A potential role of Cinnamon in improvement of glycemic control in untreated diabetic patients

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Abstract:

Objectives: The purpose of this study was to determine the effects of supplementation with a whole cinnamon on glycemic control measurements.

Methods and materials: forty eighth patients with Diabetes mellitus type II who are not received any hypoglycemic agents nor on insulin therapy, (aged ≥ 38 years and body mass index ≤ 30kg/m2),their fasting blood glucose: levels between (186–332mg/dl) were randomly assigned to supplement cinnamon 1g, 2g, and 4g or a placebo for three months. Main outcome measures were changed in fasting blood glucose, postprandial blood glucose, glycated hemoglobin, kidney function tests like: blood urea nitrogen and serum creatinine , and liver function tests represented Aspartate aminotransferase, Alanine aminotransferase ,Alkaline phosphatase measured after three months of supplementation.

Results: After 3months, all three doses of cinnamon 1g, 2g, and 4g showed significant decreases in the fasting blood glucose (16.91–18.37%), postprandial blood glucose (16.16–16.6%), and glycated hemoglobin (15.02-17.3%) levels; no significant changes were noted in the placebo groups or in kidney function tests; blood urea nitrogen, serum creatinine, and liver function tests; Aspartate aminotransferase, Alanine aminotransferase, and Alkaline phosphatase.

Conclusions: The results support the efficiency of cinnamon supplementation on reducing fasting blood glucose, postprandial blood glucose, and glycated hemoglobin in patients with the diabetes mellitus and suggest that this naturally-occurring spice can reduce risk factors associated with diabetes.

الدور المحتمل للقرفة في تحسين السيطرة على سكر الدم في مرضى السكري غير المعالج

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مفتاح البحث: مرض السكري من النوع الثاني، والقرفة، ومراقبة نسبة السكر في الدم

الخلاصة:

اجريت هذه الدراسة لمعرفة التأثير المحتمل للقرفة(الدارسين) على المرضى المصابين بداء السكر النوع الثاني, حيث تناول 48 مريضا من الذين لا يتناولون ادوية مخفضة للسكر فضلا عن الانسولين وكانت اعمارهم 38 عاما فما فوق وعامل الوزن المثالي لهم اقل من 30 كغم /المتر المربع وكان نسبة السكر لهم قبل الافطار يترواح بين 186-332 ملغم وتم توزيعهم عشوائيا لتناول جرعات مضاعفة 1 ,2 ,4 غم من القرفة(الدارسين) ومجموعات السيطرة التي فيها المرض تناولوا طحين الحنطة وبنفس القوى للجرعات الدوائية ولمدة 3 اشهر. وتم اخذ القياسات التالية لمقارنتها قبل التجربة وبعدها من اجل ملاحظة الفروق المعنوية ان وجدت وهي : نسبة السكر بعد الصيام fasting blood glucose ونسبة السكر العشوائيpostprandial blood glucose ونسبة السكر التراكمي في الخلية الحمراء glycated hemoglobin وهي تسمى مقاسات التي تخص مراقبة السكر بالدم (glycemic control) والقياسات الخاصة بالاداء الكلوي وهي اليوريا نيتروجين والكرياتينين بالدم والقياسات الخاصة بالاداء الكبدي وهن:ألانين أمينوترانسفيريز Alanine aminotransferase, أسبارتيت أمينوترانسفيريز Aspartate aminotransferase و ألكالاين فوسفيتيز Alkaline phosphatase .

النتائج: بعد 3 أشهر لوحظ ان الجرعات الثلاثة للقرفة(الدارسين) 1,2 ,2و4 غم استطاعت ان تخفض(بدلالة معنوية) نسبة السكر بالدم بعد الصيام(16.91-18.37%) ونسبة السكر بالدم العشوائي(16.16-16.6%) و نسبة السكر التراكمي هي (15.02-17.3%) وبالمقابل لم يحصل اي فرق معنوي بما يخص مجاميع السيطرة وقياسات الاداء الكلوي والكبدي مما ينفي اي تاثير للقرفة(الدارسين) على الكلى والكبد.

الاستنتاجات: تشير البيانات الى ان القرفة(الدارسين) استطاعت ان تخفض وبفروق معنوية لنسبة السكر بعد الصيام والعشوائي والتراكمي لدى المرضى المصابين بداء السكري ويقترح التركيز على البهارات الطبيعية التي تنضم اليها للقرفة(الدارسين) من اجل تقليل عوامل الخطورة الناتجة عن الاصابة بداء السكر.

Introduction:

Diabetes mellitus is the most significant chronic disease and a growing health problem in most countries. It is a metabolic disorder caused by an absolute or relative lack of insulin, and by insulin resistance of peripheral tissues in case of type II diabetes. Effective blood glucose control is key for preventing or reversing diabetic complications and improving the quality of life in diabetic patients[1].

In 1990, it was reported that compounds found in cinnamon (*Cinnamomum cassia*) has insulin-potentiating properties and may be involved in the alleviation of the signs and symptoms of diabetes and cardiovascular diseases related to insulin resistance and metabolic syndrome[2].Indeed, the antidiabetic effects of cinnamon have been attributed to multiple components, including polyphenols[13].Cinnamon polyphenols (CP) affect multiple steps related to glucose and insulin function. CP activate insulin receptors by increasing their tyrosine phosphorylation activity and by decreasing phosphatase activity that inactivates the insulin receptor[4]. CP also increase the amount of insulin receptor β and GLUT4 protein[3]. CP increase glycogen synthase activity and glycogen accumulation[14] with decreased glycogen synthetase kinase-3 β activity[4]. CP also increase the amount of the early-response anti-inflammatory protein, tristetraprolin[3]. All these activities and other potential activities may eventually lead to more efficient glucose transport and utilization[5].The blood glucose lowering potential and pharmacological properties of cinnamon has been demonstrated previously in vitro and in vivo animal studies[5].Cinnamon polyphenols display insulin like properties and stimulate glucose uptake in skeletal muscle and adipose tissue [6].

The purpose of this study was to determine the effects of cinnamon supplementation on fasting blood glucose [FBG], postprandial blood glucose[PBG] and glycated hemoglobin [HbA1C] in poor controlled diabetic patients with features of the metabolic syndrome. In addition, to assess the safety profile of this compound we measured changes in standard markers of health like kidney function tests[like blood urea nitrogen [BUN] and serum creatinine [SC]} and liver function test{ Aspartate aminotransferase [AST], Alanine aminotransferase [ALT] and Alkaline phosphatase [ALP]}.

RESEARCH DESIGN AND METHODS

A sixty male volunteer patients with diagnosed diabetes mellitus type II were selected to participate in this study and randomly assigned to take either cinnamon capsules or placebo capsule daily within meal but only 48 patients of 60 were completed the study, thus the verbal consent was taken from all patients before evaluation of this study which was done in cooperation of Al-Hakeem center for diabetic patients and Al-Sadder medical city.

Criteria for selection for the study population included the following for people with type II diabetes: age $\geq$ 38 years body mass index [BMI] $\leq$ 30,did not received any hypoglycemic drug, not on insulin therapy, and their FBG between (183–316 mg/dl).

Cinnamon and wheat flour were ground finely and put into capsules size 1 by punching method. Each capsule contained either 500 mg of cinnamon or wheat flour[7].

All patients were randomized to administer cinnamon and they were divided into 3 groups. Each group has 8-10 patients and each cinnamon group has its own placebo group, so the total of groups became 6 groups;

Group(1) Placebo 1g: patients in this group had received two capsules contained wheat flour daily.
Group(2) Cinnamon 1g: patients in this group had received two capsules contained cinnamon daily.
Group(3) Placebo 2g: patients in this group had received four capsules contained wheat flour daily.
Group(4) Cinnamon 2g: patients in this group had received four capsules contained cinnamon daily.

Group(5) Placebo 4g: patients in this group had received eight capsules contained wheat flour daily.
Group(6) Cinnamon 4g: patients in this group had received eight capsules contained cinnamon daily.
Compliance was monitored by counting the unconsumed capsules and contact with the patients regularly by mobiles on a weekly basis. The patients were advised to maintain their normal diet and to continue their habitual physical activity throughout the study as they were before the study.

Blood sampling and analytical methods

After informed consent was obtained, blood samples were collected after an overnight fast at before intervention and three months after intervention in order to measure FBG, PBG, HbA1C,kidney function tests[like BUN and SC] and liver function test which consist of AST, ALT, and ALP. For plasma preparation blood samples, taken with a heparin-containing blood sample system, were directly centrifuged at room temperature for 15 minutes at 1200 x *g*. Blood samples for serum preparation were stored for blood coagulation (20 min) and then centrifuged under the same conditions. For determination of HbA1c, EDTA blood was used. HbA1c was assessed by *Stabino* glycol hemoglobin[8] which is quantitative colorimetric determination of glycol-hemoglobin in blood.
FBG and PBG was measured by the *HK enzymatic reaction method* [9], BUN was measured by *Talke & Schubert method*[10] For the quantitative determination of blood urea nitrogen in serum, while serum creatinine determined by *Alkaline Picrate Method*[11] ,but all liver function test(AST,ALT and ALP) have done by reaction *rate assay(kinetic)*[12] which is based on decreases of NADH (340nm) and this profile has done by ARCHITECT/AEROSET technology.
All data represented as a mean ± standard error of means [S.E.M]. statistical significance (P value was 0.05 or less) was estimated by using student-t test. Two-way ANOVA and randomized complete block design were used for statistical analysis[13].

Results:

Of 60 male patients, only 48 had completed the study and twelve patients were excluded by different excuses like: 4 patients had left study due to they that have an allergic reaction to cinnamon (n= 4), 5 patients were too much busy(n= 5) and 3 patients were not satisfied (n= 3). The exclusion of female sex from this study was due to the ease of contact with male one in our society.
There were no significant differences between the cinnamon group and the placebo group in respect to the distribution between the anthropometric variables. The mean of age of all patients is 43.6± 2.6 with a BMI 27.3±1.7 kg/m2.
Other baseline variables are shown in (Table1)which demonstrated that showed significant changes were observed in the placebo for all groups between the beginning and the end of the study. In the placebo group for all doses 1g, 2g and 4g, FBG significantly increased from 186.3±0.597 mg/dL to 195.5±2.883 mg/dL, 223.5±0.500 mg/dL to 228.8±1.083 mg/dL, and 313.4±0.520 mg/dL respectively. PBG also significantly increased from 254.5±0.500 mg/dL to 270.4±4.787 mg/dL , 296.5±0.654 mg/dL to 306.0±1.591 mg/dL, and 395.8±0.915 mg/dL to 426.7±4.261 mg/dL respectively.HbA1C significantly increased from 7.400±0.057 % to 8.180±0.245, 8.38±0.061 % to 8.92±0.100 %, and 10.69±0.481% to 11.48±0.136 % respectively (Table 1).
While in the cinnamon group for all doses 1g, 2g and 4g, FBG significantly decreased from 186.1±0.737 mg/dL to 151.0±0.699 mg/dL, 223.7±0.667 mg/dL to 184.6±0.884 mg/dL, and 313.5±0.500 mg/dL to 260. 4 ±0.541 mg/dL respectively. PBG also significantly decreased from 254.2±0.290 mg/dL to 211.0±0.869 mg/dL, 296.9±0.849 mg/dL to 247.4±1.415 mg/dL, and 395.2±0.771 mg/dL to323.5±0.868 mg/dL respectively. HbA1C significantly decreased from 7.420±0.075% to 6.140±0.4 %, 8.35±0.718 % to 7.19±0.378 %, and 10.65±0.687 % to 9.050±0.341 % respectively(Table1).
At the all levels tested, there was no evidence of a dose response because the response to all three levels of cinnamon was approximately similar. Glucose values in the three placebo groups were not significantly different overall time of experiment(Table 1).

There was no significant difference noted for kidney function tests [like BUN and SC] and liver function test like[AST,ALT and ALP] pre and post intervention with cinnamon (Table 2) .

DISCUSION

First the cinnamon used in this study was obtained from local stores and due to that, there is no regulation of cinnamon as a food supplement. We did not test the purity of cinnamon in capsules. So, the patients in study had received cinnamon which is mimic to that found in local stores [14].

This study did not noted the changes in BMI and its influence in response to cinnamon doses due to our desire to show the absolute effect of cinnamon by three doses on fixed BMI, our result met the result by Khan *et al*.[7].

The significant increment in FBG, PBG, and HbA1C in placebo group for all doses after the end of experiment was expected because the patients were not receive any drug that attenuate their glycemic control measurements , our results were supported by William *et.al* [15] and Khan *et al*.[7].

The findings of this study indicated that consuming 1g, 2g, and 4g /day of cinnamon for three months led to significant improvements in several features of the glycemic control measurements (i.e., FBG, PBG, and HbA1C)(Table 1).

Previous studies have shown conflicted results about the efficiency of cinnamon to treat diabetes. These studies have a variety of results: they generally studied well-controlled patients with type II diabetes[16], some only measured fasting glucose[7]; some measured HbA1C after as little as 30 days' period[16];some had narrow age, sex[7–17]; all excluded insulin use and comorbid conditions; and none allowed medication changes. Only one included a power analysis [18].

The observed reduction in FBG in this study is less than that of Khan *et al*.[7]and similar to Mang *et al*. [19]. Khan *et al*[6]. studied the effects of 1, 3, and 6 g/d of whole cinnamon powder on FBG and serum lipids in 60 people with poorly controlled type II diabetes from Pakistan. After 40 days of supplementation, FBG decreased by 18-29%. More recently, Mang *et al*.[19] supplemented 79 people with type II diabetes from Germany with 3 g/d cinnamon powder or a placebo for four months. In both studies (as well as this study), *No* adverse effects were reported by patients taking cinnamon except allergy in patients who left the study, and this result in agreement with Mang *et al*. [19] ,but in contrast to Khan *et al*.[7]

Ashley *et al*.2012[20] were provided in their study an evidence for the glucose-lowering effect of cinnamon during the 120-minute period after a meal. Short term studies of healthy adults [3-4] that have reported decreases in postprandial blood glucose concentration ranging from 13% to 46% with ingestion of 3 to 6 g ground cinnamon**.** In this study, results regarding the significant decrease of PBG by 16% were supported by the result of Mohamed Sham *et al*.[21]Ashley *et al*.2012[20] .

Although many studies have done with no significant changes in glycosylated hemoglobin (HbA1C) were noted, but our results regarding HbA1C met of results by Paul Crawford [14].

Cinnamon ingestion in three doses 1g, 2g, and 4g may not affect the liver and kidney functions in type II diabetic individuals and its ingestion may be safe and the diabetic patients may use it for longer time for their sugar control, our results were supported by Radhia Khan *et al*.[22].

Not all studies have found beneficial effects of cinnamon on FBG like Vanschoonbeek*et al*.[16] but the benefits of this study are: (1)Recruitment of patients who are poorly controlled diabetes because they did not received any treatment for their diabetics in addition to poor daily physical activity which give a power for our study by exclusion the effect of hypoglycemic agents. (2)The use of ***all*** glycemic control measurements FBG, PBG, and HbA1C in a rare step as shown in other studies which never investigated those three parameters at all and Rajadurai *et al*. 2012[6] confirm this conclusion in their meta-analysis study. (3)This study demonstrated that ingestion of high dose like 4g of cinnamon did not improve FBG,PBG , and HbA1C like 1g and this point was consistent of results by Khan *et al*.[7](tables 3,4, 5 and 6).

Conclusion

It is concluded that the effects of cinnamon differ by population. Studies should be done to determine how specific variables have multiple influence on cinnamon ingestion and these variables are: age, ethnicity, BMI, diet, cinnamon dose, glucose levels, and concomitant medication.

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Table 1: The effect of Cinnamon on Glycemic control measurements

Parameter	State	FBG mg/dl	PBG mg/dl	HbA1c %
Group (1) Placebo 1g N=9	**before**	186.3±0.597	254.5±0.500	7.400±0.057
	after	195.5±2.883#	270.4±4.787#	8.180±0.245#
Group(2) Cinnamon 1g N=8	**before**	186.1±0.737	254.2±0.290	7.420±0.075
	after	151.0±0.699*	211.0±0.869*	6.140±0.400*
Group (3) Placebo 2g N=8	**before**	223.5±0.500	296.5±0.654	8.38±0.061
	after	228.8±1.083$	306.0±1.591$	8.92±0.100$
Group(4) Cinnamon 2g N=8	**before**	223.7±0.667	296.9±0.849	8.35±0.718
	after	184.6±0.884*	247.4±1.415*	7.19±0.378*
Group (5) Placebo 4 g N=8	**before**	313.4±0.520	395.8±0.915	10.69±0.481
	after	332.0±2.932 £	426.7±4.261 £	11.48±0.136 £
Group(6) Cinnamon 4g N=7	**before**	313.5±0.500	395.2±0.771	10.65±0.687
	after	260. 4 ±0.541*	323.5±0.868*	9.050±0.341*

#: P < 0.007 as compared with before group for 1g placebo

$: P < 0.0001 as compared with before group for 2g placebo

£: P < 0.0001 as compared with before group for 4g placebo

**: P <0.0001 as compared with before group* for cinnamon with all doses

Table 2: The effect of cinnamon on kidney function and liver function tests

Parameter	State	BUN mg/dl	SC mg/dl	AST IU/L	ALT IU/L	ALP IU/L
Group (1) Placebo1g N=9	**before**	38.10±0.481	0.731±0.004	13.80±0.416	22.30±0.472	93.80±0.316
	after	38.20±0.489	0.733±0.005	13.70±0.448	22.00±0.516	93.90±0.414
Group(2) Cinnamon1g N=8	**before**	37.90±0.458	0.729±0.003	14.00±0.516	22.5±0.401	94.00±0.365
	after	37.60±0.581	0.728±0.005	14.10±0.525	22.2±0.388	94.10±0.504
Group (3) Placebo 2g N=8	**before**	37.3±0.395	0.867±0.004	7.4±0.371	6.6±0.305	137.2±0.416
	after	37.4±0.371	0.868±0.005	7.5±0.307	6.7±0.395	137.3±0.538
Group(4) Cinnamon2g N=8	**before**	37.5±0.341	0.864±0.003	7.2±0.326	6.8±0.388	136.9±0.378
	after	37.1±0.458	0.866±0.002	7.3±0.366	6.5±0.306	136.7±0.869
Group (5) Placebo4 g N=8	**before**	27.70±0.366	0.900±0.003	14.3±0.472	12.4±0.478	112.9±0.595
	after	27.50±0.600	0.897±0.005	14.4±0.520	12.5±0.428	112.7±0.817
Group(6) Cinnamon4g N=7	**before**	27.5±0.341	0.898±0.004	13.9±0.525	12.6±0.426	112.7±0.495
	after	27.9±0.640	0.895±0.006	13.6±0.426	12.7±0.213	112.2±0.646

Table 3:The percent of reduction between before and after treatment for 1g, 2g, and 4g of Cinnamon to glycemic control measurements

Before-after	FBG (mg)	% of reduced	PBG (mg)	% of reduced	HbA1C (%)	% of reduced
1G	185-151	18.37	253.9-211	16.6	7.47-6.14	17.3
2G	224.2-184	17.66	296.9-247	16.41	8.53-7.19	15.7
4G	313.4-260.4	16.91	386-323.6	16.16	10.65-9.05	15.02

Table 4:The comparison between the doses of Cinnamon according to percent of reduction in FBG

Matching of doses as % of reduced	Mean Difference	Std. Error	Significance
1g-2g	1.38700*	0.523	.013
1g-4g	1.91700*	0.537	.001
2g-4g	0.53000*	0.530	.320

* The mean difference is significant at the 0.05 level.

Table 5: The comparison between the doses of cinnamon according to percent of reduction in PBG

Matching of doses as % of reduced	Mean Difference	Std. Error	Significance
1g-2g	0.32700*	0.584	.580
1g-4g	1.07400*	0.580	.077
2g-4g	1.40100*	0.589	.023

* The mean difference is significant at the 0.05 level.

Table 6: The comparison between the doses of cinnamon according to percent of reduction in HbA1C

Matching of doses as % of reduced	Mean Difference	Std. Error	Significance
1g-2g	3.337*	1.186	.009
1g-4g	2.195*	1.188	.075
2g-4g	1.142*	1.183	.344

* The mean difference is significant at the 0.05 level.