

Effects of metformin and cinnamon on 1,5 anhydroglucitol, adiponectin and ghrelin on newly diagnosed type 2 diabetes mellitus patients

*Shatha Hani Mohammad¹, Nabeel Najib Fadhil²,
Mohammad Daoud Mahmood³*

Abstract

Objective: Cinnamon, is one of the commonly used herbs for type 2 diabetes mellitus in spite of variable evidence. This study aimed to show the effect of cinnamon when combined with metformin on the glycemic marker; serum 1,5 anhydroglucitol, and the metabolic syndrome markers; adiponectin and ghrelin, in newly diagnosed type 2 diabetes mellitus patients.

Patients and Methods: This is a randomized controlled trial that has been conducted over 12 weeks. It included 57 males and females who were 32-60-year-old. States that may affect the results were excluded. Group 1 patients (n. 30) were treated for 12 weeks with metformin alone, 500 mg three times daily. Group 2 patients (n. 27) were treated, for 12 weeks as well, with metformin, 500mg three times daily plus crude cinnamon, 3 g per day. A control group of apparently healthy subjects (n. 33) were used for comparing the results.

Results: Metformin group showed a significant rise in 1,5 anhydroglucitol level (p 0.028) and an insignificant rise in ghrelin and adiponectin levels. The metformin plus cinnamon group showed a significant rise in 1,5 anhydroglucitol (p 0.017) and ghrelin (p 0.041), and a highly significant rise in adiponectin level (p value 0.009) that approached the control group level.

Conclusion: adding, crude cinnamon to metformin produced significant improvement in 1,5anhydroglucitol and ghrelin levels and highly significant improvement in adiponectin level, suggesting that crude cinnamon is a beneficial adjunctive therapy in treating type 2 diabetes mellitus and metabolic syndrome.

Keywords: 1,5 anhydroglucitol, Adiponectin, Cinnamon, Ghrelin, Metformin.

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¹M.B.Ch.B, Ph.D.

Lecturer, Pharmacology

College of Medicine, Mosul University

Mosul, Iraq

Email: shth_mohamad@yahoo.com

²CABM, FRCP(London)

Asst. Prof. Endocrinology and Diabetes

College of Medicine, Ninevah University

Mosul, Iraq

Email: nabeelfadhil@yahoo.com

Institute email: nabeel.fadhil@uoninevah.edu.iq

³M.B.Ch.B, Ph.D. Pharmacology

Lecturer, College of Pharmacy

College of Pharmacy, University of Mosul, Iraq

Email: phdpharmal@gmail.com

CORRESPONDING AUTHOR

Nabeel Najib Fadhil

Assistant Professor endocrinology and Diabetes

College of Medicine, Ninevah University

Email for affiliation and correspondence: nabeelfadhil@yahoo.com

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic diseases that is associated with an increased risk of coronary heart disease, stroke, hypertension, renal failure, dyslipidemia and all-cause mortality.^[1] Traditional herbal medicine has been widely used for treatment of T2DM, however, most of the herbs have been shown to exert little or no effect on glycemic control. Cinnamon, is one of the commonly used herbs for T2DM in Iraq. A study conducted in Mosul in 2003 showed that cinnamon, among other herbs, was used by 3.8% of T2DM patients at certain time of their disease course.^[2]

The bark of the *Cinnamomum cassia* contains cinnamic aldehyde, cinnamic acid, tannin, and methyl-mydroxychalcone polymer as the main components. These contents were shown to be biologically active substances with insulinomimetic properties.^[3]

In T2DM, there are many markers for glycemic control, one of them is serum level 1,5 anhydroglucitol (1,5AG). It is a 1-deoxy form of glucose that circulates in the body in its free form. When glucose levels exceeds the renal threshold for glycosuria, 1,5AG together with glucose, are excreted in the urine, thus its serum levels decreases in approximately 2 weeks.^[4] Its level is highly sensitive and specific, and a reduced level indicates diabetes mellitus. 1,5AG determinations were superior to hemoglobin A1c and fructoseamine measurements, in screening for diabetes.^[5]

Many factors affect the pathogenesis, course and complications of T2DM. Adipokines, that are secreted by adipose tissues, plays a significant role among other factors. Adiponectin (ADP) is the most abundant adipokine that is synthesized from differentiated adipocytes.^[6] It increases the hepatic effect of insulin and decreases gluconeogenesis.^[7] In addition, ADP improves insulin sensitivity by reducing the levels of free fatty acids in the plasma and by increasing their oxidation in the muscles.^[8]

Ghrelin (GHRL), a hormone secreted principally in the stomach, induces growth hormone secretion, stimulates food intake,

glucose release and suppresses insulin secretion in humans.^[9] Ghrelin levels are decreased in T2DM and are highly correlated to the degree of insulin resistance.^[10] Both ADP and GHRL were recorded to be hormonal biomarkers of metabolic syndrome in which their concentrations are reduced together with anti-inflammatory cytokines IL-10 and antioxidant factors.^[11]

Metformin, a prominent therapy of T2DM, principle action is reduction of hepatic and renal gluconeogenesis by activating the enzyme adenosine monophosphate-activated protein kinase and reducing hepatic glucose production.^[12] Recently, it is reported that metformin rapidly causes increment in plasma levels of glucagon-like peptide 1 (GLP-1).^[13] The use of metformin was also found to be associated with increased serum GHRL levels mostly due to improved insulin resistance.^[14]

In vitro and *in vivo* studies have shown that cinnamon improves insulin receptor kinase activity, autophosphorylation of insulin receptor and glycogen synthase activity.^[3] Moreover, it possesses the ability to reduce lipid levels and affects immune responses by regulating pro-inflammatory mediators.^[15] Crude cinnamon, in studies of diabetes, is generally given at dosages of 1 to 3 to 6 g/day (120 mg/day) without reported adverse reactions.^[16]

The aim of this study is to evaluate the effect metformin alone and metformin combined with cinnamon on serum 1,5AG, ADP and GHRL in newly diagnosed T2DM patients.

PATIENTS AND METHODS

This is a randomized controlled trial for twelve weeks duration conducted in a Diabetes and Endocrinology Civil Clinic in Baghdad during the period between October 1st, 2014 to September 30th, 2015.

The study included 57 randomly selected male and female patients with newly diagnosed T2DM (≤ 1 year) whose ages ranged between 32 and 60 years. Ischemic heart diseases or other comorbidities of the enrolled patients and control subjects were explored from the patients' clinical history. The presence of hypertension was assessed by a conventional

manual measurement of blood pressure, and the lipidemic profile of the enrolled patients and control subjects was also assessed (table 1). Patients who were known to have hepatobiliary disease were excluded, as well as patients with chronic kidney disease, nephrotic syndrome and hypothyroidism. Patients who are cigarette smoker or using glycemic altering drugs like oral contraceptive, corticosteroids, diuretics, and neuroleptic medications during the last month were also excluded, in addition to pregnant or lactating women or patients with hematological disorders.

To gain an impression about the normal values of the studied parameters in our community, another 33, apparently healthy, volunteer persons whose sex and age were in proportions with the enrolled patients were recruited (table 1). The control group data were obtained, tabulated and analyzed in a similar way to the enrolled patients.

The aim of the study was disclosed to the enrolled participants (n. 57) and their consents were obtained after the ethical approval of the research. The patients, thereafter, were arranged into two groups; group 1, contained 30 patients treated with metformin (Piophage® tablet provided by Pioneer Com. Iraq) in doses of 500 mg three times daily, for a duration of 12 weeks. The second group; Group 2, consisted of 27 patients treated with metformin (500 mg) three times daily together with crude cinnamon powder, in a dose of 3 capsules per day (1000 mg for each capsule), for 12 weeks.

Measurements of fasting serum ADP, fasting serum GHRL and fasting serum 1,5AG were done initially as a baseline and thereafter, after 12 weeks. Standard kits were used to measure the biochemical parameters in this study by double-sandwich ELISA method. The tests' performance and interpretation were conducted following the instructions of the kits. The data were recorded in a specially preformed case record.

Statistics were carried out using Minitab version 16.2 software statistical program. To compare between the results, independent t-test was used. *p*-values of <0.05 and <0.01 were considered significant, and highly significant

respectively throughout data analysis.

RESULTS

After 12 weeks of therapy with metformin alone, there was significant rise in serum level of 1,5AG, but non-significant rise in ADP and GHRL levels. The means \pm SD of serum levels of the three parameters before and after 12 weeks, were (4.4 \pm 1.5 vs. 12.5 \pm 0.7) μ g/ml for 1,5AG, (22.7 \pm 1.1 vs. 25.4 \pm 3.6) μ g/ml for ADP, and (0.78 \pm 0.80 vs. 0.99 \pm 0.6) ng/ml for GHRL (Table.2).

On comparing the results of metformin alone with the control group levels after 12 weeks, the parameters of metformin alone users didn't approach the control group values that are supposed to represent normal values (Table 3).

Using metformin (500mg three times daily) together with cinnamon (1000 mg three times daily) for 12 weeks showed significant increase in 1,5AG and GHRL levels and a highly significant increase in ADP levels. The means \pm SD of serum levels before and after treatment were (7.3 \pm 1.8 vs. 11.45 \pm 0.82) μ g/ml for 1,5AG, (0.66 \pm 0.05 vs. 0.85 \pm 0.69) ng/ml for GHRL, and (14.22 \pm 10.2 vs. 37.21 \pm 13.52) μ g/ml for ADP (Table 4).

On comparing metformin plus cinnamon parameters with the control group after 12 weeks of treatment, only ADP levels approached the control group level (*p* value= 0.009) (Table 5). Comparing, the studied parameters of the metformin alone group versus metformin plus cinnamon group at the end of the study showed a significantly higher level of ADP in the cinnamon plus metformin group but no difference in 1,5AG and GHRL in the two groups (Table 6).

DISCUSSION

After 12 weeks of therapy, metformin alone produced significant rise in 1,5AG but insignificant increase in ADP and GHRL levels (Table 2). Using metformin together with cinnamon for 12 weeks showed a significant increase in 1,5AG and serum GHRL levels and a highly significant improvement in serum ADP level.

The improvement of serum 1,5AG in the metformin group is expected with metformin

antihyperglycemic effect, however, there are no data about metformin effect on 1,5AG to be compared with the current study results.

Regarding GHRL and ADP response in this study, there is insignificant increase with metformin. This is in agreement with many other studies in this regard. In a meta-analysis of randomized controlled trials conducted by Ida S *et al.*, in 2017,^[17] it was also found that metformin therapy didn't show a significant increase in plasma GHRL.

Other researches' findings regarding GHRL are markedly contradictory. Some researchers reported a significant rise of GHRL after 6-12 week treatment with metformin.^[12, 18] They announce, that the GHRL increase was likely to be secondary to the improved glycemic control and weight reduction induced by metformin as GHRL inversely correlates with BMI.^[18] Another research,^[19] reported a decrease of GHRL levels after 6 months treatment with metformin. The researchers thought that metformin directly inhibit GHRL production through activation of AMPK activator that markedly inhibits GHRL secretion.

Concerning ADP, metformin alone produced an insignificant rise in ADP after three months treatment. Basios G *et al.*,^[20] in his trial of treating 31 polycystic ovary syndrome patients with 1275 mg metformin/day for 6 months, showed that plasma ADP levels were reduced after metformin treatment. Megan V. Cannon *et al.*,^[21] as well, noted a significant reduction of ADP levels after 4 months therapy with metformin. On contrary, Su JR *et al.* in,^[22] found that ADP serum levels was higher than pre-treatment levels in T2DM patients ($p < 0.001$) who were treated with metformin.

In regard to Group 2, using metformin with cinnamon therapy for 12 weeks, produced a significant rise of 1,5AG and GHRL and a highly significant rise of ADP. There are no studies concerning the effects of metformin combined with cinnamon on 1,5AG, GHRL and ADP to be compared with our results.

Comparing the beneficial increment of 1,5AG that was induced by metformin alone with that induced by metformin with cinnamon

showed no significant difference (Table 6). This means that there is no additive hypoglycemic effect of cinnamon on that of metformin alone, or that the effect of cinnamon on 1,5AG was overshadowed by metformin effect itself. In spite of that, a lot of previous researches had confirmed the hypoglycemic effects of cinnamon. Cinnamon was found to increase insulin sensitivity, and reduce hyperglycemia possibly by regulating the peroxisome proliferator-activated receptors-mediated glucose and lipid metabolism.^[23]

Susana Camacho *et al.*,^[24] detected that after 36 days supplementation with 0.2% cinnamaldehyde (CIN), an up-regulation of 3 different glucose transporters, glucose transporter 1 (GLUT1), GLUT8, and GLUT12, occurred. Hlebowicz J *et al.*,^[25] found that the ingestion of 3 g cinnamon per day reduced postprandial serum insulin and increased glucagon-like peptide 1 concentrations. Borzoei *et al.*, (2018)^[26] study showed that short term cinnamon supplementation (1.5-1 g/day) for 12 weeks improved serum glycemic indices without detectable effects on ADP.

In agreement with cinnamon effect on GHRL that was detected in this study, Khare *et al.*,^[27] demonstrated that CIN increases fasting serum GHRL ratio. Myriam Sfar *et al.*,^[28] also, had found that there was an increase in GHRL secretion with 4 g dose of cinnamon.

However, Markey O *et al.*,^[29] found that 3 g cinnamon per day did not cause any alteration in fasting GHRL level. Contrary to the above, Susana Camacho *et al.*,^[24] found that active and total GHRL secretion in a cell culture medium, 4 hours after stimulation with 100 μ M of CIN, was significantly lower (44%) than in control conditions.

Concerning cinnamon effect on ADP, Khare *et al.*,^[27] in their study, demonstrated that CIN significantly increases ADP ratio. Mohamed *et al.*,^[30] in human and Israa Ali Shatwan^[31] *et al.*, in diabetic rats, also, confirmed that cinnamon extract induces a significant elevation in fasting plasma levels of ADP. These results are in accord with the current study findings, however, the highly significant increase of ADP on using cinnamon together with

metformin in the current study is not clear whether it is due to cinnamon effect or to its interaction with metformin. Further studies are required in this regard.

In conclusion, The significant rise of

1,5AG, GHRL and highly significant rise of ADP when crude cinnamon was added to metformin, suggest that cinnamon is a beneficial adjunctive therapy in treating T2DM and metabolic syndrome.

Table 1: Demographic data of the enrolled patients and control group.

Parameter	Classification	Patients (n.57)		Control group (n. 33)	
		Male (n. 27)	Female (n. 30)	Males (n. 16)	Females (n. 17)
Age	30-49 (years)	11	8	8	8
	50-69 (years)	16	22	8	9
Comorbid diseases	Hypertension	5	11	-	-
	Dyslipidemia	6	8	-	-
	Ischemic heart disease	4	3	-	-
	Bronchial asthma	2	1	-	-
	Others if any	10	8	-	-
Weight (kg) mean (\pm SD)		76.1 (\pm 6.92)	61.4 (\pm 0.11)	74 (\pm 1.13)	63 (\pm 0.17)

Table 2: 1,5AG, ADP and GHRL of the metformin alone group at the baseline and after 12 weeks of treatment.

Parameter	Metformin alone group at the baseline	Metformin alone group after 12 weeks of treatment	p value (t-test)
1,5AG (μ g/ml)	4.4 \pm 1.5	12.5 \pm 0.7	0.028
ADP (μ g/ml)	22.7 \pm 1.1	25.4 \pm 3.6	0.061
GHRL (ng/ml)	0.78 \pm 0.80	0.99 \pm 0.6	0.058

Table 3: 1,5AG, ADP and GHRL of the metformin alone group versus the control group at the end of the study.

Parameter	Metformin alone group at the end of study	Control group at the end of study	p value (Independent samples t-test)
1,5AG (μ g/ml)	12.5 \pm 0.7	25.9 \pm 8.6	0.000
ADP (μ g/ml)	25.4 \pm 3.6	38.28 \pm 14.35	0.000
GHRL (ng/ml)	0.99 \pm 0.6	1.12 \pm 52.9	0.000

Table 4: 1,5AG, ADP and GHRL of the metformin plus cinnamon group at baseline and after

12 weeks of treatment.

Parameter	Metformin plus cinnamon group at the baseline	Metformin plus cinnamon group after 12 weeks of treatment	p value (t-test)
1,5AG ($\mu\text{g/ml}$)	7.3 + 1.8	11.45 +0.82	0.017
ADP ($\mu\text{g/ml}$)	14.22 \pm 10.2	37.21 \pm 13.52	0.009
GHRL (ng/ml)	0.66+ 0.05	0.85 \pm 0.69	0.041

Table 5: 1,5AG, ADP and GHRL of the metformin plus cinnamon group versus the control group after 12 weeks of treatment

Parameter	Metformin plus cinnamon group at the end of study	Control group at the end of study	p value (Independent Samples t-test)
1,5AG ($\mu\text{g/ml}$)	11.45 +0.82	25.9 + 8.6	0.000
ADP ($\mu\text{g/ml}$)	37.21 \pm 13.52	38.28 + 14.35	0.267
GHRL (ng/ml)	0.85 \pm 0.69	1.12+ 52.9	0.000

Table 6: 1,5AG, ADP and GHRL levels of the metformin alone group versus metformin plus cinnamon group at the end of the study.

Parameter	Metformin alone group at the end of study	Metformin plus cinnamon group at the end of study	p value (t-test)
1,5AG ($\mu\text{g/ml}$)	12.5 \pm 0.7	11.45 \pm 0.82	NS
ADP ($\mu\text{g/ml}$)	25.4 \pm 3.6	37.21 \pm 13.52	0.021
GHRL (ng/ml)	0.99 \pm 0.6	0.85 \pm 0.69	NS

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تأثير الميتفورمين مع القرفة على تراكيز 1,5 أنهيدروجلولوسيتول وأديبونيكتين وغريلين في مرضى الداء السكري من النمط 2 الذين تم تشخيصهم حديثاً

شذى هاني محمد¹، نبيل نجيب فاضل²، محمد داود محمود³

- 1 - بكالوريوس طب وجراحة عامة، دكتوراه في علم الأدوية، محاضرة بقسم الأدوية، كلية الطب، جامعة الموصل، الموصل، العراق.
- 2 - بورد عربي في الأمراض الباطنة، زميل كلية الأطباء الملكية (لندن)، استشاري الطب الباطني، أستاذ مساعد كلية الطب، جامعة نينوى، الموصل، العراق.
- 3 - بكالوريوس طب وجراحة عامة، دكتوراه في علم الأدوية، مدرس بكلية الصيدلة، جامعة الموصل، العراق.

الملخص

الخلفيات والأهداف: تُعدُّ القرفة من المواد النباتية الطبية شائعة الاستخدام لمرض الداء السكري من النمط 2 على الرغم من وجود أدلة متباينة، وهدفت هذه الدراسة إلى إظهار تأثير القرفة عند دمجها مع ميتفورمين على مؤشر كلوكوز الدم، 1,5 أنهيدروجلولوسيتول، وفي مصل الدم، وعلى مؤشري المتلازمة الأيضية، أديبونيكتين وغريلين، في مرضى الداء السكري من النمط 2 الذين تم تشخيصهم حديثاً.

المواد والطرق: هذه تجربة مُعشَّاة مقيَّسة أُجريت على مدى 12 أسبوعاً، وشملت 57 من الذكور والإناث الذين تتراوح أعمارهم بين 32-60 سنة، بعد استبعاد الحالات التي تؤثر على النتائج، ولقد عولج مرضى المجموعة الأولى (عدد 30) لمدة 12 أسبوعاً باستخدام عقار ميتفورمين وحده بجرعة 500 ملغم ثلاث مرات يومياً، وعولج مرضى المجموعة الثانية (وعدد 27) لمدة 12 أسبوعاً أيضاً بميتفورمين بجرعة 500 ملغم ثلاث مرات يومياً إضافة إلى مسحوق القرفة الخام بجرعة 3 غم يومياً، ولقد استُخدمت مجموعة قياس من الأشخاص الذين بدؤوا أصحاء (عدد 33) لمقارنة النتائج.

النتائج: أظهرت مجموعة ميتفورمين ارتفاعاً مهماً في مستوى مادة 1,5 أنهيدروجلولوسيتول في مصل الدم (قيمة $P = 0.028$) وارتفاعاً غير مهم إحصائياً في تركيزي غريلين وأديبونيكتين، فيما أظهرت مجموعة ميتفورمين مع القرفة ارتفاعاً مهماً في تركيز مادة 1,5 أنهيدروجلولوسيتول (قيمة $P = 0.017$) وغريلين (قيمة $P = 0.041$)، وارتفاعاً مهماً جداً في مستوى أديبونيكتين (قيمة $P = 0.009$) الذي اقترب من مستواه في مجموعة القياس.

الخلاصة: أدت إضافة القرفة الخام إلى عقار ميتفورمين إلى تحسني كبير في مستويات مادة 1,5 أنهيدروجلولوسيتول، و غريلين وتحسن كبير جداً في مستوى أديبونيكتين، مما يشير إلى أن القرفة الخام علاجٌ مساعدٌ مفيد في تدبير الداء السكري من النمط 2 والمتلازمة الأيضية.

الكلمات الدالة: 1,5 أنهيدروجلولوسيتول، أديبونيكتين، قرفة، غريلين، ميتفورمين.