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Effect of Betahistine and Metformin on Lipid Profile in Obese Females in Iraq: A Randomized, Placebo-Controlled Clinical Trial

Hayder H. Al-Anbari[1] *PhD*, **Adeeb A. Al-Zubaidy**[2] *PhD*, **Faris A. Khazaal**[3] *FRCP*

[1]Technical affairs Deputy Manager, Karbalaa Health Office, Karbalaa, Iraq, [2]Deen of College of Pharmacy, Al-Nahrain University, Baghdad, Iraq, [3]Head of Alkindy Obesity Unit, Alkindy College of Medicine, University of Baghdad, Iraq

Abstract

Background Obesity has become a major worldwide health problem and therefore, the associated morbidity, mortality and both medical and economical costs are expected to increase as well. Obesity increases cardiovascular risk via risk factors such as triglycerides (TG), high LDL cholesterol, low HDL cholesterol, elevated plasma glucose and insulin concentrations.

Objective To investigate the effect of metformin and betahistine along with lifestyle change on lipid profile in obese women in Iraq.

Methods This study was carried out on 78 female patients with age range of 18-50 years who were allocated into three groups: Group 1: treated with oral metformin 850 mg twice daily with lifestyle change for 12 weeks. Group 2: treated with betahistine 32 mg 3 times daily with lifestyle change for 12 weeks. Group 3: treated with placebo 500 mg twice daily with lifestyle change for 12 weeks to serve as control. Complete history was taken, in addition to clinical examination to meet inclusion criteria. Serum transaminases (ALT+AST) and estimated glomerular filtration rate (GFR) were estimated at baseline to exclude hepatic or renal abnormalities.

Results Each metformin and betahistine, along with lifestyle intervention highly significantly reduced total cholesterol level, LDL-C level, TG and VLDL level, and increased plasma level of HDL after 12 weeks in obese women with disturbed lipid profile compared to pre-treatment values, and the changes elicited by metformin and betahistine (plus lifestyle change) were highly significant compared to placebo (lifestyle change alone).

Conclusion The results obtained in this study clearly demonstrated the beneficial effect of using metformin or betahistine to obese women with dyslipidemia and confirmed the role of pharmacotherapy in targeting the lipid metabolism changes accompanying obesity.

Keywords Obesity, dyslipidemia, lifestyle change, betahistine, metformin

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List of abbreviation: ALT = Alanine aminotransferase, AMP = Adenosine mono phosphate, ANCONA = Analysis of co-variance, ANOVA = one way analysis of variance, ASP = Acylation-stimulating protein, AST = Aspartate aminotransferase, ATP = Adenosine triphosphate, BAT = Brown adipose tissue, BMI = Body mass index, CKD = Chronic kidney disease, EDTA = Ethylene diamine tetra-acetic acid, e-GFR = Estimated glomerular filtration rate, FDG-PET scans = Fluorodeoxyglucose Positron_emission_tomography scan, FFA = Free fatty acids, HDL = High-density lipoprotein, HRH1= Histamine receptor H1, HRH3 = Histamine receptor H3, HSL = Hormone-sensitive lipase, IDL Intermediate-density lipoprotein, IL = Interleukin, Kcal = Kilo calories, LCAT = Lecithin-cholesterol acyltransferase, LCD = Low-calorie diet, LDL = Low-density lipoprotein, LPL = Lipolipase enzyme, mRNA = Messenger ribo-nucleic acid, NHLBI = National heart, lung and blood institute, PPAR = Peroxisome-proliferator-activated-receptor, PUFA = Polyunsaturated fatty acids, SREBP = Sterol regulatory element-binding protein, TC = Total Cholesterol, TG = Triglyceride, TNF-α = Tumor necrosis factor-alpha, VLDL = Very Low-density lipoprotein, WAT = white adipose tissue, WHO = World Health Organization

Introduction

Obesity has become a major worldwide health problem. In every single country in the world, the incidence of obesity is raising continuously and therefore, the associated morbidity, mortality and both medical and economical costs are expected to increase as well [(1)]. The prevalence of obesity

reported by the WHO for the Iraqi population in 2005 was 8.3% and 19.1% for males and females respectively [2]. In 2008, another study concluded that obesity affects about 30% of adult population, with higher prevalence in women [3].

Obesity threatens to become the primary cause of non-communicable diseases over the world [4], with high health and social costs [5]. The medical expenditure regarding the obesity treatment in the USA was $147 billion in 2008, which has twice of that of the last ten years [6].

Obesity increases cardiovascular risk via risk factors such triglycerides (TG), higher low density cholesterol (LDL), lower high density (HDL) cholesterol, elevated plasma glucose and insulin and high blood pressure [7].

Hypertriglyceridemia might be the main cause of the other lipid abnormalities, as it leads to delayed clearance of the TG-rich lipoproteins and creation of small dense LDL, and decreased HDL-C concentrations [8]. The higher TG levels is regarded as a hallmark of dyslipidemia in obesity; partly due to the enhanced free fatty acid (FFA) entry to the liver, leading to hepatic accumulation of TG, leading to an increased hepatic synthesis of large amount of very low density lipoproteins (VLDL), which hinders the lipolysis of chylomicrons, due to competition mostly at the level of lipoprotein lipase (LPL) and increased remnant TG being conveyed to the liver [1].

Lipolysis is further compromised in obesity by lowered mRNA expression levels of lipolipase (LPL) in adipocytes and decreased LPL activity in skeletal muscle [9].

Current treatment of obesity-associated dyslipidemia concentrates on lifestyle changes including increased physical activity and a healthy diet [10]. Weight loss has been shown to markedly decrease TG concentrations, which can be caused by an increase in LPL activity [11], and an enhanced catabolism of TG-rich lipoproteins [12].

Statins are the drugs of first choice of all pharmacological agents. They do not fully correct the characteristic dyslipidemia associated with obesity, which may contribute to the residual risk after initiating statin therapy [13]. Combinations of statin with ezetimibe, can inhibits the intestinal cholesterol absorption. Fibrates are primarily indicated for hypertriglyceridemia [14]. Nicotinic acid hinders the lipolysis of adipocytes, which results in reduced FFA levels, reduced VLDL synthesis, a slight elevation in HDL production rate and lower catabolism of HDL [12,13]. Omega-3 fatty acids had also been found to increase the conversion of VLDL into IDL, suggesting an extra benefit from combining omega-3 fatty acids with statins via increased catabolism of VLDL, IDL and LDL [12].

Metformin is an anti-hyperglycemic medication for the treatment of type 2 diabetes mellitus. Its anti-hyperglycemic effect is by potentiation of insulin action via reducing insulin resistance, increasing peripheral glucose uptake and reducing gluconeogenesis. Patients on metformin therapy do not gain weight, and could lose weight [15,16]. Other effects of the use of metformin are lowering of systolic and diastolic blood pressure [17], improving glucose and lipid metabolism, and reducing blood pressure in hypertensive, obese females [18].

Betahistine is a histamine receptor H1 (HRH1) agonist and HRH3 antagonist [19] that has been used to treat Meniere disease since the early 1960s [20]. Being a histamine HRH3 auto-receptor antagonist, it increases the release of histamine. H3 hetero-receptors are present in non-histaminergic neurons, regulating release of neurotransmitters like dopamine, norepinephrine and serotonin [21]. A clinical study had shown that, in a subgroup post hoc analysis, weight loss happened in non-Hispanic women [22]. Betahistine, administered as an open-label fashion, had been reported to reduce olanzapine-associated weight gain, and improved lipid profile in patients with schizophrenia, compared with control subjects [23].

This study aims were to study the effects of betahistine and metformin along with lifestyle intervention compared to control (lifestyle

intervention alone) on dyslipidemia in obese Iraqi females.

Methods

Obese females, aged 18-50 years old, had been primarily enrolled in this study, and were divided into 3 groups. Medical history was taken from each patient. Body mass index (BMI), lipid profile, blood pressure, glomerular filtration rate (GFR) as renal professionals consider the (GFR) to be the best overall index of kidney function [24], liver transaminases (AST and ALT) were measured (as mentioned in details below). A written consent from each patient to be involved in the study was obtained.

Inclusion criteria

1. Female obese patients.
2. BMI equals or more than 30.
3. All are aged between 18-50 years, and pre-menopause.

Exclusion criteria

1. Patients with renal insufficiency: GFR less than 60 represents CKD.
2. Hepatic impairment: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) higher than two-folds the reference range.
3. Heart diseases (including unstable angina, myocardial infarction, transient ischemic attacks/stroke, clinically significant arrhythmia, congestive heart failure (increased risk of lactic acidosis), or cardiac valve abnormalities.
4. Patients with a history of seasonal allergy, asthma, or peptic ulcer.
5. Known allergy to one of the medications used in the study.
6. Pregnant or lactating women
7. Known cases of type 1 or type 2 diabetes mellitus.
8. Patients with known history of thyroid dysfunction, Cushing's syndrome or Addison's disease.

Treatment Arms

Group 1: obese patients on metformin + lifestyle intervention (1700 mg/d) for 12 weeks
Group 2: obese patients on betahistine + lifestyle intervention (96 mg/d) for 12 weeks
Group 3: control group: obese patients on Placebo + lifestyle intervention for 12 weeks

Lifestyle intervention (Diet program and physical activity)

Diet Program

The patients were instructed to follow the diet regimen adapted by the Obesity Unit At Alkindy Medical College (at which, the study was done), which provides a low-calorie diet (LCD) of 1000-1200 kcal/day. The National Heart, Lung, and Blood Institute (NHLBI) Obesity Education Initiative recommended 1,200 to 1,600 kcal/day for men, and 1,000 to 1,200 kcal/day for women as a Low-calorie diet (LCD) [25].

Physical activity

The patients were instructed to practice a medium intensity exercise for 60-90 minutes/day. The Dietary Guidelines for Americans recommend that to lose weight, obese people have to participate at least 60 to 90 minutes of moderate- to vigorous-intensity daily physical activity, along with caloric intake restrictions [26].

Lipid profile analysis

Fasting serum Total Cholesterol (TC), High-density lipoprotein (HDL) and Triglyceride (TG) level were measured. Low-density lipoprotein (LDL) and the Very low-density lipoprotein (VLDL) were derived using the Friedwalds equation.

Total cholesterol (TC)

Principle (Reflotron cholesterol): The cholesterol esters are cleaved into the corresponding fatty acid and cholesterol, which are then oxidized to cholestenone and hydrogen peroxide in the presence of oxygen. In a further reaction step catalyzed by the

enzyme peroxidase, the hydrogen peroxide oxidizes a redox indicator, resulting in a blue dye, which is proportional to the cholesterol concentration in the sample. The cholesterol is measured at a wavelength of 642 nm and at 37°C in mg/dl or mmol/l.
Device and tools: Reflotron (Roche)

Triglyceride (TG)
Principle (Reflotron triglycerides): The triglycerides are cleaved in an enzymatic reaction. Various reaction steps then lead to the formation of H_2O_2. This oxidizes a redox indicator to a blue dye in a reaction catalyzed by the enzyme peroxidase at a temperature of 37 °C the dye formed is measured at a 642 nm and the triglyceride concentration in mg/dl or mmol/l depending on how the instrument has been set.

HDL: Reflotron HDL cholesterol
Principle: The Reflotron HDL Cholesterol test (Boehringer Mannheim GmbH) directly separates and analyzes high-density lipoprotein (HDL) cholesterol in plasma collected with EDTA in an integrated dry-reagent system suitable for alternative site testing of lipoprotein. The cholesterol concentration of this HDL is then determined enzymatically. The cholesterol esters are cleaved into the corresponding fatty acid and cholesterol, which is then oxidized to cholestenone and hydrogen peroxide in the presence of oxygen. At a temperature of 37 °C the dye formed is measured at a 642 nm and the HDL cholesterol concentration displayed in mg/dl or mmol/l depending on how the instrument has been set.

LDL and VLDL
These two lipoproteins were derived using the Friedewalds equation.
Friedewald Formula (1972) :
LDL = TC - HDL - TG/5 (mg/dL)
VLDL= TG/5 (mg/dL)

The Friedewald formula (FF) is an estimation of LDL-c level that uses the following levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c): LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5. This formula became the standard method for LDL-c assessment because it is economical and simpler than direct assays, the most accurate LDL-c measurement methods [27].
BMI was calculated by dividing body weight (kg) by the square of the height (meters), an on-line calculator was used.
eGFR was calculated making use of an on-line calculator provided by the National Kidney Foundation.

Statistical analysis
The results represented as the mean ± standard deviation. Data were fed to the computer program. Statistical Package for Social Science SPSS version 16.0 under Windows Seven, was used for analysis.
Normality test (Shapiro-Wilk test) was performed first, student t-test (paired) with p-value less than or equal 0.05 ($P \leq 0.05$) were used to compare between pre- and post-treatment values within the same group. ANOVA test was used for comparing pre-treatment values among groups, and pre-intervention values were used as covariates for adjustment when comparing post-intervention results, using ANOVA test [28,29].

Results
Baseline data (table 1) of the enrolled females showed no statistically significant difference among different treatment arms concerning participants number, age, and BMI. Liver transaminases and e-GFR results showed normal liver and kidney functions, with no statistically significant difference among obese women in this regard. Baseline serum levels of TC, HDL, LDL, TG and VLDL showed also no statistically significant difference among different treatment arms.

Table 1. Baseline characteristics comparison for enrolling patients

Characteristic (Baseline)	Group 1 Metformin (n=26)	Group 2 Betahistine (n=27)	Group 3 Control (n=25)	P-value
Body Mass Index (kg/m^2)	38.2±3.30	37.7±4.0	37.08±3.28	0.875
Age years (mean ± SD)	35.81±11.47	35.39±10.04	36.32±8.85	0.966
Serum AST (i.u/ L)	22.69±7.2	21.3±8.0	22.32±5.8	0.975
Serum ALT (i.u/L)	22.88±7.3	21.41±6.15	22.52±5.2	0.674
e-GFR (ml/min/1.73m^2)	84.69±12.9	84.70±11.3	84.80±8.3	0.999
TC (mg/dl)	197.4 ±7.78	198.9 ± 9.17	196.2±6.22	0.825
HDL (mg/dl)	36.50±2.14	37.07 ± 2.16	36.04±1.88	0.559
TG (mg/dl)	156.65±13.69	157.8±10.94	156.3±11.11	0.989
LDL (mg/dl)	128±6.52	130±8.85	129±6.02	0.800
VLDL (mg/dl)	31.3±2.73	31.40±2.18	31.36±2.34	0.989

-Results represented as mean±standard deviation

- P-value >0.05 means that there is no significant difference between the groups data using ANOVA test, TC= total cholesterol, HDL= High density lipoprotein, TG= Triglycerides, LDL= Low density lipoprotein, VLDL= Very low density lipoprotein, NS= Non-significant

Table (2) showed that administration of metformin (with lifestyle intervention) to obese women with dyslipidemia (Group 1), caused highly significantly reduction in serum TC, TG, LDL and VLDL levels, and at the same time highly significantly raised serum HDL level after 12 weeks compared to pre-treatment value. Rates of change were: -14.44% for TC, -21.04% for LDL, -18.9% for TG, and -18.9 for VLDL. HDL change rate was +9.7%.

While the administration of betahistine (with lifestyle intervention) to obese women with dyslipidemia (Group 2), caused highly significantly reduction in serum TC, TG, LDL and VLDL levels, and at the same time highly significantly raise in serum HDL level after 12 weeks compared to pre-treatment value. The rates of change were: -15.28% for TC, -22.42% for LDL, -19.7% for TG, and -19.7% for VLDL, whereas HDL change rate was +10.4%.

On the other hand; placebo treated group with lifestyle intervention (group 3), revealed a significant reduction of serum TC and LDL, with a significant elevation of HDL. No statistically significant change on pre-treatment values of TG and VLDL happened after 12 weeks. The rates of change were: -3.26% for TC, -4.6% for LDL, -0.77% for TG, and -0.77% for VLDL, whereas HDL change rate was +2%.

Table 2. Lipid profile changes

Treatment	TC	P-value	LDL	P-value	TG	P-value	VLDL	P-value	HDL	P-value
Metformin	-14.44	0.000	-21.04	0.000	-18.9	0.000	-18.9	0.000	+9.7	0.000
Betahistine	-15.28	0.000	-22.42	0.000	-19.7	0.000	-19.7	0.000	+10.4	0.000
Control	-3.26	0.020	-4.6	0.010	-0.77	0.056	-0.77	0.056	+2.0	0.010

Data represent the percent of change adjusted for baseline values (ANOVA test is used). P-value of the paired t-test is used. P-value less than 0.05 means a significant difference. P ≤ 0.001 represent a highly significant difference

Pairwise comparison between each two groups demonstrated no statistically significant difference between metformin and betahistine group effects on all measured parameters (p-values are more than 0.05), whereas a highly statistically significant difference between each metformin group and betahistine group effects were found when compared to control group (p-values are less than 0.001), as shown in table (3).

Table 3. Pairwise comparisons

Treatment	TC	LDL	TG	VLDL	HDL
Metformin vs. Betahistine	0.637	0.130	0.687	0.837	0.151
Betahistine vs. Placebo	0.000	0.000	0.000	0.000	0.000
Metformin vs. Placebo	0.000	0.000	0.000	0.000	0.000

Data represent the p-values of the pairwise comparisons. P ≤ 0.001 represent a highly significant difference

Discussion

Several studies concluded that the combination of diet and physical activity was effective in normalizing the lipid profile and overwhelming obesity [30,31]. Exercise seems to enhance the ability of skeletal muscles to make use of lipids as opposed to glycogen, hence reducing plasma lipid levels [32]. The mechanisms include increasing lecithin-cholesterol acyltransferase (LCAT); an enzyme that transfers ester to HDL cholesterol, which has been found to increase following exercise training [33], and lipoprotein lipase hyperactivity, which depend upon energy expenditure [34].

Metformin, betahistine and the control groups caused a highly statistically significant reduction in TC, LDL, TG and VLDL, with a highly significant elevation in HDL. Both Metformin and Betahistine treatment groups achieved a highly statistically significant difference compared to the control group, whereas no statistically significant difference between Metformin and Betahistine treatment regarding all of the above mentioned parameters.

It is well documented that plasma FFA are raised in obese people as a consequence of an elevated fatty acid release from adipose tissue and a lowered plasma FFA clearance [35,36]. The increase in FFA and obesity-associated inflammation play a central role in the development of insulin resistance [37]. There are only 2 sources where plasma FFA can be derived from; first: lipolysis of TG-rich lipoproteins inside the circulation; and second: intracellular lipolysis within adipose tissue [1]. Several fatty acids are cytotoxic and this cytotoxicity depend on their type [38]. Polyunsaturated fatty acids (PUFA), e.g. arachidonic acid and linoleic acid, might mediate a diet-induced inflammation [39]. They can encourage the synthesis of pro-inflammatory cytokines like IL-1, IL-6 and TNF-α [40].

An “escape mechanism” should exist in order to remove FFA from the microenvironment in which they are formed. In this mechanism, both insulin and the acylation-stimulating protein (ASP) play an essential role in peripheral fatty acid trapping [1].

It has been shown that ASP mRNA expression in visceral adipose tissue is decreased by nearly 40% in obese subjects with or without insulin resistance, compared to lean subjects [9]. Furthermore, obese subjects also showed less uptake of dietary fat by adipose tissue, resulting in an increased delivery of chylomicron remnants to the liver, and consequently enhanced VLDL-TG being delivered to the peripheral adipocytes [41].

Treatment of insulin resistance has been shown to reduce plasma FFA concentrations by lowering fasting FFA levels [42].

The postprandial elevation of insulin results in an effective inhibition of hormone sensitive lipase, which is the main enzyme for hydrolysis

of intracellular lipids. FFA are up taken by adipocytes and myocytes, yet; a fraction of FFA remains in the plasma compartment where they are bound by albumin and transported to the liver [43]. When the supply of FFA for energy expenditure is inadequate like in the fasting state, FFA are mobilized from adipose tissue for oxidation in energy demanding areas like cardio myocytes [44]. Insulin hormone is also an essential regulator of FFA mobilization from adipose tissue. The scavenger receptor CD36 is the best described FFA transporter, and is abundant in muscle, fat tissue and the capillary endothelium [45]. Insulin and muscle contractions enhance the CD36 expression, therefore; facilitate FFA uptake [46]. Therefore, insulin resistance has an important influence on the metabolism of TG-rich lipoproteins and FFA [1].

Metformin inhibits glucose, lipid and protein synthesis as well as cell growth, while stimulates fatty acid oxidation and glucose uptake [47]. A study reported that the pleiotropic actions of metformin are closely related to the activation of AMP-activated protein kinase (AMPK). AMPK is viewed as a fuel gauge checking systemic and cellular energy status, which plays a vital role in protecting cellular functions during energy-restricted conditions [48]. Activated AMPK shifts cells from the anabolic to the catabolic state, shutting down the ATP-energy-consuming pathways, restoring energy balance. This control involves phosphorylation of basic metabolic enzymes and transcription factors/co-activators, and modulating gene expression by AMPK [49]. Moreover, metformin treatment of insulin resistance has been shown to lower plasma FFA concentrations by lowering fasting FFA plasma levels without any effect on catecholamine mediated lipolysis of adipocytes [42].

Betahistine has been proved to ameliorates dyslipidemia caused by chronic olanzapine treatment in rats through modulating the hepatic AMPK-SREBP-1 (sterol regulatory element-binding protein) and peroxisome-proliferator-activated-receptor (PPAR) - gamma-dependent pathways [50].

Another possible mechanism through which betahistine could improve dyslipidemia is via norepinephrine's action on β3-adrenergic receptor. Being a histamine HRH3 antagonist, it can increase norepinephrine's release, which might appear to be a useful therapeutic target for activating the brown adipose tissue (BAT), considering evidence from studies using a selective β3-agonists (CL-316,243) and knockout rodent models [51].

Catecholamines might also 'brownify' the white adipose tissue (WAT), 2 case reports of widespread brown fat deposits in omental and mesenteric areas, detected via human FDG-PET scans, point out a possible role for catecholamines in the 'browning' of WAT (52). Therapeutically, catecholamine may trans-differentiate WAT into Beige AT, but this approach need to avoid the associated sympathomimetic effects to be safe [53].

Data from several animal studies have established that through BAT activation, dyslipidemia improves and triglyceride stores inside white adipose tissue (WAT) can be exploited to generate heat via modulation of adaptive thermogenesis [54].

Catecholamine mediated lipolysis of adipocytes is another possible mechanism. Hormone-sensitive lipase (HSL) is a primary lipase for catecholamine-mediated lipolysis. The mobilization of fat stored in adipose tissue is stimulated by hormone-sensitive lipase [55].

Taken together; there may be multiple pathways that might explain how betahistine and metformin can improve lipid profile in obese women with dyslipidemia.

The results obtained in the present study clearly demonstrates the beneficial effect of using metformin or betahistine for obesity-associated dyslipidemia and confirms the role of pharmacotherapy in targeting the lipid metabolism changes accompanying obesity.

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Author contribution

Dr. Al-Anbari conducted the study, collected the data and performed the statistical analysis and drafting of the article. Dr. Al-Zubaidy contributed in the designing, organization and finalization of the protocol, and Dr. Khazaal participated in the physical examination of the patients throughout the period of study.

Conflict of interest

The authors declare no conflict of interest concerning this work.

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Correspondence to Hayder H. Al-Anbari
E-mail: haider_alanbary@yahoo.com
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