Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 05, 2023

ANALYZING THE EFFECT OF GROWTH HORMONE TREATMENT ON REDUCING ABDOMINAL VISCERAL FAT IN POSTMENOPAUSAL FEMALES HAVING ABDOMINAL OBESITY: A PLACEBO-CONTROLLED CLINICAL STUDY

Dr. Anand Jat,[1] Dr. Ravi Kumar Patel,[2] Dr. Trupti Bele[3*]

[1]MBBS, MD, Assistant professor, Department of General medicine, LN medical college and Research Centre, Bhopal, Madhya Pradesh
[2]MBBS, MD, Assistant Professor, Department of General Medicine, LN Medical College and Research Centre, Bhopal, Madhya Pradesh
MBBS, MD, Consultant Pathologist, Parbhani, Maharashtra

Address for Correspondence

Dr. Trupti Bele

E-mail: dr.truptibele247@gmail.com

Type of study: Original Research Paper
Conflict of Interest: None

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ABSTRACT

Background: In subjects with abdominal obesity, Growth hormone (GH) secretion is reduced with altered cardiovascular risk factors leading to metabolic syndrome. Treatment with GH in males with abdominal obesity showed improved metabolic functions, similar data in females is lacking.

Aims: The present study was conducted to assess the effect of GH treatment on reducing the abdominal visceral fat in post-menopausal females having abdominal obesity and to evaluate its effects on glucose tolerance and visceral fat mass.

Materials and Methods: 38 post-menopausal females were randomly divided into two groups where 1 group received placebo therapy and for other group growth hormone therapy was given. Assessment of body parameters, glucose tolerance, and insulin sensitivity was carried out at baseline (treatment start), 6 months, and 12 months after therapy, and results were formed.

Results: The serum levels of IGF-1 increased for group II from 101±6.8 at baseline to 211±15.8 ($p<0.001$) at 6 months, whereas for group I non-significant change was seen from 121±4.8 to 119±5.8g/L, whereas from 6 to 12 months no statistically significant difference was seen in both the groups. In group II, at 6 months, HDL cholesterol and total triglycerides increased following GH treatment. Visceral adipose tissue decreased in Group II after GH treatment significantly from 177.0±8.5 to 170.4±9.8, whereas an increase was seen in Group I from 161.1±7.7 to 172.0±8.7 ($p=0.002$).

Conclusion: The present study concludes that growth hormone therapy is beneficial in postmenopausal subjects with abdominal obesity resulting in improved insulin sensitivity, decreased hepatic fat levels, and other metabolic syndrome features.

Keywords: Abdominal obesity, abdominal visceral fat, growth hormone, metabolic disorder, postmenopausal females

INTRODUCTION

One of the strong and major risk factors leading to the development of Type 2 diabetes mellitus and cardiovascular disease is abdominal obesity. Diabetes mellitus type 2 is associated with dyslipidemia, hypertension, and/or insulin resistance leading to a condition termed metabolic syndrome. As per WHO (World Health Organization), metabolic syndrome is defined using insulin resistance as the etiologic factor behind this entity.[1] However, abdominal obesity is considered as a risk factor for metabolic syndrome by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP's ATP III) and National Health and Nutrition Examination Survey of 1999–2000 (NHANES III). Abdominal obesity is also related to the development of insulin resistance, atherogenic dyslipidemia, prothrombotic state, and/or proinflammatory state.[2]

Various previous literature studies suggested increased metabolic syndrome globally irrespective of defining criteria used. Earlier studies suggested more metabolic prevalence in males compared to females. However, recent literature work suggests equal gender prevalence with the same risk of developing type 2 diabetes mellitus in both genders. Concerning cardiovascular disease development, a Heart study by Framingham suggests strong risk in females compared to males with metabolic syndrome. These findings have weaker evidence and were not confirmed by other studies.[3]

Apart from 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, which in turn, are strongly related to hypertriglyceridemia, type 2 diabetes mellitus, and/or insulin resistance. 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.[4]

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.[5] Replacement of growth hormone via exogenous therapy results in improved lipid profile, decreased risk for cardiovascular disease and decreased visceral fat. Also, in males with abdominal obesity, improved insulin sensitivity was reported with 9 months of treatment with growth hormone replacement therapy.

Also, 12 weeks treatment with Growth hormone along with exercise and diet resulted in decreased truncal fat in postmenopausal females, which is similar to effects seen with exercise and diet, whereas 5 weeks treatment with Growth hormone in obese females resulted in decreased body fat mass. However, no long-term statics is available on growth hormone treatment effect in abdominal obese females, as no literature work shows better efficacy of

GH than weight reduction to decrease total body fat in simple obese subjects.[6] Hence, the present study was conducted to analyze the effect of GH treatment on reducing the abdominal visceral fat and insulin sensitivity in postmenopausal females having abdominal obesity and to evaluate its effects on glucose tolerance and visceral fat mass.

MATERIALS AND METHODS

The present study was a randomized, placebo-controlled trial conducted at after obtaining clearance from the concerned Ethical committee. The study included a total of 38 post-menopausal females from the age range of 50-56 years and a mean age of 57.4 years. The subjects were the females recruited from the menopausal females visiting the Outpatient Department, Department of Obstetrics and Gynaecology.

The inclusion criteria for the study were obese postmenopausal females from the age group of 50-70 years, serum IGF-1 levels between -1 and -2 sd, waist-to-hip (W/H) ratio and/or a sagittal diameter larger than 0.85 and 21.0 cm respectively, and BMI (body mass index) in range of 25-35 kg/m^2. The exclusion criteria for the study were subjects with cardiovascular disease, diabetes mellitus, stroke, hormone treatment including estrogen replacement therapy, claudicatio intermittent, and malignancy. A total of 160 females were screened and 38 females were finally included after inspecting exclusion and inclusion criteria.

After final inclusion, 38 study subjects were randomly divided into two groups where 1 group received placebo therapy and for other group growth hormone therapy was given. Randomization was done by using the flip of a coin. The growth hormone group was treated with GH before going to bed. The initial dose given was 0.13 mg/day followed by an increase at 2 weeks to 0.27 mg/day, then 0.4 mg/day after 4 weeks, 0.53mg/day after 5 weeks, and 0.67mg/day after 6 weeks. Any adverse effects, signs, and symptoms were recorded at each visit. For side-effects related to fluids, the GH dose was reduced by half. At every visit, written as well as oral instructions were given to all subjects. Treatment compliance was evaluated by counting the number of returned empty vials, expressing the vials percentage required for treatment.

Assessment of body parameters, glucose tolerance, and insulin sensitivity was carried out at baseline (treatment start), 6 months, and 12 months after therapy. Quality of life, physical activity, and CT (Computed tomography) for the thigh and abdomen region was done only at baseline and 12 months. Laboratory examination and physical examination were performed at 1 month, 2, 3, 6, 9, and 12 months, and 1 month after treatment completion.

Concerning body composition, total body potassium, fat-free mass, and total body fat were calculated. Thigh muscle and abdominal adipose tissues were measured using CT. 4 scans were done for the mid-thigh region, fourth lumbar vertebra, mid-liver level, and fourth cervical vertebra level. Hepatic fat content was also evaluated using a biochemical approach where fatty liver was taken after a cut-off value of30/less liver attenuation. Insulin sensitivity was also assessed. OGTT (oral glucose tolerance test) was done at baseline, 6 months, and 12 months, and 1 month after treatment completion. From the collected blood samples, IGF-1, triglycerides, serum insulin, blood glucose, and Serum total cholesterol were assessed.

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 two groups were matched concerning demographic characteristics at the baseline for mean age, BMI, alcohol intake, smoking history, and hypertensive status where the non-significant difference between all the characteristics was seen concerning all mentioned demographics where the mean age of study subjects for group I and II was 56.42 and 58.28 respectively, and BMI was 30.2±0.6 and 30.8±0.5 respectively as described in Table 1.

The study groups were also matched well at baseline for waist, weight, free fat mass, total body fat, waist-hip ratio, sagittal diameter, Mean Liver Attenuation, Visceral adipose tissue area, Abdominal adipose tissue area, and Thigh muscle area with the respective p-values of 0.6, 0.8, 0.8, 0.8, 0.2, 0.7, 0.5, 0.02, 0.7, and 0.02 showing all non-significant differences (Table 2).

The growth hormone dose at 12 months was 0.50±0.03 in Group II and was 0.62±0.01 for Group I, showing a statistically significant difference (p=0.001). The serum levels of IGF-1 increased for group II from 101±6.8 at baseline to 211±15.8 ($p<0.001$) at 6 months, whereas for group I non-significant change was seen from 121±4.8 to 119±5.8g/L, whereas from 6 to 12 months no statistically significant difference was seen in both the groups (Table 3).

Concerning complications seen, in Group II (GH), 9 females experienced mild to moderate fluid retentive side effects at 4 weeks of therapy, in one subject, the symptoms subsided without intervention after 8 weeks, whereas for the other 8 females dose was reduced to half which was followed by the disappearance of the symptoms. In group I, 2 females reported these effects which again subsided with dose adjustments.

Glucose disposal rate (GDR) at baseline had no statistically significant difference in the two groups, also at 12 months, no significant difference was seen in the two groups (p=0.2). For Group II, on intragroup analysis, GDR increased at 12 months with a statistically significant difference from baseline compared to Group I. Significant changes were also not seen in 2-hour glucose values, and fasting plasma glucose levels in both groups (=0.8 and 0.5 respectively) as shown in Table 3.

Concerning lipid and cholesterol metabolism, LDL cholesterol and total cholesterol levels were decreased in Group II (4.31±0.14 to 3.85±0.16) compared to Group I (4.37±0.22 to 4.27±0.18) from baseline to 6 months to 12 months. In group II, at 6 months, HDL cholesterol and total triglycerides increased following GH treatment. Apo lipoprotein A/B (g/L) showed no difference in both the groups after GH treatment/Placebo (Table 4).

Bodyweight in Group I and Group II increased from baseline to 12 months, with more than 1kg weight gain in 14 and 10 subjects from Group I and II respectively with a p-value of 0.8 showing no statistically significant difference between groups. Total body fat values for Group I and II at baseline was 46.7±1.1 and 48.5±1.1 respectively with no inter-group difference in both groups concerning free fat mass and total body fat at any recall interval (p=0.8). Similarly, no significant difference was seen in Abdominal adipose tissue and thigh muscles between groups p=0.7 and 0.002 respectively. Visceral adipose tissue decreased significantly in Group II after GH treatment from 177.0±8.5 to 170.4±9.8, whereas an

increase was seen in Group I from 161.1±7.7 to 172.0±8.7 (p=0.002). Quality of life was also the same for both groups.

DISCUSSION

The two groups were matched concerning demographic characteristics at the baseline for mean age, BMI, alcohol intake, smoking history, and hypertensive status where the non-significant difference between all the characteristics was seen concerning all mentioned demographics where the mean age of study subjects for group I and II was 56.42 and 58.28 respectively, and BMI was 30.2±0.6 and 30.8±0.5 respectively. The study groups were also matched well at baseline for waist, weight, free fat mass, total body fat, waist-hip ratio, sagittal diameter, Mean Liver Attenuation, Visceral adipose tissue area, Abdominal adipose tissue area, and Thigh muscle area with the respective p-values of 0.6, 0.8, 0.8, 0.8, 0.2, 0.7, 0.5, 0.02, 0.7, and 0.02 showing all non-significant differences. These demographics were similar to Taaffe DR et al[7] in 2007 and Tomlinson JW et al[8] in 2004 where authors reported similar demographics.

The serum levels of IGF-1 increased for group II from 101±6.8 at baseline to 211±15.8 ($p<0.001$) at 6 months, whereas for group I non-significant change was seen from 121±4.8 to 119±5.8g/L, whereas from 6 to 12 months no statistically significant difference was seen in both the groups. Glucose disposal rate (GDR) at baseline had no statistically significant difference in the two groups, also at 12 months, no significant difference was seen in the two groups (p=0.2). For Group II, on intragroup analysis, GDR increased at 12 months with a statistically significant difference from baseline compared to Group I. Significant changes were also not seen in 2-hour glucose values, and fasting plasma glucose levels in both groups (=0.8 and 0.5 respectively). These results were in agreement with the findings of Nam SY et al[9] in 2001 and Ferrara CM et al[10] in 2002 where authors reported comparable results to the present study.

Concerning lipid and cholesterol metabolism, LDL cholesterol and total cholesterol levels were decreased in Group II (4.31±0.14 to 3.85±0.16) compared to Group I (4.37±0.22 to 4.27±0.18) from baseline to 6 months to 12 months. In group II, at 6 months, HDL cholesterol and total triglycerides increased following GH treatment. Apo lipoprotein A/B (g/L) showed no difference in both the groups after GH treatment/Placebo. Bodyweight in Group I and Group II increased from baseline to 12 months, with more than 1kg weight gain in 14 and 10 subjects from Group I and II respectively with a p-value of 0.8 showing no statistically significant difference between groups. Total body fat values for Group I and II at baseline was 46.7±1.1 and 48.5±1.1 respectively with no inter-group difference in both groups concerning free fat mass and total body fat at any recall interval (p=0.8). Similarly, no significant difference was seen in Abdominal adipose tissue and thigh muscles between groups p=0.7 and 0.002 respectively. Visceral adipose tissue decreased significantly in Group II after GH treatment from 177.0±8.5 to 170.4±9.8, whereas an increase was seen in Group I from 161.1±7.7 to 172.0±8.7 (p=0.002). Quality of life was also the same for both groups. These results were similar to the results of Johanson EH et al[11] in 2003 and Sesmilo G et al[12] in 2000 where similar results concerning body fat, free fat mass, and lipid profile were described by the authors.

CONCLUSION

Within its limitations, the present study concludes that growth hormone therapy is beneficial in postmenopausal subjects with abdominal obesity resulting in improved insulin sensitivity, decreased hepatic fat levels, and other metabolic syndrome features. This might result in decreased risk for cardiovascular diseases. 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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TABLES

Characteristics	Group I (Placebo therapy) % (n)	Group II (GH therapy) % (n)
Total number	19	19
Mean age (years)	56.42	58.28
Smoking		
Positive	21.05 (4)	21.05 (4)
Negative	78.94 (15)	78.94 (15)
Alcohol		
Positive	100 (19)	100 (19)
Negative	0	0
Hypertension (under medication)	15.78 (3)	15.78 (3)
BMI (kg/m^2)	30.2±0.6	30.8±0.5

Table 1: Demographic characteristics of the study subjects

Characteristics	Group I (Placebo therapy) (Mean±S.D)			Group II (GH therapy) (Mean±S.D)			p-value
	Baseline	6 months	12 months	Baseline	6 months	12months	
Waist (cm)	102.04±1.4	102.04±1.6	102.04±1.8	104±1.3	103±1.4	104±1.5	0.6
Weight (kg)	80.7±2.0	80.5±2.1	81.6±2.1	86.0±2.2	86.1±2.4	87.0±2.3	0.8
Free fat mass (kg)	46.7±1.1	47.4±1.1	46.6±1.2	48.5±1.1	48.7±1.1	48.0±1.1	0.8
Total Body Fat (kg)	34.0±1.6	33.0±1.6	35.0±1.5	37.2±1.7	37.1±1.9	38.7±1.8	0.8
Waist: Hip ratio	0.92±0.010	0.92±0.01	0.91±0.01	0.91±0.01	0.90±0.01	0.91±0.01	0.2
Sagittal diameter (cm)	25.0±0.43	24.6±0.46	24.9±0.54	25.6±0.32	25.2±0.41	25.5±0.38	0.7
Mean Liver Attenuation	51.0±2.7	-	51.2±2.3	49.0±2.1	-	51.1±2.0	0.5
Visceral adipose tissue area (cm^2)	161.1±7.7	-	172.0±8.7	177.0±8.5	-	170.4±9.8	0.002
Abdominal adipose tissue area (cm^2)	400.7±20.6	-	400.2±21.8	430.2±22.0	-	432±22.1	0.7
Thigh muscle area (cm^2)	110.7±3.2	-	110.5±3.0	110.2±2.5	-	113.0±2.3	0.002

Table 2: Body diameter and anthropometric characteristics of the study subjects

Characteristics	Group I (Placebo therapy) (Mean±S.D)			Group II (GH therapy) (Mean±S.D)			p-value
	Baseline	6 months	12 months	Baseline	6 months	12months	
Glucose Disposal rate (mg/kg min)	7.76±0.46	7.79±0.49	8.07±0.52	8.25±0.55	7.45±0.43	8.55±0.54	0.2
Fasting Insulin (mU/lit)	9.5±0.8	9.8±0.8	10.2±0.7	9.9±0.8	12.6±1.4	13.5±1.1	0.5
2h Glucose (mmol/min)	5.7±0.1	6.9±0.2	6.4±0.2	6.1±0.1	7.2±0.3	6.9±0.2	0.8
Fasting Glucose (mmol/min)	5.0±0.1	5.2±0.1	5.2±0.1	5.0±0.1	5.1±0.1	5.3±0.1	0.2
IGF-1 (µg/liter)	121±4.8	119±5.8	120±6.8	101±6.8	211±15.8	206±18.8	<0.001

Table 3: Insulin and Glucose parameters assessment in the study subjects

Parameter	Group I (Placebo therapy) (Mean±S.D)			Group II (GH therapy) (Mean±S.D)			p-value
	Baseline	6 months	12 months	Baseline	6 months	12months	
Apo lipoprotein A/B (g/L)	0.6±0.03	0.7±0.04	0.6±0.03	0.6±0.01	0.6±0.02	0.6±0.02	0.3
Lipoprotein (g/L)	0.40±0.05	0.41±0.05	0.40±0.05	0.26±0.02	0.28±0.03	0.28±0.03	0.6
Triglycerides (mmol/L)	1.47±0.08	1.72±0.22	1.59±0.12	1.47±0.10	1.69±0.17	1.53±0.13	0.7
HDL cholesterol (mmol/L)	1.25±0.06	1.22±0.06	1.25±0.05	1.29±0.04	1.21±0.04	1.29±0.03	0.5
LDL cholesterol (mmol/L)	4.37±0.22	4.27±0.18	4.19±0.21	4.31±0.14	3.85±0.16	4.11±0.15	<0.05
Total cholesterol (mmol/L)	6.32±0.24	6.28±0.21	6.19±0.22	6.29±0.13	5.80±0.16	6.07±0.14	0.05

Table 4: Cholesterol, Lipoprotein, and Apolipoprotein assessment in the study subjects