Research Article

Antiinflmmatory and Antihyperlipidemic Effect of Adjuvant Cinnamon in Type 2 Diabetic Patients

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ABSTRACT

This study aimed to determine the effect of adjuvant cinnamon on inflammatory markers and lipid profile in poorly controlled type 2 diabetic patients. This study was carried out on twenty six patients who are poorly controlled type 2 diabetics with dyslipidemia , the patients of both sexes, aged 49.1 ⬜ 6.0, treated only with hypoglycemic agents glibenclamide were randomly assigned to receive either 1g of cinnamon or placebo daily for 12 weeks. The serum level of tumor necrosis factor alpha was reduced after administration of cinnamon 1000mg after six weeks by 6.19%, the level reduced significantly (P≤0.05) by 11.38% after 12 weeks of treatment compared to baseline value, At the same time periods, the value of C-reactive protein reduced in cinnamon treated group by (6.94%) and (15%) after six and 12 weeks respectively compared to baseline value; concerning lipid profile, the cholesterol serum level reduced by 2.88% and 7.52% after six and 12 weeks respectively compared to baseline value, the reduction in the mean value of triglyceride was 5.9% after six weeks and 7.48% after 12 weeks of intervention, Concerning the serum high density lipoprotein cholesterol level, treatment of diabetic patients with cinnamon resulted in 9.8% elevation after six weeks compared to baseline value and 22.54% elevation after 12 weeks although this change was statistically not significant, finally administration of cinnamon to diabetic patients for 12 weeks resulted in 3.1% and 10.1% reduction in LDL serum level after 6 and 12 weeks of cinnamon treatment respectively. Administration of 1g of cinnamon powder for 12 weeks to poorly controlled type 2 diabetic patients reduced the level of inflammatory markers and improved the lipid profile of patients, indicating the beneficial adjuvant effect of cinnamon along with conventional medications used to treat type 2 diabetes mellitus.

Keywords: Cinnamon, type 2 Diabetes, poorly controlled DM, antioxidants.

INTRODUCTION

The rapid growing of type 2 diabetes mellitus (T2DM) worldwide mandate hard efforts regarding the mechanisms contributing to complications of the disease and at the same time fast and comprehensive scanning of old agents and investigation of new agents that acting by different mechanisms of action which may be beneficial to prevent or slow the appearance of diabetic complications[1]. Targeting of complications like inflammation and dyslipidemia in T2DM represent interesting strategy along with the main goal which is good glycemic control. Many studies reporting the relation between inflammation and T2DM have showed the role of inflammation in development of insulin resistance and other pathogenic processes of T2DM [3]. It has been shown that the proinflammatory cytokine TNF-α was able to induce insulin resistance[4]. It has been suggested that abnormal levels of chemokines released by adipose tissue activate monocytes and increase the secretion of pro-inflammatory adipokines. Such cytokines in turn enhance insulin resistance in adipose and other tissues, thereby increasing the risk for T2DM [5].

Exposure to exogenous factors triggers the release of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α and other interleukins, These cytokines are derived primarily from macrophages and can directly enhance insulin resistance in adipocytes, muscle and liver cells [6].Cytokines also act on the liver to increase the production of very-low density lipoproteins (VLDL),

leading to diabetic dyslipidemia [7], furthermore, cytokines deactivate the liver X receptors (LXR), resulting in an increased rate of cholesterol accumulation [8] , and ultimately trigger the hepatic production and secretion of acute-phase proteins such as C-reactive protein (CRP), The synthesis of acute-phase reactants following the cytokine release characterizes the early stages of T2DM and exhibits graded increases as the disease progresses and clinical complications ensue [9,10].

Tumor Necrosis Factor-alpha (TNF-α)

The major cellular source of TNF-α is activated mononuclear phagocytes, antigen-stimulated T-cells, natural killer (NK) cells, and mast cells. The TNF-α gene is constitutively expressed in adipose tissue, where it originates principally from macrophage infiltration rather than from the adipocytes themselves, high TNF-α is related to the pathophysiology of insulin resistance and T2DM, possibly through its impact on insulin receptor substrate (IRS-1) [11].

C-Reactive Protein (CRP)

CRP is an acute-phase reactant produced primarily in the liver under the stimulation of adipocyte-derived IL-6 and TNF-α. It exhibits several characteristics that imply a fundamental immune-regulatory function. CRP also enhances leukocyte reactivity, complement fixation, modulation of platelet activation, and clearance of cellular debris from sites of active inflammation [(12)]. The magnitude of its induction in innate immune response, as

well as its ease of measurement, makes CRP a common marker for inflammation. Furthermore, CRP is invariably correlated with various parameters relevant to diabetes, including obesity, lipogenesis, and adiponectin. These findings make a role for CRP as a possible candidate biomarker for early T2DM risk detection [13].

It has been reported that the mechanism by which CRP plays a critical role in T2DM is primarily by its action on pancreatic β-cell. CRP significantly inhibits cell proliferation and increases the rates of apoptotic cell death. This effect was connected to the CRP-mediated modulation of protein kinase B (PKB), a key factor for cell survival pathways and to its ability to induce the production of TNF-α, IL-1β and matrix metalloproteinase-9 (MMP-9) in a concentration-dependent manner [14].

Dyslipidemia

Dyslipidemia is a risk factor for macrovascular complications in patients with type 2 diabetes. Dyslipidemia associated with type II diabetes includes elevated triglycerides, low levels of HDL-C, and increase level of small dense LDL particles. The cornerstone of treatment for diabetic dyslipidemia is therapeutic lifestyle change. In addition to these measures, recent clinical trials have demonstrated the benefits of statin therapy. Statins are the first-line drugs for most lipid disorders. However, they cannot be used to treat all aspects of dyslipidemia. Numerous novel therapeutic compounds are currently being developed [15].

Cinnamon

There was a long history of using Cinnamon as spices in the food, and as medicinal plant. Traditional medicine has used cinnamon extracts for different health conditions. The dry bark of cinnamon trees is rich in polyphenols and has been used to improve general health and treat a variety of disease conditions including diabetes [16]. In addition to anti-diabetic properties, cinnamon is known to have anti- inflammatory, anti-bacterial and antioxidant properties [17]. Several studies have indicated the anti-inflammatory activities of cinnamon [18]. It has been reported that 2'-hydroxycinnamaldehyde isolated from C. cassia bark exhibited an inhibitory effect on the production of nitric oxide by inhibiting the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), indicating that this substance can potentially be used as an anti-inflammatory agent [19]. Various compounds contained in C. ramulus showed anti-inflammatory effects by suppressing the expression of inducible nitric oxide synthesis (iNOS), cyclooxygenase-2 (COX-2), and nitric oxide (NO) production in the central nervous system (CNS). Furthermore, the aqueous extract of cinnamon decreases the lipopolysaccharide-induced tumor necrosis factor-α level in the serum [20]. By this mechanism, Cinnamon could be a potential therapeutic herbal agent for the treatment of inflammation-mediated diseases such as T2DM. The administration of cinnamon positively affected the lipid profile in an animal studies, it

has been shown that the plasma total cholesterol, triglycerides and LDL-C were reduced [21]. A study by Khan et al. reported that the administration of cinnamon at 1, 3, and 6 g doses per day caused a reduction in serum glucose, triglyceride, total cholesterol, and LDL cholesterol levels in humans [22].

PATIENTS AND METHODS

This study was carried out on twenty six patients who are poorly controlled type 2 diabetics with dyslipidemia who attend the Specialized Center for Endocrinology and Diabetes-AL-Risafa, Directoratc of Health-Baghdad. The inclusion criteria: patients with type 2 diabetes mellitus of both sexes on sulfonylurea (glibenclamide), with age range 40-65 years (49.1 ± 6.0), and have disease duration of 5-10 years, the fasting blood glucose level was ≥10 mmol/l and Glycosylated hemoglobin HbA1c ≥8. The exclusion criteria: they should not have other associated chronic diseases like liver and kidney disorders and cardiovascular complications. Patients who are pregnant and breast feeding are excluded. They should not be on insulin therapy or other antidiabetic drugs, or on antioxidant drugs like aspirin, and any associated drugs should be considered. They should not taking other hypolipidemic agent; anti-inflammatory or nonsteroidal anti-inflammatory drugs. The patients treated previously with full maximum dose of sulfonylurea (glibenclamide) (15 mg/day) and kept on dietary control, but with poor glycemic control as evidenced by abnormal values of fasting plasma glucose and glycated hemoglobin; those patients are carefully evaluated while they are on their already established treatment program for DM control for 2 weeks before randomization:

1-Group (A): includes 13 patients treated with placebo in capsule dosage form in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control, for 12 Weeks.

2-Group (B): includes 13 patients treated with cinnamon powder 500mg hard gelatin capsule twice daily (1000mg/day) in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 Weeks.

Sample Collection and Preparation

After 12 hours fasting, blood samples were collected from all subjects by venepuncture (10 ml), before starting drug treatment (as base line samples) and then after 6 weeks and 12 weeks of treatment to follow the changes in the studied parameters. Blood samples were collected in plane tube, and then centrifuged at 3000 rpm for 10 min at 4°C. after centrifugation and isolation of cellular fraction; the obtained plasma fraction was divided into two parts in ependorff tubes and stored frozen until analysis performed.

Biochemical Assay Methods

Measurement of serum Tumer necrosis factor-α (TNF-α) levels

TNF-α human ELISA is a sandwich assay for the determination of TNF-α in serum. During the first incubation period, TNF-α in patient serum samples are captured by the monoclonal antibody to human TNF-α coated on the wall of the microtiter wells. After washing away the unbound components from samples, a peroxidase-labelled second monoclonal antibody conjugate is added to each well and then incubated. After a second washing step, the bound enzymatic activity is detected by addition of tetramethylbenzidine (TMB) chromogen-substrate. Finally the reaction is terminated with an acidic stop solution. The intensity of reaction color is directly proportional to the concentration of human TNF-α in sample [23].

Measurement of serum C-reactive protein (CRP) levels

Microtiter strips coated with anti-CRP are incubated with diluted standard sera and patient samples. During this incubation step CRP is bound specifically to the wells. After removal of the unbound serum proteins by a washing procedure, the antigen-antibody complex in each well is detected with specific peroxidase-conjugated antibodies. After removal of the unbound conjugate, the strips are incubated with a chromogen solution containing tetramethylbenzidine and hydrogen peroxide; a blue color develops in proportion to the amount of immunocomplex bound to the wells of the strips. The enzymatic reaction isstopped by the addition of 1N acidic solution and the absorbance values at 450 nm are determined [24].

Measurement of Serum Lipid Profile

A- Serum Total Cholesterol (TC) Determination

Serum total cholesterol was estimated according to the method of Richmond [25] where a readymade kit is used for this purpose, based on the oxidation of cholesterol, which resulted in the formation of H_2O_2, and when the later is reacted with phenol, a red colored quinonimine was formed and the intensity of color was measured at 505 nm and compared with standard cholesterol solution. The results were expressed as mmol cholesterol /L.

B- Serum Triglyceride (TG) Determination

Serum triglyceride levels were determined according to the method of Fossati and Prencipe [26] and a readymade kit was utilized for this purpose, based on enzymatic oxidation of the glycerol-3-phosphate, which is generated from the hydrolysis of triglyceride moiety. The oxidation process resulted in the formation of H_2O_2 which is measured spectrophotometrically as indicated before. The results were expressed in mmol TG/L.

C. Dtermination of serum High and Low Density Lipoprotein Cholesterol (HDL-C and LDL-C)

Serum HDL-C levels were estimated according to the method of Burstein (Burstein et al,1970); through which LDL-C and VLDL-C was determined calorimetrically by measurement of light absorbance at 505 nm, using a readymade kit for this purpose.

Plasma LDL-C was calculated by using this formula:

$$LDL\text{-}C = Total\ cholesterol - (TG/2.2) - (HDL\text{-}C)$$

Results were expressed in mmol/L [27].

Statistical analysis

The results were expressed as mean ±SD. Student t-test for paired and unpaired sample and ANOVA test was used to examine the degree of significance, P-value less than 0.05 considered significant and less than 0.001 considered highly significant.

RESULTS

The serum level of the inflammatory marker tumor necrosis factor alpha was reduced after administration of cinnamon 1000mg to diabetic patients, although the percent reduction was not significant after six weeks 6.19%, the level reduced significantly (P≤0.05) by 11.38% after 12 weeks of treatment compared to baseline value, also, the there is significant change in the mean value of TNF-α level between placebo and cinnamon treated group after 12 weeks of intervention (figure 1).
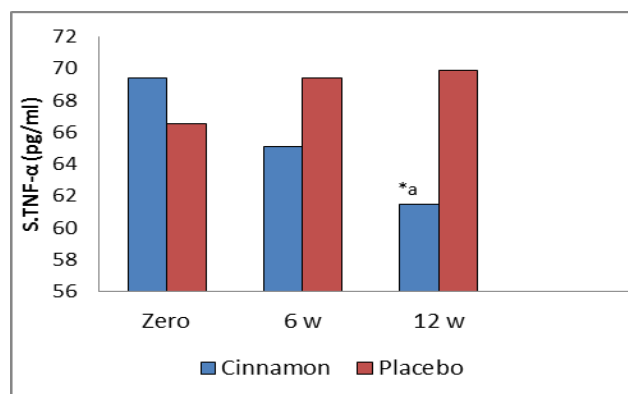
* = Significant difference from basline (P<0.05), a= Significant difference (p<0.05) between cinnamon group and placebo group at corresponding duration.

Figure 1: Effect of Cinnamon on Tumor Necrosis Factor-α Serum Level in Type 2 Diabetic Patients.

At the same time periods, the value of C-reactive protein reduced in cinnamon treated group by (6.94%) and (15%) after six and 12 weeks respectively (figure 2), although this reduction was non-significant compared to baseline value, but it was in line with that of TNF-α level; and both changes give an indication about the anti-inflammatory effect of cinnamon in type 2 diabetic patients.
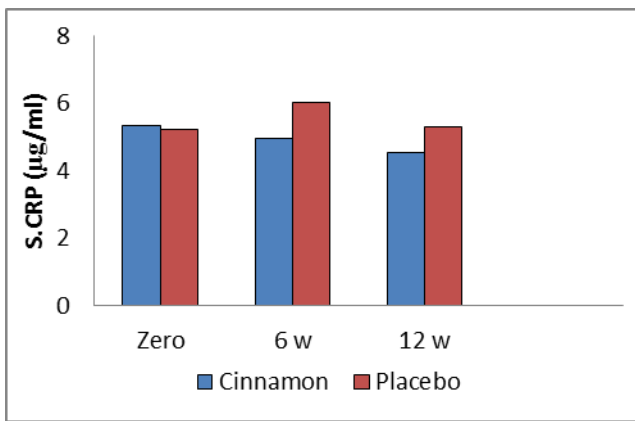
Figure 2: Effect of Cinnamon on C - reactive protein Serum Level in Type 2 Diabetic Patients.

Figure 3 showed that the cholesterol serum level reduced by 2.88% and 7.52% after six and 12 weeks respectively compared to baseline value.
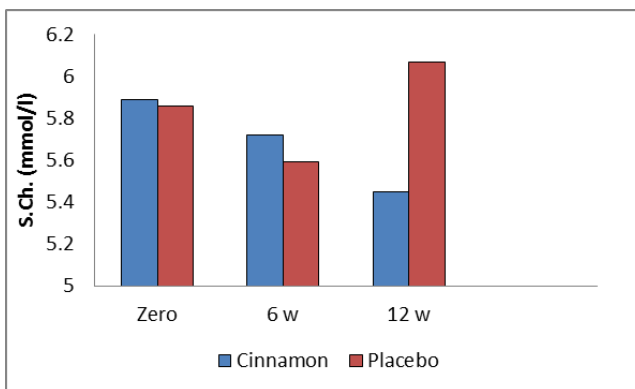

Figure 3: Effect of Cinnamon on Serum Cholesterol Level in Type 2 Diabetic Patients.

The reduction in the mean value of triglyceride was non-significant compared to baseline value; the percent reduction was 5.9% after six weeks and 7.48% after 12 weeks of intervention (figure 4). It is clear that there is a baseline difference in TG serum level exists between placebo and cinnamon treated group.
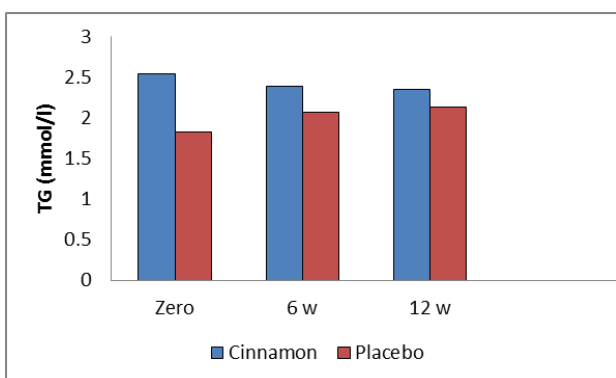

Figure 4: Effect of Cinnamon on Serum Triglyceride Level in Type 2 Diabetic Patients.

Concerning the serum high density lipoprotein cholesterol level, treatment of diabetic patients with cinnamon resulted in 9.8% elevation after six weeks compared to baseline value and 22.54% elevation after 12 weeks

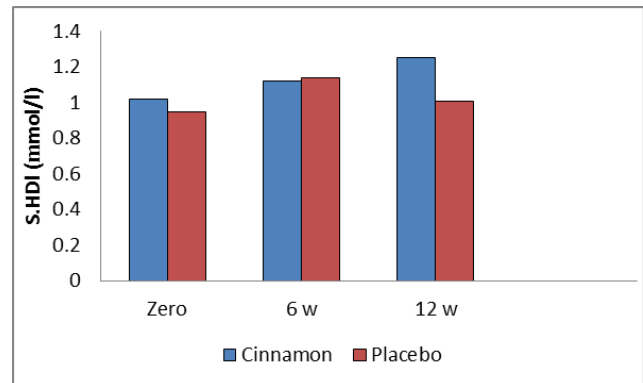although this change was statistically not significant (figure 5).

Figure 5: Effect of Cinnamon on High Density Lipoprotein Serum Level in Type 2 Diabetic Patients.

Finally, results of this study showed that there was significant ($P \leq 0.05$) difference in the baseline value of serum low density lipoprotein cholesterol between placebo and cinnamon treated groups, and highly significant difference exists between the placebo and cinnamon values after six weeks of treatment, in spite of that, administration of cinnamon to diabetic patients for 12 weeks resulted in 3.1% and 10.1% reduction in LDL serum level after 6 and 12 weeks of cinnamon treatment respectively (figure 6).
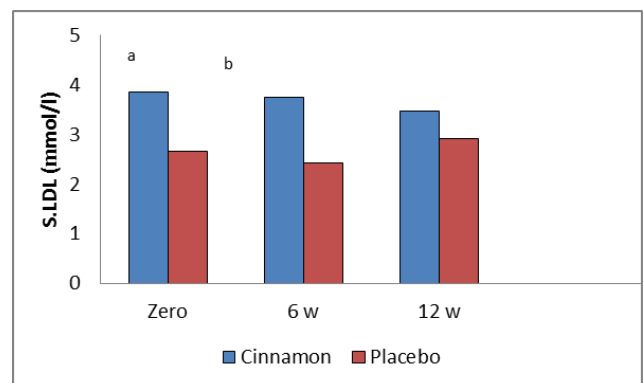

Figure 6: Effect of Cinnamon on Low Density Lipoprotein Serum Level in Type 2 Diabetic Patients.

a= Significant difference (p<0.05) between cinnamon group and placebo group at corresponding duration. b= Highly significant difference (p<0.001) between cinnamon group and placebo group at corresponding duration.

DISCUSSION

This study demonstrates the antiinflammatory and antihyperlipidemic effects of one gram cinnamon powder daily in combination with classical treatment (glibenclaimide) for type 2 diabetic patients, the used cinnamon dose was well tolerated by the patients and there was no any adverse effect appear during treatment course. In this regard, Qin et al suggest that a water extract of cinnamon reverses TNF-alpha-induced overproduction of intestinal apoB48 by regulating gene expression involving inflammatory, insulin, and lipoprotein signaling pathways [28]. In separate study, Qin

et al, review the effect of cinnamon in diabetic patients with metabolic syndrome, they reported that cinnamon and components of cinnamon have beneficial effects on essentially all of the factors associated with metabolic syndrome, including insulin sensitivity, glucose, lipids, antioxidants, inflammation, blood pressure, and body weight [29].Hong et al showed that treatment with cinnamon water extract decreased LPS-induced TNF-α in serum. In vitro inhibition of TNF-α gene by cinnamon water extract may occur via the modulation of IκBα degradation and JNK, p38, and ERK1/2 activation. They suggest that the observed anti-inflammatory action of cinnamon water extract may originate from the presence of polyphenols [30].In animal model of inflammation and arthritis, Rathi et al concluded that cinnamon produce prominent action in animal models of inflammation and arthritis through inhibiting many cytokines, and therefore can be considered as a potential anti-rheumatic agent with disease-modifying action [31].In a double-blind, placebo-controlled trial with two parallel groups, fifty patients with nonalcoholic fatty liver disease were randomized to receive daily supplementation with either two capsules of cinnamon each capsule contain 750 mg cinnamon or two placebo capsules, daily for 12 weeks. Patients in the treatment group showed significant decreases in fasting blood glucose, total cholesterol, triglyceride, liver enzymes, and high-sensitivity C-reactive protein, but there was no significant change in serum high-density lipoproteins levels. In both groups, low-density lipoproteins decreased significantly (P < 0.05). They suggest that taking 1500 mg cinnamon daily may be effective and beneficial in such condition [32]. In this study, administration of one gram of cinnamon powder to diabetic patients resulted in reduction of tumor necrosis factor alpha level in the serum of these patients after six and twelve weeks of treatment, the level of C-reactive protein also reduced at the same durations of TNF-α indicating the anti-inflammatory effect of cinnamon powder. The values of lipids including total serum cholesterol, serum triglycerides and low density lipoprotein cholesterol reduced in diabetic patients after cinnamon administration compared to placebo group, while high density lipoprotein cholesterol level increased in the serum of diabetic patients compared to placebo group, although these changes are not significant, but they give indication about the improvement in lipid profile of diabetic patients; results in several studies are compatible with results obtained in this study, Khan et al. reported that cinnamon improves the blood glucose, triglyceride, total cholesterol, HDL cholesterol and LDL cholesterol levels in patients with type 2 diabetes [33]. It has been suggested that Cinnamon extract regulates plasma levels of adipose-derived factors and expression of multiple genes related to carbohydrate metabolism and lipogenesis in adipose tissue of fructose-fed rats via regulation of the expression of multiple genes involved in insulin sensitivity and lipogenesis [34]. In a type 2 diabetic animal model Kim and Choung suggested that cinnamon extract significantly increases insulin sensitivity, reduces

serum, and hepatic lipids, and improves hyperglycemia and hyperlipidemia possibly by regulating the PPAR-medicated glucose and lipid metabolism [35]. Javed et al showed that administration of cinnamon extract to hyperlipidemic albino rabbits resulted in improvement of lipid profile of the animals effectively compared to simvastatin [36]. Ranasinghe et al showed that administration of Ceylon cinnamon extract to diabetes induced rats lowered blood glucose, reduced food intake, and improved lipid parameters in these animals after short and long term use [37]. Furthermore, Li et al showed that cinnamaldehyde an active and major compound in cinnamon has antihyperglycemic and antihyperlipidemic actions in db/db mice and could be useful in the treatment of type-2 diabetes [38]. Finally, in a double blind, randomized, placebo controlled clinical trial, Vafa et al showed that administration of three grams per day of cinnamon to type 2 diabetic patients for eight weeks period resulted in reduction of fasting blood glucose level, HbA1c, triglyceride, weight, BMI and body fat mass significantly compared to baseline, but not in placebo group; they suggest that cinnamon may have a moderate effect in improving glycemic status indicators[39]. In conclusion, administration of 1g of cinnamon powder for 12 weeks to poorly controlled type 2 diabetic patients reduced the level of inflammatory markers and improved the lipid profile of patients, indicating the beneficial adjuvant effect of cinnamon along with conventional medications used to treat type 2 diabetes mellitus.

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