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Effect of cinnamon supplementation on resistin and ghrelin in obese diabetic men

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The object of this study was to determine the effect of Cinnamomum zeylanicum (cinnamon) on glycemic/lipid balance, resistin and ghrelin. 84 obese Type 2 diabetic patients were assigned in 2 groups which consumed 8 g and 4 g of cinnamon powder. Anthropometric, hormonal and biochemical parameters were measured before and after 10 weeks of treatment. We found that cinnamon decrease BMI and waist circumference respectively of -5.52±1.47 kg/m² and -10.72±6.12 cm for group 2 of and a decrease of -4.45±1.46 kg/m² and -6.86±5.5 cm in group 1. Our results also showed a decrease of the glucose level of -1,173±0, 75 mmol/L in group 2 and -0, 8932±0, 72 mmol/L in group 1 and a decrease of insulin levels of -3.24±2.85 µUI/L in group 2 and -2.54±2.8 µUI/L in group 1. The assays showed that resistin secretion decreased by -2.08±1.09 ng/mL for the 8 g dose and -1.59±0.926 ng/mL for the 4 g dose, and there was an increase in ghrelin secretion of +1.55±2.21 µg/mL for the 8 g dose and + 2.49±1.13 µg/mL for the 4 g dose.

The results confirmed the anti-hyperglycemic and hypolipidemic effects of cinnamon opening a new approach to studying how the compounds derived from certain spices regulate the endogenous release of hormones such as ghrelin and resistin for therapeutic intervention.

Keywords: Cinnamon, Diabetes, Ghrelin, Obesity, Resistin

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Obesity is a serious public health problem of the 21st century on account of the increased associated risk of hypertension, coronary heart disease, Type 2 diabetes, stroke, certain types of cancer, osteoarthritis, sleep apnea and other disorders such as infertility[1].

Despite the global voluntary goal of curbing rising obesity by 2025[2,3], overweight and obesity was increased in almost all countries. In 2014, more than one in three adults over the age of 18 was overweight and more than one in ten was obese[2].

Tunisia is affected by this public health problem and is at an advanced stage. Moreover, the obesity prevalence had more than doubled in the last two decades in our country[4]. It was a complex and multifactorial disease with overeating, physical inactivity and genetic susceptibility as the primary causal factors.

On the other hand, being obese or overweight is strongly related to diabetes. Adiposity was the most critical risk factor for diabetes. In addition, diabetes, whose complications (blindness, amputations, kidney failure) were expensive, can represent a weighty burden in the long term for health budgets[5].

The usual recommendations were aimed at improving lifestyles such as switching to a healthier diet, increasing physical activity and medication compliance. However, there were problems faced with the difficulty of lifestyle change and its long-term maintenance and side effects associated with the medication.

Herbal medicine can represent an alternative or a valuable addition to the conventional prescription of drugs. In this context, several experimental studies had described the effects of *Cinnamomum zeylanicum* (cinnamon) on various biological parameters such as blood glucose, lipid profile, adiposity and inflammatory markers.

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In addition to its antioxidant, anti-microbial, anti-cancer and its effects enhancing the components of cardiovascular disease, cinnamon had also been known to have effects against neurological diseases, such as Parkinson's and Alzheimer's. It contained mainly essential oils and other by-products, such as cinnamaldehyde, cinnamic acid and cinnamate[6].

In this work, we proposed to study the interest of the use of cinnamon on blood glucose, lipids, resistin and ghrelin in a population of obese and diabetic men.

Materials and methods

Study participants

This work was a prospective analytical study carried out on male patients followed during the consultation by the specialist doctor of the 'C' service of Diabetology and metabolic diseases at the National Institute of Nutrition of Tunis, Tunisia.

In this study, 84 male patients were selected to participate in using the exclusion and inclusion criteria. The criteria of exclusion were: Type 1 diabetics, the diabetes age >5 years, patients treated with insulin, diabetics with dental problems and chewing difficulties, associated disease states such as renal, cardiac and hepatic insufficiency, taking of any prescribed medication, restricted diets and any allergic antecedents to cinnamon products.

Patients were selected for enrollment met the following criteria: male, obese patients with Type 2 diabetes, the age of diabetes=<5 years, 30 years old and over, under oral antidiabetic (OAD) treatment, with unbalanced glycemic counts during previous consultations and following a diet.

All the procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation of the National Institute of Nutrition and Food Technology of Tunis, Tunisia and the Helsinki Declaration of 1975 revised in 2008. Eligible patients gave written informed consent to participate in the study.

Study Design

All participants were interviewed and informed about the principles of the study during the consultation. Patients were divided into two groups of 34 and 50 subjects. Patients in the first group (N=34) received a dose of 4 g of cinnamon powder daily for 10 weeks. Patients in the second group (N=50) received a dose of 8 g of cinnamon powder daily for 10 weeks. Cinnamon powder doses weighed using an electronic balance. Food and the quantities placed hygienically in bags to be distributed to patients. We recommended that patients regularly take a cinnamon powder at breakfast with a sugar-free yogurt or with a glass of milk for the group with a dose of 4 g/day and take a second time at night for the group having a dose 8 g/day. We provided for each subject of the 2 groups the number of bags needed for a week. Each patient returns at the end of the week to recover the bags of the following week and this schedule was adhered to throughout the investigation until the end of the 10th week. The patients were seen by the dietician each time to check if there is a difficulty in applying the protocol to which he voluntarily adhered.

Biochemical Analysis

The assays were carried out in collaboration with the Laboratory of Biochemistry and Biotechnology at the Faculty of Sciences of Tunis. A 5 mL blood sample was collected from each patient in the morning after 12 h fasting. Fasting lipid profile including total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C) and fasting blood glucose (FBG) was determined for each patient at baseline using the standard enzymatic method, Beckman kit on Beckman DXC 600 analyzer. The HbA1c assay was performed by HPLC (High-Pressure Liquid Chromatography) ion exchange on the Tosoh G8 analyzer. Measurement of the resistin was determined by the ELISA method "Millipore#EZHR-95K with a sensitivity ranging from 0.16 ng/mL to 10 ng/mL". Insulin was assayed by IRMA (Immunoradiometric Assay). The "HOMAR-IR" (Homeostatic model assessment of insulin resistance) was calculating. Measurement of ghrelin was carried out with the RIA technique (radioimmunoassay) by competition using commercial kits for research by the lab Linco (LINCO Research, Inc., Missouri, United States) kit: GHRA-88 HK for ghrelin active with a sensitivity of 7.8 pg/mL.

Anthropometric and Physical Measurements

The body weight (kg), the size (m), the Body Mass Index (BMI) defined by the ratio in kg of height in meters squared, waist circumference (WC), systolic (SAP) and diastolic (DAP) arterial pressures measured. A digital electronic balance measured the body weight; height was measured with a graduated measuring rod in centimeters. All anthropometric, dietary intakes, blood sampling and biochemical measurements were re-evaluated at the end of the intervention period in both groups.

Statistical analyses

The data was entered on Excel 2007 and analyzed using SPSS software in version 13.0. We used Student's statistical test for paired series. The significance level is $p<0.05$.

Results and discussion

The purpose of this investigation was to evaluate the interest of cinnamon, taken at two different doses on anthropometric, hormonal and lipid parameters in two groups of obese and diabetic men.

We had searched for the different correlations between the various parameters studied before and after the treatment and the different variations of these parameters observed after taking a dose of 8 g of cinnamon and a dose of 4 g of cinnamon for 10 weeks.

The population sample consisted of a group 1 of 34 men who followed a diet and received a dose of 4 g of cinnamon and a group 2 of 50 men who received a dose of 8 g obese and diabetic whose average age is 48±4 years old. It consists of evaluating lipid parameters, blood glucose, insulin, resist in and ghrelin in two groups of obese and diabetic men before and after taking cinnamon according to a well-defined protocol.

Effect of Cinnamon on Anthropometric Parameters

We compared the anthropometric parameters before and after the management of this population. We found a good evolution of the different measures. Indeed, there was a decrease in BMI (Fig. 1 & Fig. 2), waist circumference respectively of -5.52±1.47 kg/m² and -10.72±6.12 cm for subjects who received a dose of 8 g of cinnamon and a decrease of -4.45±1.46 kg/m² and -6.86±5.5 cm in subjects who received a 4 g dose of cinnamon (Table1). A study by Akilen *et al.* in a group of 58 patients with Type 2 diabetes (33 females and 25 males) aged 54.9±9.8 years treated with oral antidiabetic only and who received a dose of 2 g of cinnamon per day for 12 weeks showed a significant diminution in BMI, weight and waist circumference ($p<0.05$). They also highlighted the improvement in systolic and diastolic blood pressure[7] in accordance with our results in which these values were reduced by -1.9±1.5 mmHg for PAS and -4.79±231 mmHg for PAD at the dose of 4g and -24.16±1.87 mmHg for PAS and -7.59±358 mmHg for PAD at the dose of 8 g. This effect on blood pressure was also demonstrated by the study of Ziegenfuss *et al.* conducted on 22 people consuming 500 mg per day of a cinnamon extract for 12 weeks[8] as well as the results of Preuss work. HG *et al.* on hypertensive rats in a series of three experiments, received different amounts of cinnamon, the results showed a dose-dependent effect on the regulation of diastolic and systolic blood pressure[9]. However, there were other studies which did not report a significant decrease in BMI, weight or waist circumference compared with a placebo in a control group like Wickenberg J *et al.*[10] and Vafa *et al.*[11]. The latter showed that after consuming 3 g/ day of cinnamon for 8 weeks, there was no significant difference between the group treated with cinnamon and the group received placebo for anthropometric variables. There were also no changes in systolic and diastolic blood pressure after the intervention compared to the baseline in this study[11]. These differences could be due, among other things, to the limits of studies regarding duration or dose as well as the ethnic and physiological

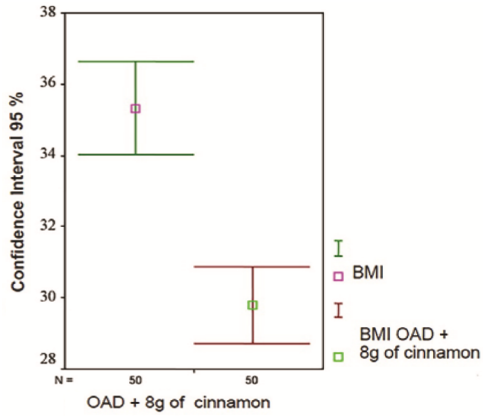

Fig. 1 — Variation in BMI before and after taking 8 g of cinnamon

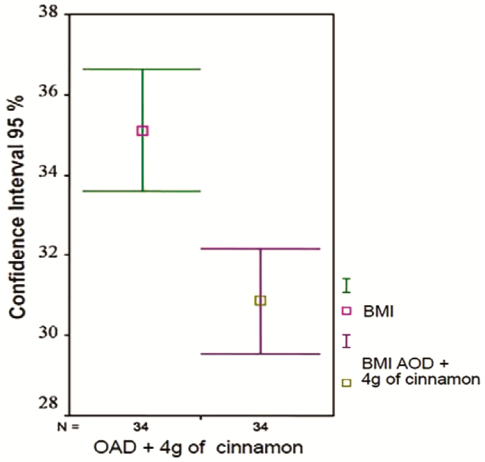

Fig. 2 — Variation in BMI before and after taking 4 g of cinnamon

Table 1 — Anthropometric parameters in both groups before and after taking cinnamon

Parameters	Group	N	Means before 10 weeks of cinnamon intake	Means after 10 weeks of cinnamon intake	Mean deviation	p
Age (year)	OAD + 8 g of Cinnamon per day	50	48,16±4,36	_	_	_
	OAD + 4 g of Cinnamon per day	34	48,47±4,48	_	_	_
BMI (kg/m2)	OAD + 8 g of Cinnamon per day	50	35,31±4,58	29 ,79±3,75	5,52±1,47	0,00
	OAD + 4 g of Cinnamon per day	34	35,11±4,37	30,85±3,76	4,25±1,46	0,00
WC (cm)	OAD + 8 g of Cinnamon per day	50	105,36±9,37	94,64±8,20	10,72±6,12	0,00
	OAD + 4 g of Cinnamon per day	34	106,53±9,33	99,66±8,36	6,86±5,51	0,00
SBP (mmHg)	OAD + 8 g of Cinnamon per day	50	142,10±11,02	117,94±8,20	24,16±1,87	0,00
	OAD + 4 g of Cinnamon per day	34	141,18±10,80	121,28±9,28	1,99±1,52	0,00
DBP (mmHg)	OAD + 8 g of Cinnamon per day	50	89,32±4,20	81,73±3,84	7,59±0,35	0,00
	OAD + 4 g of Cinnamon per day	34	88,91±4,28	84,12±4,05	4 ,79±0,23	0,00

particularities of the populations studied. According to the Preuss HG *et al.* research on animals, the mechanism by which cinnamon acts on blood pressure was explained by peripheral vasodilatation[9]. Mollazadeh *et al.* demonstrated that this vasodilation might be partially due to Ca2+channel blockage. Indeed, the normalization of the vascular contractility by the restoration of the normal influx of Ca2+in parallel with its insulinotropic effect were the main mechanisms of prevention of the development of hypertension in patients with insulin deficiency and insulin resistance[12,13].

Effect of cinnamon on blood glucose and insulin

On the glycemic balance, our results showed a decrease of the mean glucose level of -1,173±0,75 mmol/L in the group that received 8 g of cinnamon (Fig. 3) and -0,8932±0,72 mmol/L in the group that benefited 4 g of cinnamon (Fig. 4) as showed in Table 2. A decrease in mean insulin levels of -3.24±2.85 µUI/L in group 2 and -2.54±2.8 µUI/L in group 1 (Table 3 and Fig. 5). HbA1c decreased by (-1.1254±0.18) % after taking 8 g of cinnamon while it remained high after taking 4 g of cinnamon (Table 2). This difference could be explained by insufficient adaptation time or an ineffective dose in the first group. The decreased in insulin and blood glucose indicated the decline in the average of the HOMA-IR of -1.75±1.43 after taking 8 g of cinnamon as showed in Table 3. Several studies noted the role of cinnamon in regulating the glycemic balance, which was quoted by Khan *et al.* who had demonstrated, after 40 days, in a group of 60 individuals (30 women and 30 men) diabetics aged 52.2±6.32 years, that the addition of 1, 3 or 6 g of cinnamon per day to the diet showed a significant decrease in blood glucose. Values were

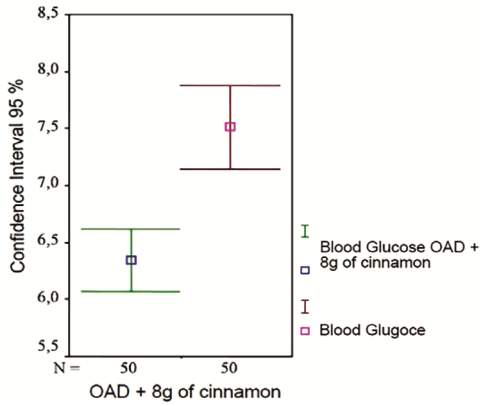

Fig. 3 — Variation in blood glucose before and after taking 8 g of cinnamon

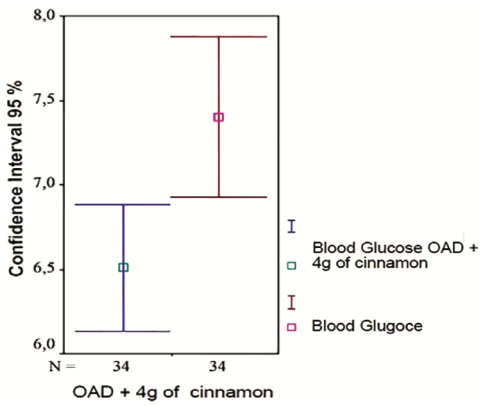

Fig. 4 — Variation in blood glucose before and after taking 4 g of cinnamon

significantly lower only in the group receiving 6 g cinnamon ($p<0.05$) after 20 days[14].

Similarly, in our study, the result was less important in the group receiving 4 g of cinnamon. The effect of cinnamon on blood sugar is dose-dependent. The study of Suksomboon, *et al.* also confirmed the effect of

Table 2 — Serum glucose, HbA1c, TG, total cholesterol, Triglyceride, HDL-C concentrations in both groups before and after 10 weeks of cinnamon intake

Parameters	Group	N	Means before 10 weeks of cinnamon intake	Means after 10 weeks of cinnamon intake	Mean deviation	p
FBG (mg/dL)	OAD + 8 g of Cinnamon per day	50	7,51±1,29	6,34±0,97	1,17±0,75	0,00
	OAD + 4 g of Cinnamon per day	34	7,40±1,35	6,50±1,08	0,89±0,71	0,00
HbA1c (mmol/mol)	OAD + 8 g of Cinnamon per day	50	9,37±1,54	8,25±1,35	1,12±0,18	0,00
	OAD + 4 g of Cinnamon per day	34	9,92±1,51	1,08±1,47	0,05±1,28	0,794
CT (mmol/l)	OAD + 8 g of Cinnamon per day	50	5,31±1,06	4,67±0,94	0,63±0,12	0,00
	OAD + 4 g of Cinnamon per day	34	5,53±1,12	5,04±1,02	0,49±0,10	0,00
TG (mmol/l)	OAD + 8 g of Cinnamon per day	50	1,82±0,22	0,94±0,19	0,20±0,02	0,00
	OAD + 4 g of Cinnamon per day	34	1,80±0,02	1,66±0,21	0,14±0,01	0,00
HDL-C (mmol/l)	OAD + 8 g of Cinnamon per day	50	0,75±0,18	0,94±0,23	0,18±0,18	0,00
	OAD + 4 g of Cinnamon per day	34	0,72±0,14	0,94±0,21	0,21±0,20	0,00

Table 3 — Insulin, resistin, ghrelin and HOMA-IR concentration in both groups before and after taking cinnamon

Parameters	Group	N	Means before 10 weeks of cinnamon intake	Means after 10 weeks of cinnamon intake	Mean deviation	p
Insulin µUI/L	OAD +8 g of Cinnamon per day	50	14,47±4,55	11,23±3,23	3,24±2,85	0,00
	OAD +4 g of Cinnamon per day	34	14,45±4,89	11,90±3,80	2,54±2,80	0,00
Resistinpg/mL	OAD +8 g of Cinnamon per day	50	10,60±3,21	2,08±1,09	2,08±1,09	0,00
	OAD +4 g of Cinnamon per day	34	10,09±3,16	8,50±2,63	1,59±0,92	0,00
Ghrelin pg/mL	OAD +8 g of Cinnamon per day	50	20,42±5,24	21,97±6,53	-1,55±2,21	0,00
	OAD +4 g of Cinnamon per day	34	19,59±5,20	22,09±6,16	-2,49±1,13	0,00
HOMA-IR	OAD +8 g of Cinnamon per day	50	4,99±2,24	3,23±1,31	1,75±1,43	0,00
	OAD +4 g of Cinnamon per day	34	4,94±2,43	3,43±1.51	1,51±1,4	0,00

cinnamon on the regulation of glycemia[15,16]. Magistrelli *et al.* Suggested that cinnamon could be efficient in moderating postprandial glucose levels inobese and normal adults[17]. Recently, Anderson RA *et al.* in a study of 137 diabetic subjects who received a commercial preparation of cinnamon (500 mg/day) or placebo for 2 months, showed a significant decrease in fasting and postprandial glucose. Insulin sensitivity, assessed by HOMA-IR, was also significantly enhanced by cinnamon extract[18]. Crowford *et al.* did a study of 109 age-matched Type 2 diabetics at a military base in the United States. He founded that cinnamon reduced HbA1C by 0.83% compared to the usual care alone that lowers HbA1C 0.37%[19]. An efficient blood glucose control was the key to preventing the complications of diabetes and improve quality of life in diabetic patients. A sustained reduction of hyperglycemia decreased the risk of developing microvascular complications. However, Blevins *et al.* reported that cinnamon administration had no significant effect on blood glucose, lipid and HbA1c levels in people with Type 2 diabetes[20]. These results did not agree with what was found. The difference could be assigned to the fact that the dose studied is not the same, which could affirm that the cinnamon effect on these parameters is dose-dependent. The hypoglycemic activity of cinnamon was since it prevented the insulin resistance development, in part by improving insulin signaling possibly via the NO pathway in skeletal muscle[21]. In another study, the reduction in blood sugar with cinnamon was explained by various mechanisms like reducing intestinal absorption of glucose, stimulation of cellular uptake of glucose, glycogen synthesis, the release of insulin, potentiation of insulin receptor activity and inhibition of gluconeogenesis[6]. Still, cinnamon bark extracts were demonstrated potentially useful for controlling the

absorption of glucose in people with diabetes by inhibiting intestinal a-glucosidase and pancreatic alpha-amylase[22].

Effect of Cinnamon on Lipid Profile

Regarding the lipid profile (Table 2), our study showed a significant decrease after administration of cinnamon total cholesterol and triglyceride levels, each with a difference of -0.6378±0.12 mmol/L (p=0,000) and -0, 2006±0.02 mmol/L (p=0,000) for the dose of 8 g and a difference of -0.493±0.100 mmol/L (p=0,000) and -0.1424±,018 mmol/L (p=0,000) for the dose of 4 g. On the other hand, there was an increase in HDL-cholesterol of 0.189±0.182 mmol/L for the intake of 8 g and 0.2150±0.205 mmol/L (p=0,000) for taking a dose of 4 g. Cholesterol-lowering and lipid effects of cinnamon showed in numerous studies. Kim *et al.* also reported that levels of triglycerides and total cholesterol decreased, and the level of HDL cholesterol increased in dB/dB mice treated with cinnamon[23]. The study by Badalzadeh *et al.* showed that 200 mg/kg of cinnamon per day significantly reduced serum levels of total cholesterol, LDL-cholesterol and raised HDL-cholesterol and HDL-C/LDL-C levels compared to the control group for 8 weeks[24]. The study by Khan *et al.*[15] also showed a diminution in triglyceride, total cholesterol and LDL-cholesterol levels in humans. Shatwan IA *et al.* found that HDL-cholesterol increased significantly, while cholesterol, LDL-cholesterol and triglycerides decreased in streptozotocin-induced diabetic rats and fed 5% cinnamon for 8 weeks[25]. Cinnamon had strong inhibiting activity against the oxidation of LDL-C mediated by copper, phagocytosis LDL-C by macrophages and possesses potent inhibitory activity transfer protein of cholesteryl ester (CETP)[26]. Actual evidence overwhelming confirmed the role of LDL-C in the atherosclerosis pathogenesis and the risk of cardiovascular disease (CVD). The decreased in LDL-C was associated with a reduced risk of CVD[27].

Effect of Cinnamon on the Hormones of Satiety Ghrelin and Resistin

The assays showed (Table 3) that resistin secretion decreased by -2.08±1.09 ng/mL for the 8 g dose (Fig. 6) and -1.59±0.926 ng/mL for the 4 g dose, there was an increase in ghrelin secretion of +1.55±2.21 µg/mL for the 8 g dose (Fig. 7) and +2.49±1.13 µg/mL for the 4 g dose (Fig. 8). It was known that adiponectin, leptin and resistin are 3 adipokines, which played a major role in the regulation of insulin sensitivity. While adiponectin was an anti-inflammatory mediator, leptin and resistin exert pro-inflammatory activity. The studies of Baranova *et al.* demonstrated that adiponectin levels were decreased in obese patients with insulin resistance given elevated plasma concentrations of resistin[28]. These high concentrations of leptin and resistin in obese subjects were at the origin of various complications, including cardiovascular complications. In our study, we found that after treatment, there was a drop in its plasma levels of resistin. This decrease would result from the drop of the fat mass, besides, IMC and resistin had negative correlations (r=0.444, p=0.001). As for ghrelin, our

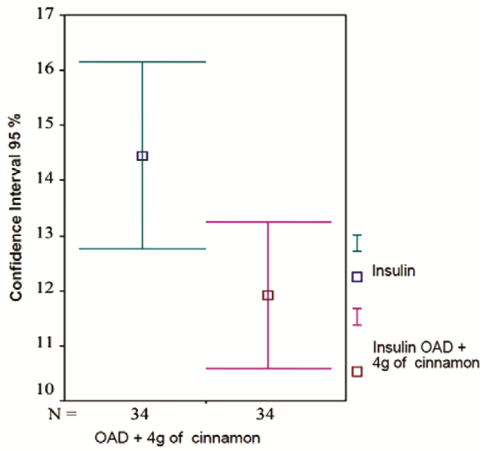

Fig. 5 — Variation in insulin levels before and after taking 4 g of cinnamon

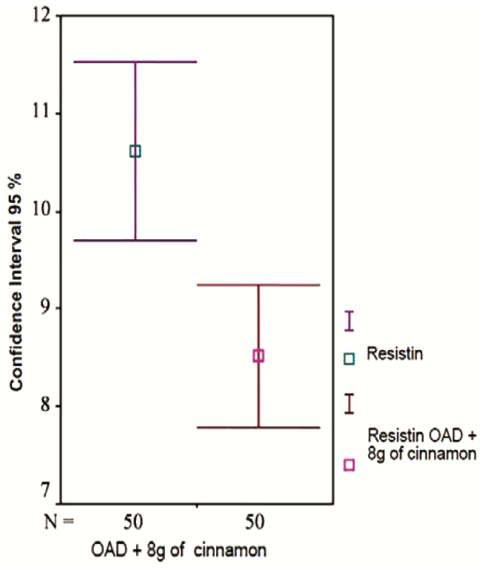

Fig. 6 — Variation in resistin level before and after taking 8 g of cinnamon

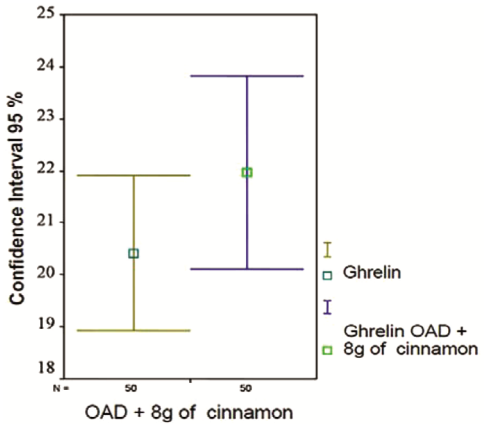

Fig. 7 — Variation in ghrelin levels before and after taking 8 g of cinnamon

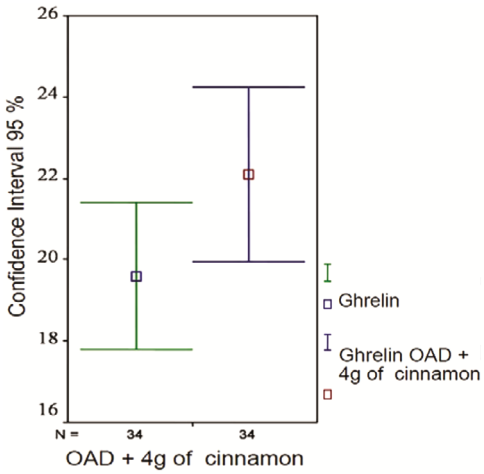

Fig. 8 — Variation in ghrelin levels before and after taking 4 g of cinnamon

results showed a rise in its rates. It was correlated negatively with BMI (p=-0.489, r=0.000).

Ghrelin is a leptin antagonist hormone, they had negative correlations between them, as demonstrated by the study of Scerif *et al.*[29]. As a result, increased plasma ghrelin levels in our patients showed a decline in leptin levels, reducing the inflammatory and cardiovascular risks that arise from hyperleptinemia in obese subjects. Studies on the effect of cinnamon on resistin and ghrelin were few. By studying the impact of DLBS3233, a combination of standardized extracts containing *Lagerstroemia speciosa* and *Cinnamomumburmannii* on glucose uptake, insulin signaling and adiponectin secretion, Mayasari *et al.* showed that DLBS3233 up-regulated adiponectin and down-regulated resistin. The mechanism of action of DLBS3233 was via PPARγ, increasing insulin sensitivity and decreasing insulin resistance[30]. However, the team of Joanna Hlebowicz, *et al.* conducted studies on 15 healthy individuals (9 men and 6 women) in order to explore the effect of 1 g and 3 g cinnamon per day, results suggested a lower but negligible ghrelin, this difference may be due to the reduced number of subjects treated[31]. Another study demonstrated that cinnamaldehyde as a transient receptor potential ankyrin 1 (TRPA1) agonist in mouse stomach epithelial cells reduced the secretion of ghrelin in vitro[32]. The same results were found by Camacho *et al.*[33]. Thus, in other studies, the rate of ghrelin decreased with cinnamon intake, contrary to the results obtained in our study.

There was an improvement in the different parameters after having cinnamon except for HDL-cholesterol and ghrelin. Taking cinnamon promoted a better glycemic and lipid profile by improving insulin sensitivity and increasing the level of HDL-cholesterol. Ghrelin and resistin levels decreased, lowering the adverse effects of this latter on insulin sensitivity and its pro-inflammatory roles. The results confirmed the anti-hyperglycemic and hypolipidemic effects of cinnamon opening a new approach to studying how the compounds derived from certain spices regulate the endogenous release of hormones such as ghrelin and resistin for therapeutic intervention. However, it should be noted that these studies examined the immediate effect of cinnamon on hormones, while our target the long-term effect. Also, there were differences in the population studied and the methods and protocols used. Let's add that different species of cinnamon do not all have the same effect.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

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