	0.1	<0.8	0.2	<0.3	0.2	<0.4	0.2	<0.2	0.1	<0.6
Half-life (min)	0.4	< 0.06	0.1	<0.7	-0.1	<0.5	-0.3	<0.1	0.3	<0.2	-0.1	<0.6
Basal GH secretion log (µg/l/minx sampling duration)	-0.0004	<0.8	-0.6	<0.001	-0.4	<0.05	0.4	<0.05	-0.5	<0.01	-0.2	<0.3
Pulsatile GH secretion (peak no. x mean area)	-0.04	<0.8	-0.06	<0.02	-0.3	<0.2	0.3	<0.1	-0.7	<0.002	-0.02	<0.8
Total (pulsatile+basal) secretion	-0.03	<0.8	-0.6	<0.01	-0.4	<0.1	0.3	<0.1	-0.7	<0.002	-0.02	<0.8
Pulsatile %(pulsatile/total x 100)	-0.2	<0.3	-0.1	<0.5	0.1	<0.5	0.1	<0.3	-0.5	<0.04	0.3	<0.1

Table 1: Correlation of GH secretion and regional fat deposition in the study subjects

Parameter	Muscle attenuation		Liver attenuation		Visceral adipose tissue		Abdominal sc adipose tissue		Thigh intermuscular adipose tissue	
	r	p	r	p	r	p	r	p	r	p
GH binding protein (pmol/l)	0.001	<0.99	-0.1	<0.7	0.4	<0.03	0.5	<0.01	0.2	<0.2
Plasma Insulin (mU/l)	-0.4	<0.08	-0.2	<0.4	0.7	<0.001	0.4	<0.06	0.7	<0.001
2h- Glucose (mmol/l)	-0.3	<0.1	-0.1	<0.6	0.6	<0.001	0.6	<0.001	0.4	<0.05
Fasting Glucose (mmol/l)	0.1	<0.1	0.2	<0.6	0.6	<0.001	0.1	<0.001	0.2	<0.05
Triglycerides (mmol/l)	-0.6	<0.02	-0.1	<0.6	0.2	<0.2	0.1	<0.6	0.3	<0.2
Serum Free Fatty acids(mmol/l)	-0.6	<0.02	-0.6	<0.01	0.5	<0.02	0.4	<0.03	0.3	<0.01
Glucose Disposal Rate (mg/kg min)	0.3	<0.1	0.6	<0.002	-0.5	<0.02	-0.7	<0.001	-0.5	<0.03

Table 2: Correlation of metabolic parameters and regional fat deposition in the study subjects

Variables	r value (Single Regression)	p-value	r value (Multiple Regression)	p-value (Multiple Regression)
Pulsatile GH secretion				
Triglycerides	-0.4	<0.05	-0.18	0.3
Visceral adipose tissue	-0.5	<0.05	0.39	0.2
Fasting Glucose	-0.4	<0.05	-0.37	0.1
Fasting Insulin	-0.4	<0.05	0.27	0.2
IGF- binding protein 1	0.5	<0.01	0.38	0.07

Thigh intermuscular adipose tissue	-0.6	<0.01	-0.87	0.01
Basal GH secretion				
Triglycerides	-0.4	<0.04	-0.21	0.2
IGF- binding protein 1	0.5	<0.01	0.27	0.14
Visceral adipose tissue	-0.6	0.02	-0.51	0.01

Table 3: Correlation of metabolic parameters, regional fat deposition, and GH secretion in the study subjects