

Effect of Low Glycemic Index Diet Versus Metformin on Metabolic Syndrome

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Background: Metabolic syndrome (MetS) continues to be highly prevalent and contributes to a rapidly growing problem worldwide. The most important therapeutic intervention for metabolic syndrome is diet modification, an intervention whose efficacy has been proven for metabolic syndrome.

Objectives: The aim of the present study was to compare the effects of low glycemic index diet versus metformin on MetS components in adults with MetS.

Patients and Methods: Fifty-one adults with MetS participated in this randomized controlled clinical trial. Patients were randomly allocated to two groups of metformin and low glycemic index diet. The intervention period was eight weeks. The studied participants were compared at baseline and the end of the trial, regarding the following factors: weight, blood pressure, waist circumference, fasting blood sugar, hemoglobin A1c and lipid profiles (Triglyceride (TG), Total Cholesterol (TC), Low-Density Lipoprotein (LDL) cholesterol, and High-Density Lipoprotein (HDL) cholesterol).

Results: The anthropometric measurements, Fasting Blood Sugar (FBS), Hemoglobin A1c, serum lipid profiles (TG, TC, LDL-C, HDL-C) and lipoprotein ratio (LDL/HDL) showed a significant decrease after the intervention in both groups ($P < 0.05$). Comparison of the difference between the two groups was not significant, except for the mean reduction in FBS, which was more in the metformin group although this was not clinically significant.

Conclusions: This study supports the assumption that low glycemic index diet as well as metformin can positively affect metabolic syndrome components.

Keywords: Glycemic Index, Metabolic Syndrome X; Metformin

1. Background

Metabolic syndrome (MetS) is a constellation of risk factors associated with increased risk of diabetes and cardiovascular disease (1). In 2001, the national cholesterol education program (NCEP) adult treatment panel III (ATP III) provided a new definition for MetS, focusing on easily measurable clinical parameters such as abdominal obesity, increased fasting blood sugar, increased serum concentration of triglyceride, low serum high-density lipoprotein cholesterol (HDL-C) and/or elevated blood pressure. In 2004, the threshold for fasting blood sugar was reduced to ≥ 100 mg/dL (5.6 mmol/L) in concordance with the American diabetes association criteria for impaired fasting glucose (2). The new international diabetes federation (IDF) definition in 2006 included a lower waist circumference (3). Metabolic Syndrome is a growing public health problem worldwide in both developed and developing countries (4). There is a general agreement that high prevalence of MetS

(33.2% and 10.1% among Iranian adults and adolescents, respectively) basically deals with increasing incidence of obesity (5-7). A strong relationship between MetS and dietary pattern, tobacco use and physical inactivity has been reported in the literature (8).

The most important therapeutic intervention that has been proven to be effective in metabolic syndrome is lifestyle modification with focus on dietary change and physical activity (2, 9). Drug therapy is also another common intervention for MetS. Metformin has been proven to improve insulin sensitivity and shown to be effective on weight loss, although it has minor side effects (10). Recent evidence suggests that lifestyle modifications can be a decent way to reduce metabolic and cardiovascular risk factors. The study of Giugliano et al. reported that lifestyle modification (25%) has more benefits in resolution of MetS compared to drug therapy (19%) (9).

In 1981, Jenkins classified carbohydrate-containing

foods, based on the glycemic index (GI). This index was then defined as 'the incremental area under the blood glucose response curve to a test food, relative to a standard control food (glucose or white bread) with the same amount of carbohydrate. Glycemic Index differs according to the rate of digestion and absorption, which depends on the type of carbohydrate and protein, fat and fiber content of the food (11). High GI carbohydrates have been shown to be positively associated with insulin resistance and metabolic syndrome (12). A low GI diet will improve postprandial glycemia and as a result reduce insulin resistance, B-cell dysfunction and hyperinsulinemia (11). The results of a recent pilot study showed that a short-duration low glycemic index fitness program could improve anthropometric and physiological measures in MetS subjects (13). Also, a systemic review in 2013 provided evidence that administering a low GI diet was helpful in prevention of obesity-associated diseases (14).

2. Objectives

The present study was designed to examine the effect of low GI diet versus metformin on adults with MetS.

3. Patients and Methods

Sixty adults with MetS, aged 25 to 65 years, participated in this randomized clinical controlled trial. Patients were included in the study according to the following inclusion criteria: having metabolic syndrome characteristics according to IDF, waist circumference ≥ 90 for males or ≥ 80 cm for females (3), blood pressure ≥ 135 (systole) or ≥ 85 (diastole) mmHg, Fasting Blood Sugar (FBS) ≥ 100 mg/dL (newly diagnosed pre-diabetic patients), triglycerides ≥ 150 mg/dL, and high-density lipoproteins (HDL) < 40 (male) or < 50 mg/dL (female), and not taking any drug that might affect either blood pressure, blood lipid or blood glucose level. Patients were excluded from the study if they had any sign of liver, kidney or GI disorders during the study. All patients gave their written informed consent to participate. The protocol was approved by the Shiraz university of medical sciences ethics committee.

Patients were randomly allocated to two groups of drug (metformin) or diet therapy (low glycemic index) for eight weeks. The method of randomization was carried out and as the patients registered for entering the trial, they were put in their own group accord their number. For the diet group, the percentage of required energy was calculated by the Harris-Benedict formula. The percentages of macronutrients were the same for all participants, i.e. 55% for carbohydrates, 30% for fat and 15% for proteins. The only difference with normal diet was the use of low GI foods in the diet plan for the diet group. The foods were chosen from the Foster-Powel and Taleban Table (15, 16), with medium (55 - 70) and low (less than 55) glycemic index. The metformin dos-

age was 500 mg (one oral tablet per day) as the patients' routine treatment for eight weeks. Patients were seen every two weeks in order to make sure about their consumption of metformin and low GI diet regimen.

A 24-hour dietary recall was taken for all patients at each follow-up visit. Body weight, blood pressure, waist circumference, serum lipid profiles, fasting blood sugar and hemoglobin A1c were also measured at the beginning and the end of the trial. Anthropometric data including weight were measured by means of an analog scale (Seca), while the participants were in light clothing and had no shoes on. Height was measured using a stadiometer. The Body Mass Index (BMI) was calculated through dividing weight (in kilograms) by height squared (in meters). Waist circumference was measured to the nearest 0.5 cm between the iliac crest and the lowest rib at the narrowest point. Blood pressure was measured with a piezometer. The mean of the two measurements was used. Subjects rested for 15 minutes before blood pressure measurements. Blood samples were obtained at baseline and at the end of the intervention, after overnight fasting, and analyzed for glucose and lipid profiles by the colorimetric method on a Blue tetrazolium (BT) 1500 auto analyzer. The Hemoglobin A1c was measured by high-performance liquid chromatography (HPLC), using C18 column with a variable wavelength detector (Agilent 1100 series, Germany).

The trial data were analyzed using the Statistical Package for the Social Sciences, version 14 (SPSS Inc. Chicago, IL, USA). The results were expressed as mean \pm standard deviation (SD). The Shapiro test was used to check normality of the obtained data. Mann-Whitney U and Wilcoxon tests were performed to make statistical comparisons between and within groups, respectively. P values of < 0.05 were considered statistically significant.

4. Results

Fifty-one participants (10 males and 41 females) with a mean age of 44.6 ± 6.1 years completed the study. Baseline characteristics and dietary intake components of the patients are shown in Table 1. There were no significant differences in dietary intake components between the diet and metformin groups during the eight-week trial (Table 2). After the intervention, body weight, BMI, waist circumference and blood pressure decreased significantly in both groups ($P < 0.05$), although comparison between the groups showed no considerable differences (Table 3).

Fasting blood sugar, hemoglobin A1c, lipid profiles (Triglyceride (TG), Total Cholesterol (TC), Low-Density Lipoprotein-Cholesterol (LDL-C), High-Density Lipoprotein-Cholesterol (HDL-C)) and lipoprotein ratio (LDL/HDL) showed a significant decrease after the intervention either by drug or diet ($P < 0.05$). The comparison of the mean differences of serum lipid profiles, lipoprotein ratio (LDL/HDL) and hemoglobin A1c showed no significant difference between the groups. However, the difference in FBS was significant ($P < 0.05$) (Table 3).

Table 1. Baseline Characteristics and Dietary Intake Components of Patients With Metabolic Syndrome^a

Variable	Metformin Group (N = 25)	Low Glycemic Index Diet Group (N = 26)
Male/Female	6 (11.7)/19 (37.2)	4 (7.8)/22 (43)
Age, y	43.5 ± 6.65	45.6 ± 5.62
Energy, Kcal	2149.61 ± 286.6	2292.9 ± 238.8
Carbohydrate, %	59.7 ± 5.8	58.3 ± 6.7
Protein, %	12.1 ± 1.6	12.4 ± 1.13
Fat, %	28.2 ± 5.6	29.3 ± 4.4

^a Values are presented as mean ± SD or No. (%).

Table 2. Dietary Intake Components of Patients in the Eight-Week Intervention Group^a

Variable	Metformin Group (N = 25)	Low Glycemic Index Diet Group (N = 26)	P Value ^b
Energy, Kcal	2181 ± 283	2103 ± 189	0.12
Carbohydrate, %	58.9 ± 7.7	55.3 ± 2.2	0.202
Protein, %	13.1 ± 0.87	17.4 ± 0.51	0.148
Fat, %	28 ± 5.2	27.3 ± 1.1	0.172

^a Values are presented as mean ± SD.

^b Mann-Whitney U test to compare change between groups.

Table 3. Anthropometric and Biochemical Parameters of the Participants at Baseline and at the End of the Intervention^a

Variables	Metformin Group (N = 25) ^b		Low Glycemic Index diet Group (N = 26) ^b		P Value ^c
	Before	After	Before	After	
Weight, kg	82.32 ± 9.75	80 ± 9.75	79.58 ± 7.87	77.29 ± 7.88	0.689
P value ^d	< 0.001	< 0.001	< 0.001	< 0.001	
BMI, kg/m ²	3.43 ± 30.88	3.22 ± 29.99	2.72 ± 29.42	2.55 ± 28.55	0.932
P value	< 0.001	< 0.001	< 0.001	< 0.001	
WC, cm	6.46 ± 103.7	6.65 ± 101.6	7.03 ± 101.9	7 ± 99.88	0.756
P value	< 0.001	< 0.001	< 0.001	< 0.001	
Systolic BP, mm/Hg	10.4 ± 123.6	9.74 ± 120.96	8.93 ± 126.27	8.42 ± 123.38	0.781
P value	0.001	0.001	< 0.001	< 0.001	
Diastolic BP, mm/Hg	5.4 ± 80.12	5.61 ± 79.4	5.89 ± 80.58	5.59 ± 80.04	0.898
P value	0.033	0.033	0.026	0.026	
FBS, mg/dL	8.34 ± 108.9	9.28 ± 99.08	6.31 ± 107.6	7.87 ± 101	0.017 ^e
P value	< 0.001	< 0.001	< 0.001	< 0.001	
HbA1c, %	0.32 ± 6.6	0.35 ± 6.27	0.24 ± 6.5	0.3 ± 6.28	0.43
P value	< 0.001	< 0.001	< 0.001	< 0.001	
TG, mg/dL	44.15 ± 173.56	44.6 ± 167.8	57.9 ± 182.6	58.6 ± 176.5	0.801
P value	< 0.001	< 0.001	< 0.001	< 0.001	
TC, mg/dL	23.5 ± 181.52	22.6 ± 166.6	31.7 ± 190.6	30.9 ± 175.1	0.387
P value	< 0.001	< 0.001	< 0.001	< 0.001	
LDL, mg/dL	20.9 ± 101.2	19.4 ± 88.3	24.3 ± 108.8	23.3 ± 95.7	0.378
P value	< 0.001	< 0.001	< 0.001	< 0.001	
HDL, mg/dL	9.2 ± 45.6	9.21 ± 44.4	7.2 ± 42.9	7.7 ± 41.6	0.654
P value	0.002	0.002	0.002	0.002	
LDL/HDL Ratio	0.63 ± 2.3	0.58 ± 2	0.73 ± 2.6	0.71 ± 2.3	0.23
P value	< 0.001	< 0.001	< 0.001	< 0.001	

^a Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; FBS, Fasting Blood Sugar; HbA1c, Hemoglobin A1c; SD, Standard Deviation; TG, Triglyceride; TC, Total Cholesterol; WC, Waist Circumference.

^b Values are presented as mean ± SD.

^c Mann-Whitney U test to compare changes between baseline and final values of the groups.

^d Wilcoxon test to compare values within the groups.

^e $P < 0.05$.

5. Discussion

The most important finding of this trial was that low GI diet as well as metformin reduced body weight, BMI, blood pressure and lipid profiles of patients with MetS after eight weeks of treatment. A slightly larger decrease was found in fasting blood sugar of patients who took metformin as compared to those on a low GI diet yet the difference was not clinically marked. These findings further support the idea that low GI diet could be as effective as metformin in MetS treatment.

Better regulation of glucose homeostasis following low GI diet was demonstrated in a number of studies (17, 18). The results of a previous meta-analysis of studies that investigated the effect of legumes as part of low GI diet in type 2 diabetes indicated a significant reduction (0.48%) in HbA_{1c} values (19). Fasting blood sugar and HbA_{1c} were reduced significantly in the low GI diet group of the current study. Metformin has also been shown to have beneficial effects on insulin sensitivity and glucose metabolism, which has been documented in the literature since 1993 (20, 21). It is likely that metformin exerts a direct inhibitory effect on hepatic glucose output, which coincides with the inhibition of gluconeogenesis in hepatocytes (22). A significant reduction in HbA_{1c} was observed in a (Cerebral abnormalities in Migraine, an Epidemiological Risk Analysis) study on non-diabetic patients, taking metformin for 18 months (23). These findings are in agreement with the results of the present study.

Low GI diet is more satiating than a high GI diet, as the former has slower rates of digestion and absorption. As a consequence, nutrient receptors in the gastrointestinal tract are stimulated for a longer time period and the signals by cholecystokinin and glucagon-like peptide-1 to the brain satiety center will become prolonged. In addition, low GI diet can decrease postprandial glucose, insulin and plasma cortisol level that inhibits muscle catabolism. Overall, these mechanisms can result in lower weight gain (24). Ludwig et al. reported that a low GI meal enhanced satiety and diminished appetite much more than a high GI meal (25). In a study by Bahadori et al. in 2004, low GI diet reduced body weight (six kilograms in six months) in obese participants (26). Melanson et al. also reported that 12-week treatment with low GI diet in overweight and obese subjects resulted in a significant decrease in body weight (3.39 kg), BMI (1.11) and waist circumference (3.31 cm) (27). The findings of the present study also showed a significant reduction in body weight and waist circumference as well. The larger mean reduction in the study of Melanson et al. might be due to a longer period of treatment (12 weeks).

Metformin, by its insulin-sensitizing virtue and by reducing hyperleptinemia, appears to be effective in reducing body weight and centripetal obesity. In one study, metformin therapy in non-diabetic, obese and morbidly obese (BMI > 30) subjects significantly reduced body weight and waist circumference (28). Regarding the ben-

eficial effect of metformin on lipid profiles, it diminished Rho (small GTP-binding protein, which is generated in the process of cholesterol biosynthesis) kinase activity in hyperlipidemic rats (29). It may also have positive effects on lipid profiles by decreasing hyperinsulinemia. Landin et al. reported that metformin administration can ameliorate TG, total cholesterol and LDL-C levels in six weeks; this is in agreement with the results obtained in the current study (30).

Low GI diet may also have the ability to decrease blood lipids by reducing hyperinsulinemia. The investigation of Bouch et al. showed that eight-week consumption of low GI diet improved lipid profiles significantly in overweight and non-diabetic subjects (31). Moreover, Heilbronn et al. observed that low GI diet leads to a noticeable decrease in TG, total cholesterol and LDL in type 2 diabetic patients (32). Also, the outcome of a systemic review suggested that low GI diet could significantly reduce LDL and total cholesterol (33). The present study also showed that low GI diet diminished lipid profile and lipoprotein ratio (LDL/HDL) in patients with metabolic syndrome.

Low GI diet also has positive effects on blood pressure through its reducing effects on obesity, hyperglycemia and hyperinsulinemia (11). Moreover, low insulin concentration can lead to a reduction in sympathetic nervous system activities, which decrease heart rate, cardiac output and sodium retention and thus blood pressure (34). In the present study, low GI diet reduced systolic and diastolic blood pressure. These results are consistent with those of Sloth et al. who found that low GI diet decreased systolic blood pressure markedly in overweight females during a ten-week trial (35). Moreover, in the study of Melanson et al., low GI diet decreased blood pressure, although not significantly (27).

The current study showed that metformin intake was also associated with significant alterations in Blood Pressure (BP). The mechanism underlying the BP-lowering effect of metformin is obscure, yet a decrease in peripheral hyperinsulinemia may be implicated (36). Moreover, a reduction in sympathetic nervous system activity, as suggested by a 25% decrease in plasma norepinephrine after metformin consumption could also contribute to the condition (37). Giugliano obtained similar results for BP in obese-hypertensive subjects; a considerable reduction was detected after three months (21).

The inconsistent results of studies on the effects of low GI diet or metformin on metabolic parameters in obese or diabetic individuals can be attributed to different features of studies. These include differences in design, sample size, dosage and length of metformin administration.

In conclusion, eight weeks of low GI diet and metformin therapy in MetS could significantly decrease body weight, waist circumference, blood pressure, FBS, HbA_{1c}, lipid profiles and lipoprotein ratio (LDL/HDL), although the difference between groups was not noticeable except for

FBS, for which the reduction was slightly larger (3 mg/dL) in the metformin group, yet this was not clinically considerable. Since metformin may cause side effects such as lactic acidosis, vitamin B12 deficiency, gastrointestinal disturbances and hepatotoxicity (38), low GI diet can be safer in managing MetS. To the best of our knowledge, the present study was the first trial on MetS that compared low GI diet and metformin drug therapy although with a small sample size. In addition, the short duration of the intervention was the other limitation of this clinical trial. Further investigations with larger populations and longer periods are required to confirm whether metformin therapy can be replaced by low GI diet.

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Authors' Contributions

Zohreh Mazloom, Hamid Reza Tabatabaee and Shirin Rajabi developed the original idea and the protocol, abstracted and analyzed the data, wrote the manuscript, and were the guarantors. Shirin Rajabi, Ali Zamani and Zohreh Mazloom contributed to the development of the protocol, abstracted data, and prepared the manuscript.

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