Effects of metformin alone or in combination with vitamin C and E on serum glucose concentration and lipid profile in type 2 diabetic patients

[*] **Zeina Abdul Munim Al-Thanoon, [**] Isam Hamo Mahmood, [***] Imad Abdul Jabbar**

[*] , [**] *PhD Pharmacology; Department of Pharmacology and Toxicology ;College of Pharmacy ,University of Mosul., Mosul, Iraq*

[***] *PhD Pharmacology ; Department of Pharmacology; College of Medicine ,University of Mosul, Mosul, Iraq.*

Received 9/10/202 Accepted 27/3/2013

Abstract

The present study was aimed to evaluate the effects of metformin alone or in combination with vitamin C and E on fasting serum glucose (FSG) concentration and lipid profile in type 2 diabetic patients. One hundred and three newly diagnosed type 2 diabetic patients participated in this study. They were divided into 3 groups according to treatment. The first group involved 32 patients were kept on metformin therapy alone. The second group involved 37 patients were kept on combination of metformin and vitamin C and vitamin E . Whereas the third group involved 34 patients were have no drug therapy but kept on diet restriction. The duration of treatment was for 2 months . Another group consisted of 35 healthy subjects participated in the study as a control group. Body mass index (BMI) was calculated by Quetelet index (Weight/Height2). Fasting serum blood samples were used for measuring serum glucose concentrations and lipid profile using special commercial kits. Serum LDL-c concentration was calculated by Friedewald equation and atherogenic Index was calculated as TC /HDL-c . The results found that there were a significant elevation in weight, BMI, FSG, Tc ,TGS, LDL-c and AI and a significant reduction in HDL-c in type 2 diabetic patient before starting treatment as compared with control group. The results also found that metformin group showed a reduction only in weight, BMI, FSG and Tc whereas the combination group showed a highly significant reduction of all studied parameters and significant elevation of HDL-c. The diet group showed non significant changes in all of the studied parameters. This study has been concluded that the addition of Vitamin C and E to metformin therapy produce additional beneficial effects on weight, BMI ,FSG and lipid profile over metformin alone or diet therapy alone in type 2 diabetic patients.

Key Words: Type 2 diabetes mellitus, metformin, vitamins C and E, FSG, lipid profile.

تأثيرات المتفورمين لوحده أو بالإضافة مع فيتامين ج و هـ على مستوى سكر الدم الصيامي والدهون في مصل الدم لدى المرضى الذين يعانون من داء السكري من النوع الثاني

زينة عبد المنعم الذنون **عصام حمو محمود**

عماد عبد الجبار

الملخص

إن الهدف من الدراسة الحالية هو تقييم تأثيرات عقار المتفورمين لوحده أو بإضافته مع فيتامين ج و هـ على مستوى سكر الدم الصيامي والدهون في مصل الدم في المرضى الذين يعانون من داء السكري من النوع الثاني. أجريت هذه الدراسة على 103 مريضا شخصوا حديثا بداء السكري من النوع الثاني . قسمت مجموعة المرضى الى 3 مجاميع حسب العلاج المعطى لهم . أعطيت المجموعة الأولى (32 مريضا) عقار المتفورمين لوحده ، اعطيت المجموعة الثانية (37 مريضا) عقار المتفورمين وفيتامين ج وفيتامين هـ ، أما المجموعة الثالثة فقد خضعت لإستخدام حمية غذائية فقط .استغرقت فترة العلاج مدة شهرين. كما شارك في الدراسة 35 شخصا سليما من المتطوعين (يبدون أصحاء) ليكونوا مجموعة الضبط. تم قياس الوزن . كما تم قياس مؤشر كتلة الجسم عن طريق استعمال معادلة الكويتلت (الوزن / الطول 2) . أستعمل الدم الوريدي والذي تم جمعه من كل فرد وهم في حالة صوم لتحليل مستوى السكر في مصل الدم ومستوى الدهون (الكولسترول ألكلي ،الشحوم ألثلاثية والبروتين الدهني العالي الكثافة) باستخدام عدّد فحص تجارية خاصة. تم حساب البروتين الدهني الواطىء الكثافة باستخدام معادلة فريدوالد ومؤشر التعصد باستخدام معادلة (الكولسترول الكلي / البروتين الدهني العالي الكثافة) . أجريت هذه القياسات لكل من مجموعة المرضى (قبل وبعد العلاج) ومجموعة الضبط. أعطت نتائج هذه الدراسة ارتفاعا معنويا في الو زن ومؤشر كتلة الجسم و مستوى سكر الدم الصيامي ومستوى الدهون (الكولسترول ألكلي ،الشحوم ألثلاثية والبروتين الدهني الواطيء الكثافة) و مؤشر التعصد وانخفاضا في البروتين الدهني العالي الكثافة قبل بدء العلاج بالمقارنة مع مجموعة الضبط . كذلك وجد أن مجموعة المتفورمين أظهرت فقط انخفاضا معنويا في الوزن و مؤشر كتلة الجسم و الكولسترول الكلي في حين أن المجموعة التي أعطيت عقار المتفورمين مع فيتامين ج وفيتامين هـ أظهرت انخفاضا معنويا ملحوظا في الوزن ومؤشر كتلة الجسم ومستوى الدهون (الكولسترول الكلي، الشحوم الثلاثية، البر وتين الدهني الواطىء الكثافة ومؤشر التعصد) وارتفاعا معنويا ملحوضا في البروتين الدهني العالي الكثافة .ولم تظهر مجموعة الحمية الغذائية اية تغييرات معنوية ملحوظة لجميع المتغيرات .أستنتج من هذه الدراسة أن إضافة فيتامين ج و فيتامين هـ الى عقار المتفورمين يعطي تأ ثيرات مفيدة إضافية على الوزن ومؤشر كتلة الجسم ومستوى سكر الدم الصيامي ومستوى الدهون في مصل الدم أكثر من العلاج باستخدام عقار المتفورمين لوحده أو العلاج باستخدام الحمية الغذائية لوحده ا للمرضى الذين يعانون من داء السكري من النوع الثاني.

كلمات الدلالة : داء السكري من النوع الثاني، المتفورمين، الفيتامينات ج وهـ ، سكر الدم الصيامي، مستوى الدهون .

Introduction

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids, and proteins. The characteristic feature of diabetes is an abnormal elevation in blood glucose levels (hyperglycemia) which is due to a deficiency in insulin secretion caused by pancreatic β-cell dysfunction and/ or insulin resistance in liver and muscle (1). It can be classified as primary and secondary diabetes mellitus. Primary diabetes mellitus can be divided into type 1 diabetes results from cellular

mediated autoimmune destruction of pancreatic β-cells, usually leading to loss of insulin secretion and type 2 diabetes mellitus, which is the most frequent form of the disease. It develops because of interactions of genetic and environmental risk factors, which lead to relative deficiency of insulin with coexisting resistance to its activity (2).

Diabetes and obesity are closely linked diseases with rising prevalence and incidence in developed and developing countries. Westernized eating habits and lifestyle are presumed to be the major reasons for this epidemic. Official guidelines recommended diets with low fat contents and high amounts of carbohydrates although it has never been proven that these are effective in reducing cardiovascular disease morbidity and mortality, the major health problems connected with diabetes and obesity. Reducing body weight is considered an important therapeutic intervention to treat patients with type 2 diabetes and is a major challenge in ambulatory settings (3). Metformin, a biguanide hypoglycemic agent, is the most common prescribed oral hypoglycemic agent in the world. It continues to maintain its position despite of the fact that several other classes of oral agents have been introduced both as initial therapy and in combination with these newer drugs for prevention and treatment of type 2 diabetes mellitus (4). Metformin does not stimulate appetite and consequently useful in the majority of type 2 patients who are obese and fail on treatment with diet alone. It reduces plasma concentrations of LDL and VLDL, effects that could theoretically be useful in reducing atheroma (5).

Vitamin E helps maintain health primarily through antioxidant actions. Specifically, the vitamin helps protect against peroxidation of lipids. A large body of evidence suggests that large doses of vitamin E may protect against chronic diseases. Vitamin C a water soluble vitamin precipitate in multiple biochemical reactions such as synthesis of adrenal steroids and conversion of folic acid to folinic acid. In addition, vitamin C has antioxidant activity and facilitates gastrointestinal absorption of iron (6). Available literature suggests conflicting results related to supplementation of vitamin C and E for improvement of blood glucose level and lipid profile (7). Accordingly, the present study aimed to determine the effects of addition of vitamin C and E to metformin therapy on blood glucose and lipid profile in patients with type 2 diabetes mellitus.

Patients and methods

One hundred and three type 2 diabetic patients were participated in this study. They were divided into 3 groups according to the treatment. The first group involved 32 patients (Male= 15/ Female= 17) were kept on metformin therapy (500 mg twice daily). The second group involved 37 patients (Male=17/ Female= 20) were kept on combination of metformin (500 mg twice daily), vitamin C 500 mg twice daily and vitamin E, 400 IU twice daily. Whereas the third group involved 34 patients (Male= 20/ Female= 14) who have no drug therapy but kept on diet restriction alone.

Another group consist of 35 healthy subjects (Male= 19/Female= 16) participated in the study as a control group.

The study was randomized, open, controlled comparative study, performed in the college of pharmacy and A1-Wafaa Center of Diabetes Management and Research, during the period between first June 2010 to first December 2011. The study design was approved by the department of pharmacology in Mosul pharmacy college and research committee of Mosul Health Administration. The participitants were newly diagnosed type 2 diabetic patients (According to American Diabetic association criteria, 2001) (1). They were kept on drug or diet therapy for a period of 3 months, during this period they were followed up (8).

Patients with current insulin therapy or received insulin for more than six weeks in last 3 months, were had known hypersensitivity to metformin, or on chronic medication known to affect the outcome of the study were excluded from the study. Also patients with renal, hepatic or cardiac disease and pregnant or lactating women were excluded from the study. Patients who have received vitamin C, vitamin E or any other antioxidant over the last three months were also excluded from the study.

Venous blood samples were withdrawn from each patient and control subject after overnight fasting .Serum glucose concentrations and lipid profile including total-cholesterol (Tc), Low density lipoprotein cholesterol (LDL-c), High density lipoprotein cholesterol (HDL-c) and triglycerides (TGs) were determined at the start and at the end of the study. Fasting serum glucose (FSG) concentration was estimated by glucose-oxidase-peroxidase colorimetric method by using a kit supplied by BIOCON (Germany). Serum triglycerides concentration was measured by enzymatic method using a kit supplied from BIOMERIEUX (France). Serum Tc concentration and serum HDL concentration is determined by using kits provided from BIOLABO (France). Serum LDL-c concentration was calculated by Friedewald equation (9). Atherogenic Index is calculated as AI=TC /HDL-c (10). Calculation of BMI was done for each patient before and after treatment and control by using Quetelet index (Weight/Height2).

Statistical Methods: Unpaired t-test is used to compare between baseline data of the control group and other groups. Paired t-test is used to compare between data of before treatment and after treatment of metformin group, combination group and diet group. Data were expressed as Mean±SD. P- value of ≤ 0.05 is considered statistically significant (11).

Results

The ages of the four groups were 43.61±1.66, 46.80± 1.12, 45.60± 1.22, and 48.25± 1.30 years for control, diet, metformin and combination groups, respectively. The four groups were matched for age (P>0.05) but not for BMI.

Comparison of the baseline data of the diabetic groups with those of the control group showed

higher values for all parameters (except HDL-c) for diabetic groups as compared with the control group. HDL-c shows a low values for diabetic groups as compared with control group (Table 1).

A Significant reduction only of the weight, BMI, FSG, and Tc were obtained after treatment with metformin alone (Table 2), whereas a reduction of all parameters and elevation of HDL-c were obtained after treatment with combination therapy (Table 3). Treatment with diet restriction alone showed no significant reduction for all studied parameters (Table 4).

Discussion

The results of the present study showed reduction of all parameters and elevation of HDL-c after treatment with a combination of metformin and vitamin C and E whereas treatment with metformin alone produce less beneficial effects as that with diet restriction alone. These results indicate that vitamin C and E have favorable effects on serum glucose concentration and lipid profile.

Many previous studies also reported beneficial effects of vitamin C and E on serum glucose concentration or lipid profile. Dakhale et al. (7) reported that addition of vitamin C to metformin treatment in type 2 diabetic patients reduce serum glucose concentration. Sridulyakul, et al. (10) and Ardekani, et al. (12) also demonstrated serum glucose concentration reduction by the use of vitamin C. Chronic vitamin C administration has beneficial effects on glucose and lipid metabolism in type 2 diabetic patients as the administration of vitamin C is associated with a decline in serum glucose concentration, total and LDL-c and triglycerides (13). Vitamin C was found to be significantly decreasing the elevated levels of glucose, cholesterol, triglycerides and low-density lipoprotein (LDL) in T2DM (14).

Gaur and dixit (15) reported that vitamin C administration in a number of individuals leads to decrease total-c, triglycerides and LDL-c concentrations. The effects of vitamin C and E was studied in a number of type 2 diabetic patients. A significant decrease in FBS, TG, LDL-c and HbA1c was seen in the supplemented groups after three months (16). Another study reported decreased level of lipid profile, peroxidation and free radical production by vitamin E and C supplementation (17). High doses of vitamins C and E have been shown to decrease blood glucose, plasma cholesterol and triglyceride in T2DM patients (18).

The results of the present study demonstrated a reduction of serum glucose concentrations and lipid profile by vitamin C and E supplementation. Increased serum concentrations and lipid profile in type 2 diabetic patients constitute risk factors for the development of cardiovascular diseases (19). Moreover, Vitamin C and E are important antioxidant in humans, able of scavenging oxygen-derived free radicals, improved hyperlipidemia and decreased blood pressure (20). Vitamin C is structurally similar to glucose and can replace it in many chemical

reactions, and thus is effective in prevention of non-enzymatic glycosylation of proteins. Several studies showed increased oxidative stress, and decreased basal vitamin C and E levels in diabetic patients (21). Type 2 diabetes mellitus, hypertension and dyslipidemia are associated with insulin resistance and an increased risk of coronary heart disease. Therefore, reducing fat intake, increasing antioxidants, particularly vitamins C and E intake, should be encouraged (22).

Conclusion: The addition of Vitamin C and E to metformin therapy produce additional beneficial effects over metformin alone or diet therapy alone. Accordingly the continuous use of vitamin C and E with hypoglycemic agents is recommended in type 2 diabetic patients.

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Table (1):- Comparison between baseline data of the control group and other groups (Mean ± SD).

Parameter	Control Group N= 35	Diet Group N= 34	Metformin Group N= 32	Combination Group N= 37
Weight(Kg)	76.15±12.5	83.70 ± 8.00***	86.52±8.55***	84.31 ± 2.5***
BMI(Kg/m2)	23.70 ±1.4	32.41 ± 1.32***	33.44±1.40***	29.35 ± 2.24***
FSG (mmol/L)	4.55 ± 0.9	7.10±0.42***	7.64 ± 3.13***	8.72 ± 0.21***
Total-c (mmol/L)	4.46 ± 0.6	5.54±0.70***	5.21 ± 0.93***	4.85 ± 0.21***
TG (mmol/L)	1.42 ± 0.6	1.90±0.39***	2.70 ± 1.01***	1.68 ± 0.47*
HDL-c (mmol/L)	1.5 ± 0.4	1.49±0.22***	1.05 ± 0.27***	0.93 ± 0.10***
LDL-c (mmol/L)	2.31±0.7	3.19±0.30***	2.93±0.20***	3.51±0.10***
Atherogenic Index	2.97±1.5	3.71±3.18***	5.05±1.63***	5.21±2.1***

*** Significant difference from control at P<0.001 using unpaired t-test

* Significant difference from control at P<0.01 using unpaired t-test

Table (2) :- Comparison between parameters before and after treatment with metformin (Mean±SD).

Parameter	Before Treatment	After Treatment	P- value
Weight(Kg)	86.52±8.55	84.96±3.53	<0.001
BMI(Kg/m2)	33.44±1.40	31.75±1.21	<0.001
FSG (mmol/L)	7.64 ± 3.13	6.42 ± 3.07	<0.001
Total-c (mmol/L)	5.21 ± 0.93	5.08 ± 0.86	0.05
TG (mmol/L)	2.70 ± 1.01	2.50 ± 1.05	0.064(NS)
HDL-c (mmol/L)	1.05 ± 0.27	1.11 ± 0.26	0.240(NS)
LDL-c (mmol/L)	2.93±0.20	2.83±0.12	0.123(NS)
Atherogenic Index	5.05±1.63	4.48±1.18	0.098(NS)

Using paired t- test (n=32).

NS= Not significant.

Table (3) :- Comparison between parameters before and after treatment with metformin + vitamin E and C (Mean ± SD).

Parameter	Before Treatment	After Treatment	P-value
Weight(Kg)	84.31 ± 2.5	82.96 ± 1.13	<0.001
BMI(Kg/m2)	29.35 ± 2.24	27.84 ± 2.20	<0.001
FSG (mmol/L)	8.72 ± 0.21	7.86 ± 0.61	<0.001
Total-c (mmol/L)	4.85 ± 0.21	4.61 ± 0.22	<0.001
TG (mmol/L)	1.68 ± 0.47	1.50 ± 0.61	<0.001
HDL-c (mmol/L)	0.93 ± 0.10	1.11 ± 0.21	<0.001
LDL-c (mmol/L)	3.51±0.10	2.81± 0.10	<0.001
Atherogenic Index	5.21±2.1	4.15±1.05	<0.001

Using paired t- test (n=37).

Table (4) :- Comparison between parameters before and after treatment with diet (Mean±SD).

Parameter	Before	After	p-value
Weight(Kg)	83.70 ± 8.00	82.01±6.90	0.145(NS)
BMI(Kg/m2)	32.41 ± 1.32	31.31±1.36	0.340(NS)
FSG (mmol/L)	7.10±0.42	6.56±0.75	0.236(NS)
Total-c (mmol/L)	5.54±0.70	5.46±0.76	0.135(NS)
TG (mmol/L)	1.90±0.39	1.82±0.37	0.220(NS)
HDL-c (mmol/L)	1.49±0.22	1.57±0.39	0.148(NS)
LDL-c (mmol/L)	3.19±0.30	3.06±0.20	0.240(NS)
Atherogenic Index	3.71±3.18	3.47±1.94	0.152(NS)

Using paired t- test (n=34).
NS= Not significant.