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Anthropometric changes in diabetic steatohepatitic patients treated pharmacologically versus dietetically

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis, to inflammatory non- alcoholic steatohepatitis (NASH); with increasing levels of fibrosis and ultimately cirrhosis. Pioglitazone is an insulin sensitizer of the TZD class of Antidiabetic agents that lead to improvement of insulin sensitivity through perosisome proliferators activated receptor and improving the biochemical and histological indices in NASH patients.

To evaluate the effect of pioglitazone, calorie restriction and combining the two methods; this study was performed; where 90 patients were subdivided equally among 3 groups. The first group received pioglitazone in a 30 mg daily dose, the second group followed a restricted calorie diet with caloric reduction of (500 -1000 calorie) for females and (1000 -1200 calorie) for males of the original caloric intake, while the third group was subjected to a combination of both medical treatment and calorie restriction in the same doses as the first and second group. Concerning our patients treated with pioglitazone; the mean BMI & Mean abdominal girth significantly increased after the study; while mid arm circumference non significantly increased. Patients on restricted calories diet showed the same anthropometric results. The same was for the third group. The adverse effect of weight gain was proven in both groups A and C; where pioglitazone was a component of the treatment, also caloric restriction failed to control body weight and anthropometric measures; but it may have effect if longer time and stronger adherence to the associated calorie restriction model occurs.

Key words: Anthropometry – Diet, Pharmacological therapy, Non alcoholic steatohepatitis patients

1. Introduction

Non alcoholic fatty liver disease (NAFLD) is a clinico-pathological entity with histological features resembling alcohol-induced liver injury, though occurring in patients with little or no history of alcohol consumption. Its prevalence ranges from 9-36.9 % in the general population worldwide, and rises markedly in patients with diabetes, dyslipidemia and, especially, obesity *(Tokushige et al., 2011).* Non-alcoholic steatohepatitis (NASH) is part of the spectrum of NAFLD characterized by steatosis, lobular inflammation and progressive pericellular fibrosis *(Fan 2008).* The relation between body mass index and development of NAFLD documented in many studies, for example, *Uchil et al*, (2009) studied the development of NAFLD in

1003 people attending the health check-up and found that in the NAFLD group normal body mass index (BMI) was present in only 49/225 (20%) of the subjects, while 119/225 (52.8%) were overweight and 56/225 (24.8%) were obese. Generally, in obese populations NAFLD may affect up to 75% of subjects. In the morbidly obese, steatosis has been found in almost all subjects , with NASH being present in 25–70% of these individuals *(Utzschneider and Kahn 2006)*. Obesity, especially visceral obesity, is frequently associated with NAFLD and their coexistence in the same individual increases the likelihood of having more advanced forms of liver disease *(Jeong et al., 2008).* The incidence of type 2 DM is increasing throughout the world, reaching levels of a pandemic in countries like India and China. Only recently has liver disease been recognized as a major complication of type 2 DM with standard mortality rates for cirrhosis greater than that for cardiovascular disease *(Prashanth et al., 2009).* Additionally, the presence of diabetes has been identified as a risk factor for NASH, with one autopsy series showing a 2.6-fold increased risk of steatohepatitis in individuals who were hyperglycemic *(Utzschneider and Kahn 2006)*.

The BARD score is a simple scoring system that can be used as a predictive tool in assessing fibrosis in patients with NAFLD. It combines three variables; the BMI, AST/ALT ratio (AAR), and the presence of diabetes *(Harrison et al., 2008).* The simplified European Liver Fibrosis (ELF) panel excluded age, but did not change the diagnostic performance of the panel. The addition of five markers, including the BMI, presence of diabetes/impaired fasting glucose, AAR, platelet count, and albumin concentration, to the ELF test improved its diagnostic accuracy for the diagnosis of severe, moderate and no fibrosis, respectively *(Guha et al., 2008).*

A large number of studies were tried for the discovery of treatment modalities for NASH, but the number of well controlled trials is low. An ideal treatment of NAFLD should improve the liver damage and or its progression, both directly or through the modulation of its pathophysiological events *(Trappoliere et al., 2005).* Therefore drugs should ameliorate body weight, insulin resistance and other metabolic associated alterations, reduce the linkage between adipose tissue and liver by acting as anti inflammatory and/or immune modulatory agents, and modulate the progression of liver steatosis to inflammation and fibrosis by blocking the oxidative and nitrosamine stress. *(Trappoliere et al., 2005).* Patients with NAFLD typically are overweight or obese, insulin resistant, and have a consistently higher energy intake when compared with individuals without hepatic steatosis *(Capristo et al., 2005).* Data have shown that in the setting of obesity, moderate weight loss of approximately 6% via caloric restriction improves insulin resistance and intrahepatic lipid content *(Palmer and Schaffner 1990)*. Two classes of drugs have been shown to correct insulin resistance: biguanides (e.g., metformin) and thiazolidinediones (e.g., pioglitazone). At the moment, the use of these drugs remains experimental *(Trappoliere et al., 2005).* In uncontrolled studies, both rosiglitazone and pioglitazone treatment for 12 months resulted in histological improvement in up to two-third of patients *(Promrat et al., 2004).*

This investigation is to detect anthropometric changes on treatment of NASH associated with type II Diabetes Mellitus, comparing the pharmacological methods of treatment and dietary methods.

2. Patients and Methods

This study included 90 patients from obesity clinic; with hepatomegaly and elevated liver enzymes. All causes of elevated liver enzymes except NASH were excluded. The laboratory investigations and imaging processes were performed at the outpatient clinics at Theodor Bilharis Research Institute and National Research Center of Cairo, Egypt. Informed consent was obtained from each patient for being included in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and national) and with Helsinki Declaration of 1975, as revised in 2008 (5). All patients were subjected to careful history taking and clinical examination. They were divided into 3 groups. Patients were 20-60 years old; of both sexes. With elevated liver enzymes with no other cause of liver damage and no other life threatening conditions as malignancy, heart failure, renal impairment, liver cell failure, any type of malignancy. Maximum postprandial blood glucose was 240mg/dl. ALT and AST were less than 2.5 folds of the upper normal range. Exclusion criteria included organ cell failure, positive viral markers, alcohol intake, positive autoimmune markers, metabolic disorders, primary biliary cirrhosis, primary sclerosing cholangitis, history of hepatotoxic drugs and history of receiving metformin or insulin. After selection and assessment, subjects were randomized into 3 groups (A, B & C); where the first group received pioglitazone in a 30 mg daily dose, the second group followed a restricted calorie diet with calorie reduction of (500 -1000 calorie) for females and (1000 -1200 calorie) for males of the original caloric intake, while the third group was subjected to a combination of both medical treatment and caloric restriction in the same doses as the first and second group. Follow up of the treated groups included BMI (kg/m^2), abdominal girth (cm) and mid arm circumference (cm). The three groups were followed up for 6 months to observe the results of our study.

3. Results

The symptoms and signs of the examined cases of the 3 groups were displayed in tables: 1, 2&3. No significant difference between group-A, group-B and group-C before treatment as regards to mean BMI. In the change period mean BMI significantly increased in groups-A, B and C. After treatment group-C had highest mean BMI, followed by group-A then B, but the difference was statistically non-significant (Table: 4).

No significant difference between groups-A, B and C before treatment as regards to mean abdominal girth. In the change period mean abdominal girth significantly increased in groups-A, B and C. No significant difference between groups-A and C after treatment as regards to mean abdominal girth, both had significantly higher mean Abdominal girth than group-B(Table:5).

No significant difference between group-A, group-B and group-C before treatment as regards to mean mid arm circumference. In the change period mean mid arm circumference non significantly increased in group-A, group-B and group-C. No significant difference between group-A and group-C after treatment as regards to mean mid arm circumference, both had non significantly lower mean mid arm circumference than group-B(Table:6).

There was no significant difference in anthropometric measures between males and females of groups A, B &C (Tables: 7, 8&9). There was a significant positive correlation between age and BMI change in group A. (Table: 10, 11&12).

4. Discussion

Concerning our patients of group A treated with pioglitazone 30mg/day for 6 months; the mean BMI significantly increased after the study. These results coincided with the results by *Promrat et al.,(2004);* where the mean BMI increased in nearly significant manner with a P value 0.004 after treatment with 30 mg pioglitazone daily for 48 weeks. Also it coincided with the study of *Boettcher et al.,(2012)* ;where the BMI increased in a significant manner with a P value < 0.005; in which they used 30 mg pioglitazone for 9 months.

Mean abdominal girth increased in a significant manner after 6 months of pioglitazone therapy. These results were non coinciding with the results of *Promrat et al., (2004)* after treatment with 30 mg pioglitazone daily for 48 weeks; where the mean abdominal girth decreased, but in a non significant manner, may be due to longer duration of treatment. These results were coinciding with results of *Jonker et al., (2010);* where the abdominal girth increased in a significant manner after 2 years 30 mg daily pioglitazone therapy.

Mid arm circumference non significantly increased in our study group. These results were coinciding with the results by*(Smith et al., (2005)*; where the mid arm circumference increased in a non significant manner after pioglitazone 45 mg / day for the same 6 month duration.

As regards group B; where patients were on restricted calorie diet 500-1000K calorie/ day for females and 1000-1200K calorie/ day for male; the Mean BMI was significantly increased in our study. This was non coinciding with the results of *Huang et al., (2005);* where the BMI reduced but in a non significant manner and this may be attributed to longer duration of calorie restriction for 12 months. Our results also were non coinciding with results of *Belfort et al., (2006)* ; where there was non significant decrease in the BMI and this may be related to closer adherence to the feeding program and dietary education performed prior to their study with calorie restriction of 6 months. Also, these results were non coinciding with the results proven by *Samaha et al. ,(2003)* ; where his study showed after 6 months dietary restriction a significant drop in BMI; which could be attributed to the use of low carbohydrate diet. It was coinciding with the results of *Riley et al.,(2008)* ; where there was non significant change in the BMI after calorie restriction in his study for a period of 1 year.

Also, mean abdominal girth and mid arm circumference increased significantly and non significantly respectively in our study. These results are non coinciding with the results of *Huang et al., (2005)* ;where the abdominal girth and the mid arm circumference dropped ;but in a none significant manner and this was also owed to the longer duration of therapy (12 months) , and may be due to the poor compliance

and adherence of our patients to the dietary program. These results were non coinciding with results of *Promrat et al., (2010);* where the abdominal girth significantly dropped but after calorie restriction for 48 weeks.

For group C; mean BMI significantly increased in our study after 6 months treatment. These results coincided with the results proven by *Belfort et al., (2006)* ; where BMI increased in a significant manner after 6 months treatment with combination of pioglitazone and calorie restriction. This was non coinciding with the results proved by *Nakamura et al.,(2001)* ; where there was significant decrease of BMI along the course of 12 months duration with pioglitazone and calorie restriction diet, and this may be due to the longer duration of his study, and the behavioral modification performed by the study group.

Mean waist circumference and mid arm circumference significantly increased and non significantly increased respectively in our study. These results were non coinciding with the study of *Gupta et al., (1993)* ;where there was a significant drop in the waist circumference and mid arm circumference after use of 45 mg pioglitazone for 16 weeks aided with dietary restriction and this may be due to the stronger adherence to the associated calorie restriction model.

5. Tables

Table (1): The symptoms and signs observed in group A.

Symptom	Number of patients	Percentage
Obesity	28	93%
Easy fatigability	15	50%
Epigastric pain	10	33%
Distension	16	53.3%
Dyspepsia	9	30%
Constipation	11	36.6%
Diarrhea	7	23.3%
Signs	**Number of patients**	**Percentage**
Hepatomegaly	27	90%
Spleenomegaly	7	23.3%
Hepatospleenomegaly	5	16.6%

Peripheral neuropathy	3	10%

Table (2): The symptoms and signs observed in group B.

Symptom	Number of patients	Percentage
Obesity	27	90%
Easy fatigability	18	60%
Epigastric pain	5	16.6%
Distension	19	63.3%
Dyspepsia	7	23.3%
Constipation	12	40%
Diarrhea	7	23.3%
Signs	**Number of patients**	**Percentage**
Hepatomegaly	25	83.3%
Spleenomegaly	2	6.6%
Hepatospleenomegaly	3	10%
Peripheral neuropathy	2	6.6%

Table (3): The symptoms and signs observed in group C.

Symptom	Number of patients	Percentage
Obesity	29	96.6%
Easy fatigability	21	70%
Epigastric pain	8	26.6%
Distension	15	50%
Dyspepsia	11	36.6%

Constipation	7	23.3%
Diarrhea	8	26.6%
Signs	**Number of patients**	**Percentage**
Hepatomegaly	26	86.6%
spleenomegaly	4	13.3%
hepatospleenomegaly	2	6.6%
Peripheral neuropathy	3	10%

Table (4): Comparison between group-A, group-B and group-C before and after treatment as regards to BMI (kg/m^2)

Before					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**p**
A	33.9±5.9	28.3–48.0	**A/B**	-0.265	0.792
B	34.3±4.9	28.3–46.1	**A/C**	-0.288	0.774
C	34.4±6.5	28.5–45.6	**B/C**	-0.061	0.952
Change# (After-Before)					
Group	**Mean±SD**	**Range**	**Comp.**	**t_p**	**p**
A	2.2±0.6	1.3–3.6	**A/A**	-20.758	**<0.001***
B	1.8±0.5	0.0–3.0	**B/B**	-21.000	**<0.001***
C	2.1±0.3	1.3–2.9	**C/C**	-40.319	**<0.001***
After					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**P**
A	36.1±5.8	30.5–49.8	**A/B**	0.010	0.992
B	36.1±5.0	29.5–47.9	**A/C**	-0.231	0.818

C	36.5±6.5	29.6–47.7	**B/C**	-0.254	0.800

t_i: Independent t-test, **t_p:** Paired t-test**, Comp.:** Comparison groups

*****Significant **#** minus values indicate reduction

Table (5): Comparison between group-A, group-B and group-C before and after treatment as regards to Abdominal girth (cm)

Before					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**P**
A	97.2±16.2	69.0–132.0	**A/B**	-0.049	0.961
B	97.4±15.4	70.0–135.0	**A/C**	-0.092	0.927
C	97.6±14.7	71.0–133.0	**B/C**	-0.043	0.966
Change$^{\#}$ (After-Before)					
Group	**Mean±SD**	**Range**	**Comp.**	**t_p**	**P**
A	11.2±25.9	-65.4–64.9	**A/A**	2.372	**0.025***
B	6.0±16.1	-44.2–26.5	**B/B**	-2.051	**0.049***
C	10.3±27.1	-64.5–65.0	**C/C**	2.090	**0.046***
After					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**P**
A	108.4±23.3	69.0–141.0	**A/B**	-3.044	**0.004***
B	103.5±21.1	77.0–153.0	**A/C**	-0.175	**0.862**
C	107.9±31.4	70.0–143.0	**B/C**	2.346	**0.022***

t_i: Independent t-test, **t_p:** Paired t-test**, Comp.:** Comparison groups

*****Significant **#** minus values indicate reduction

Table (6): Comparison between group-A, group-B and group-C before and after treatment as regards to Mid arm circumference (cm).

Before					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**p**
A	36.9±5.9	27.0–49.0	**A/B**	-0.452	0.653
B	37.6±6.1	27.0–49.0	**A/C**	-0.610	0.544
C	37.8±6.0	28.0–49.0	**B/C**	-0.149	0.882
Change# (After-Before)					
Group	**Mean±SD**	**Range**	**Comp.**	**t_p**	**P**
A	1.2±5.4	-13.5–6.0	**A/A**	2.983	**0.059**
B	1.6±4.5	-16.6–8.7	**B/B**	-1.935	**0.063**
C	1.4±7.9	-15.0–26.0	**C/C**	2.015	**0.061**
After					
Group	**Mean±SD**	**Range**	**Comp.**	**t_i**	**P**
A	38.1±7.5	19.0–49.0	**A/B**	-2.804	0.648
B	39.2±7.0	24.0–52.0	**A/C**	-0.452	0.653
C	39.2±9.2	19.0–55.0	**B/C**	2.034	0.652

t_i: Independent t-test, **t_p:** Paired t-test**, Comp.:** Comparison groups

*****Significant **#** minus values indicate reduction

Table (7): Comparison between males and females of group-A as regards to change (after-before) in different studied parameters.

Variables	**Male (N=12)**	**Female (N=18)**	**t_i**	**p**
BMI (kg/m^2)	2.0±0.3	2.3±0.7	1.416	0.168
Abdominal girth (mm)	10.0±15.3	12.1±31.5	0.211	0.835
Mid arm circumference (mm)	4.1±6.1	2.2±5.0	0.906	0.373

t_i: Independent t-test

Table (8): Comparison between males and females of group-B as regards to change (after-before) in different studied parameters.

Variables	Male (N=11)	Female (N=19)	t_i	p
BMI (kg/m^2)	1.8±0.2	1.8±0.6	-0.36	0.721
Abdominal girth (mm)	11.2±10.6	3.0±18.2	-1.36	0.185
Mid arm circumfer.(mm)	3.0±3.3	0.8±5.0	1.310	0.201

t_i: Independent t-test, Minus values indicate reduction

Table (9): Comparison between males and females of group-C as regards to change (after-before) in different studied parameters.

Variables	Male (N=11)	Female (N=19)	t_i	p
BMI (kg/m^2)	2.2±0.3	2.0±0.3	-1.501	0.145
Abdominal girth (mm)	18.4±28.2	5.7±26.1	1.255	0.220
Mid arm circumference (mm)	3.8±7.1	2.4±8.5	0.442	0.662

t_i: Independent t-test, Minus values indicate reduction

Table (10): Correlation between age and change (after-before) in different studied parameters of group-A.

Variables	R	P
BMI (kg/m^2)	0.522	**0.003***
Abdominal girth (mm)	0.032	0.866
Mid arm circumference (mm)	0.123	0.517

r: Pearson correlation test

Table (11): Correlation between age and change (after-before) in different studied parameters of group-B.

Variables	R	P
BMI (kg/m^2)	0.134	0.481
Abdominal girth (mm)	0.089	0.639
Mid arm circumference (mm)	0.082	0.667

r: Pearson correlation test

Table (12): Correlation between age and change (after-before) in different studied parameters of group-C.

Variables	R	P
BMI (kg/m^2)	-0.208	0.270
Abdominal girth (mm)	0.030	0.874
Mid arm circumference (mm)	0.113	0.554

r: Pearson correlation test

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