Research Article

Hypolipidaemic and Anti-inflammatory effects of Curcumin versus Atorvastatin in Type 2 Diabetic Patients

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ABSTRACT

This study aimed to determine the effect of curcumin versus atorvastatin on inflammatory markers and lipid profile in poorly controlled type 2 diabetic patients. Disturbance of lipid metabolism appears to be an early event in the development of type 2 diabetes. This study was carried out on forty eight patients who are poorly controlled type 2 diabetics with dyslipidemia , the patients of both sexes on sulfonylurea (glibenclamide), with age range 35-60 years (46.76 ± 7.89), and have disease duration of 5-10 years,patients were randomly assigned to receive either placebo, atorvastatin , or curcumin daily for 12 weeks. In comparison with a placebo-treated group at corresponding after 12 weeks of treatment, there was a high significant decrease in S. Ch. Was found in Atorvastatin, and Curcumin groups. a significant increase in S. HDL of Atorvastatin and a high significant increase in S. HDL of Curcumin group. Corresponding to S. LDL there was no significant difference in S. LDL of and Curcumin groups and a significant decrease in S. LDL of Atorvastatin group were found. In comparison with a placebo-treated group at corresponding duration, after 12 weeks of treatment, there was no significant difference in S. TNF- α of Atorvastatin group, and a high significant decrease in S. TNF-α of Curcumin groups were seen. Corresponding to S. CRP, in comparison with a placebo-treated group at corresponding duration after 12 weeks of treatment, no significant difference in S. CRP of Atorvastatin group, while a significant decrease in S. CRP of Curcumin groups. In conclusion the administration of 1g of Curcumin powder for 12 weeks to type 2 diabetic patients poorly controlled decreased the levels 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: Curcumin, Atorvastatin, type 2 Diabetes, CRP, TNF- α.

INTRODUCTION

Disturbance of lipid metabolism appears to be an early event in the development of type 2 diabetes, potentially preceding the disease by several years [1]; however, even with adequate LDL-C lowering via statin therapy, CVD risk remains high in many patients [2].

The role of endothelial dysfunction in T2DM is very complicated, due to the many independent factors involved, including ageing, obesity, hyperlipidemia, hypertension, low grade inflammation, insulin resistance, and hyperglycemia. The relation between endothelial dysfunction and the individual factors mentioned above, starting with insulin resistance [3]. Insulin resistance is associated with an increased free fatty acids (FFA) release from adipose tissue, which results in dyslipidemia, including VLDL hypertriglyceridemia, high plasma FFA, and low HDL-cholesterol concentrations [4]. The existence of chronic inflammation in diabetes is mainly based on the increased plasma concentrations of C-reactive protein (CRP), fibrinogen, interleukin-6 (IL- 6), interleukin-1 (IL-1), and TNFα [5]. The search for novel anti-diabetic medicines has focused on medicinal plants because of their efficacy in human clinical trials and the minimal side-effects of drugs derived from medicinal plants [6]. Therefore, a need for alternative therapy especially the natural plant sources having minimal side effects has arisen.

Atorvastatin is structural analogue of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). It is most

effective in reducing LDL. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions [7]. However, the reductase inhibitors clearly induce an increase in high-affinity LDL receptors. This effect increases both the fractional catabolic rate of LDL and the liver's extraction of LDL precursors (VLDL remnants), thus reducing plasma LDL. In evidence of hepatic toxicity this agent should be used with caution and in reduced dosage in patients with hepatic parenchymal disease. In general, aminotransferase activity should be measured at baseline, at 1–2 months, and then every 6 months (if stable) [8].

The curcumin (1, 7-bis [4-hydroxy-3-methoxyphenyl]-1, 6-heptadiene-3, 5-Dione) is the active ingredient in the herbal remedy and dietary spice turmeric (Curcuma longa Linn). Curcumin is an orange yellow crystalline powder. Minor amount of oils and resins naturally occurring in turmeric are usually present [9].The origin of the plant Curcuma longa L. (Family Zingiberaceae) is India. Curcumin has been found to have antioxidant, anti-tumor, antiinflammatory, antiviral, antibacterial, antifungal properties and thus has a potential against various diseases including diabetes [10]. The active constituent of turmeric is known as curcumin reduces inflammation by lowering histamine levels and possibly by increasing the production of natural cortisone by the adrenal glands[11]. In vitro studies have shown that curcumin inhibit the production of pro-inflammatory

monocyte/macrophage derived cytokine i.e. Interleukin-8 & 1β, monocyte chemotactic protein-1 and tumor necrosis factor-α in lipopolysaccharide stimulated peripheral blood monocytes and alveolar macrophages [12]. In vivo studies also an inhibitory effect of curcumin on inflammation has demonstrated clearly. Curcumin inhibited the inflammation induced by carrageenan [13].

Aims of the study

To investigate the effectiveness of Atorvastatin, and Curcumin, that possess anti-inflammatory and/or hypolipidemic effects on the changes that occur in patients with type 2 diabetes mellitus that are poorly controlled by conventional therapy.

PATIENTS, MATERIALS AND METHODS

Patients Selection and Drug Treatment

This case control study was carried out on one forty eight (48) patients with type 2 diabetes mellitus (DM) who attend the Al-Imamain Al-Kadhimain Medical City-AL-Karkh Directoratc of Health-Baghdad were enrolled from December 2014 to April 2016. A total of 27 patients did not finish the study, due to poor compliance, poor cooperation, or personal reasons such as sickness, no available time (the data of these patients have been excluded from the data at the base line). The remaining patients included in this study are 48 patients.

Inclusion criteria

Patients with type 2 diabetes mellitus and hyperlipidemia of both sexes on sulfonylurea (glibenclamide), with age range 35-60 years (46.76 ± 7.89), and have disease duration of 5-10 years.

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 anti-diabetic drugs, or on antioxidant drugs like aspirin, and any associated drugs should be considered. They should not taking other hypolipidemic agent; anti-inflammatory or non-steroidal anti-inflammatory drugs. All the selected patients have no another marked pathological disorders like hypertension and ischemic heart diseases as revealed by the clinical investigation.

Forty 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; glycated hemoglobin; and dyslipidemia; those patients are carefully evaluated while they are on their already established treatment program for DM control for 2 weeks before randomization into three groups:

1- Group (A):

Includes 16 patients treated with placebo (starch 50 mg) in capsule dosage form in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control, for 12 Weeks.

2- Group (B):

Includes 16 patients treated with Atorvastatin tablets 20mg (AvasR) Micro,India given after meal as single daily doses in a tablet dosage form, in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 Weeks.

3- Group (C):

Includes 16 patients treated with Curcumin capsules 1000mg/serving Walgreen Co., Deerfield, IL., USA. Curcumin 500 mg hard gelatin capsule twice daily (1000mg/day) after meal, 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 venepunture (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 divided into two tubes, one heparinized tube (1ml of whole blood used for HbAlC determination) and the other part was collected in plane tube, then centrifuged at 3000 rpm for 10 min at 4 $^{\circ}$C. after centrifugation and isolation of cellular fraction; the obtained plasma fraction was divided into three parts in ependorff tubes and stored frozen until analysis performed.

Biochemical Assay Methods

Serum glucose level was evaluated using a ready-made Glucose kit [LABKIT, Spain] for this purpose, according to the method of [14].

The VARIANT hemoglobin A_{IC} program

[Hemoglobin A1c Variant HbAlc, Bio–Rad. Lab., USA] utilizes the principles of ion exchange high performance liquid chromatography (HPLC) for the automatic and accurate separation of hemoglobin AlC (HbAlC). Samples are first diluted with hemolysis reagent and then incubated at 18-28°C for a minimum of 15 minutes [15].

Measurement of Serum Lipid Profile

Serum total cholesterol was estimated according to the method of Richmand [16], where a ready-made Total cholesterol kit [Bio Merieux, France] is used for this purpose.

Serum triglyceride levels were determined according to the method of Fossati and Prencipe [17] and a ready-made Triglyceride kit [Bio Merieux, France] was utilized for this purpose

Serum HDL-C levels were estimated according to the method of Burstein [18]; through which LDL-C and VLDL-C was determined calorimetrically by measurement of light absorbance at 505 nm, using a ready-made HDL–cholesterol kit [Bio Merieux, France] for this purpose.

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 by TNF-α human ELIZA kit [Demeditec Diagnostics Gmbh,Germany].The intensity of reaction color is directly proportional to the concentration of human TNF-α in sample [19].

Measurement of serum C-reactive protein (CRP) levels

Microtiter strips coated with anti-CRP are incubated with diluted standard sera and patient samples. 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 is stopped by the addition of 1N acidic solution and the absorbance values at 450 nm are determined [20].

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.

RESULTS

This study demonstrated that in comparison with value at baseline in the same group after 6 weeks of treatment there a significant increase in FBS was recorded within Atorvastatin group. There was no significant difference in FBS of Curcumin. After 12 weeks of treatment, no significant difference in FBS of Placebo; Atorvastatin and Curcumin groups were recorded with a high significant decrease in FBS of Table (1). After 12 weeks of treatment, no significant difference in FBS of Atorvastatin and Curcumin groups with a high significant decrease were recorded. Table (1) also shows that in comparison with value at baseline in the same group after 6 weeks of treatment there is significant decrease in S. HbA1c of Placebo group, high significant decrease in S. HbA1c of Curcumin group and significant increase in Atorvastatin group. After 12 weeks of treatment, no significant difference in S. HbA1c of Placebo and Atorvastatin groups, and high significant decrease in S. HbA1c of Curcumin groups recorded. In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there was no significant difference in S. HbA1c of Atorvastatin group and a significant decrease in S. HbA1c in Curcumin group were seen in Table (1). After 12 weeks of treatment, no significant difference in S. HbA1c of Atorvastatin and Curcumin groups were seen in Table (1).

Table 1: Comparison of FBS and S. HBA1c at different duration of treatment in each group

Group	FBS (mmol/l)			S. HbA1c (%)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Placebo (n=16)	11.68±3.64	10.62±2.94*	11.62±2.79	8.35±1.93	8.6±1.94	8.15±1.61
Atorvastatin (n=16)	11.92±3.22	14.26±4.8*a	13.27±2.88	8.19±1.24	8.83±1.39*	8.57±1.52
Curcumin (n=16)	10.58±2.86	9.26±2.64*	8.32±1.6**a	8.0±0.91	7.35±0.78**a	6.88±0.7**a

Comparison is with baseline value * = Significant difference from basline (P<0.05), ** = highly Significant difference from baseline (P<0.001). a= significant difference (p<0.05) between drug group and placebo group at corresponding duration.

The study demonstrated that in comparison with value at baseline in the same group after 6 weeks of treatment there was no significant difference in S. Ch. of Placebo group and significant decrease in S.Ch. of Curcumin group, with a high significant decrease in S. Ch. was found in Atorvastatin group. After 12 weeks, there was no significant difference in S. Ch. of Placebo group and a high significant decrease in S. Ch. Was found in Atorvastatin, and Curcumin groups (Table 2). In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there was no significant difference in S. Ch. of Atorvastatin, and Curcumin groups. While after 12 weeks of treatment, a significant decrease in S. Ch. was found in Curcumin groups, with a highly significant decrease in S. Ch. of Atorvastatin were found. Table (2). Corresponding to S. TG, in comparison with value at baseline in the same group after 6 weeks of treatment

there was no significant difference in S. TG of Placebo, and Curcumin group, significant decrease in S. TG of Atorvastatin groups. After 12 weeks of treatment, no significant difference in S. TG of Placebo group, a significant decrease in S. TG of Atorvastatin, and Curcumin groups were recorded in Table (2). In comparison with a placebo-treated group at corresponding duration, after 6 and 12 weeks of treatment there was no significant difference in S. TG of Atorvastatin, and Curcumin groups were found. Table (2). Corresponding to S. HDL, in comparison with value at baseline in the same group after 6 weeks of treatment there was no significant difference in S. HDL of Atorvastatin, and Curcumin groups, a significant increase in S. HDL of Placebo group. After 12 weeks of treatment, there was no significant difference in S. HDL of Placebo and Atorvastatin groups, a significant increase in S. HDL of

Curcumin group. In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there was no significant difference in S. HDL of Curcumin group and a significant increase in Atorvastatin group were found. After 12 weeks of treatment a significant increase in S. HDL of Atorvastatin and a high significant increase in S. HDL of Curcumin group. Table (2). Corresponding to S. LDL, in comparison with value at baseline in the same group after 6 weeks of treatment there was no significant difference in Atorvastatin and Curcumin groups, a significant decrease in S. LDL of Placebo group. After 12 weeks of treatment, there was no

significant difference in S. LDL of Curcumin group, a significant decrease in S. LDL a significant increase in S. LDL of Placebo group and a high significant decrease in S. LDL of Atorvastatin, group were found. In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there was no significant difference in S.LDL of Atorvastatin, and Curcumin groups. After 12 weeks of treatment, there was no significant difference in S. LDL of and Curcumin groups and a significant decrease in S. LDL of Atorvastatin group were found (Table 2).

Table 2: Comparison of lipid profile at different duration of treatment in each group

Group	S. Ch. (mmol/l)			S. TG (mmol/l)			S. HDL (mmol/l)			S. LDL (mmol/l)		
	Base line	6 Weeks	12 weeks	Base line	6 weeks	12 weeks	Base line	6 Weeks	12 Weeks	Base line	6 weeks	12 weeks
Placebo (n=16)	5.77±1.25	5.68± 0.89	6.08± 0.95	1.92± 0.83	2.07± 1.2	2.12± 0.86	0.99± 0.3	1.16± 0.21*	1.04± 0.22	2.72± 1.02	2.51± 1.01*	2.94± 0.96*
Atorvastatin (n=16)	6.79±1.77	5.84± 1.39 **	4.65± 1.01 **b	2.55± 1.53	1.76± 1.04*	1.5± 0.83*	1.39± 0.25a	1.38± 0.24a	1.39± 0.29a	2.96± 1.39	2.38± 0.56	2.12± 0.82 **a
Curcu-min (n=16)	5.54±1.56	4.99± 1.08*	4.71± 1.17 **a	2.18± 0.67	1.98± 0.77*	1.78± 0.54*	1.19± 0.24	1.13± 0.18	1.35± 0.1*b	2.82± 0.33	2.78± 0.25	2.62± 0.38*

Comparison is with baseline value * = Significant difference from basline (P<0.05), ** = highly Significant difference from baseline (P<0.001). a= significant difference (p<0.05) between drug group and placebo group at corresponding duration. b= highly significant difference (p<0.001) between drug group and placebo group at corresponding duration.

This study demonstrated that in comparison of value at the baseline of the same group with value after 6 weeks of treatment, there was no significant difference in S. TNF-α of Placebo, Atorvastatin and a high significant decrease in S. TNF-α of Curcumin groups. While after 12 weeks of treatment, a significant increase in S. TNF-α of Placebo and Atorvastatin groups and a high significant decrease in S. TNF- α of Curcumin groups were recorded. Table (3). In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment, no significant difference in S. TNF-α of Atorvastatin and a significant decrease in S. TNF-α in Curcumin groups. After 12 weeks of treatment, there was no significant difference in S. TNF- α of Atorvastatin group, and a high

significant decrease in S. TNF-α of Curcumin groups were seen. Table (3). Corresponding to S. CRP, in comparison with value at baseline of the same group after 6 and 12 weeks of treatment, there was no significant difference in S. CRP of Placebo and Atorvastatin groups, while a high significant decrease in S. CRP of Curcumin groups were recorded. Table (3). In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment, no significant difference in S. CRP of group, significant decrease in S. CRP of Atorvastatin group. After 12 weeks of treatment, no significant difference in S. CRP of Atorvastatin group, while a significant decrease in S. CRP of Curcumin groups, Table (3).

Table 3: Comparison of inflammatory markers at different duration of treatment in each group

Group	S. TNF-α (pg/ml)			S. CRP (μg/ml)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Placebo (n=16)	65.92±9.25	69.0±8.18	69.46±9.42*	5.22±1.88	6.05±2.01	5.25±1.79
Atorvastatin (n=16)	66.43±7.33	67.43±8.88	68.14±6.74*	4.84±2.16	4.7±1.34a	4.51±0.32
Curcumin (n=16)	68.15±8.01	61.31±5.31**a	56.85±5.73**b	5.68±1.84	4.87±1.64**	4.38±1.53**a

Comparison is with baseline value * = Significant difference from basline (P<0.05), ** = highly Significant difference from baseline (P<0.001). a= significant difference (p<0.05) between drug group and placebo group at corresponding duration. b= highly significant difference (p<0.001) between drug group and placebo group at corresponding duration.

DISCUSSION

Several studies reported that curcumin treatment induced hypoglycemia in rats with streptozocin (STZ)-induced DM [21, 22]. But the study of [23] showed that administration of oral pure curcumin to diabetic rats significantly decreased blood glucose levels and increased the plasma insulin compared with the diabetic group. However, both levels did not reach those of normal controls. Curcumin (turmeric) exhibits therapeutic actions in diabetes mellitus, another study [24] reported that insulin secretion, and heme-oxygenase-1 (HO-1) gene expression and HO activity were significantly increased when isolated islets of Langerhans in rat were incubated in curcumin. This result is agreed with the result obtained in the present study as shown in (table 1). Several mechanisms may explain how mediates its hypoglycemic effects. Best and his colleagues [25] reported that curcumin activated the volume-regulated anion channels in β-cells which was accompanied by the depolarization of the cell membrane potential, the generation of electrical activity, and enhanced insulin secretion. Another report indicated that curcumin treatment enhances islet recovery by inducing heat-shock protein (Hsp70), a response protein, during cryopreservation [26]. However, numerous studies have also shown that curcumin does not significantly alter blood glucose levels [27, 28]. An early study examined the effect of curcumin on fatty acid metabolism; it showed that curcumin can lower serum and liver cholesterol levels in rats [29]. Those studies are agreed with the results of the present study showing the effects of administration of 1 gm curcumin for 12 weeks on type 2 diabetics with dydlipidemia (table 1-3). Similarly, Haitham demonstrated that oral administration of phytomedicine (1g of cinnamon) for 12 weeks to poorly controlled type 2 diabetic patients reduced the level of inflammatory markers and improved the lipid profile of patients [30]. In addition, a study done by Jang *et al* [31] examined the effect of curcumin on insulin resistance in hamsters fed a high-fat and high-cholesterol diet. They found that curcumin (50 mg/100 g diet) lowered the levels of free fatty acids (FFAs), total cholesterol, triglycerides, and leptin levels and suppressed insulin resistance. It also elevated the levels of HDL and apolipoprotein A-1 and paraoxonase activity in plasma and lowered hepatic cholesterol and triglyceride levels. Curcumin treatment inhibited NF-κB activation and resulted in a reduction of TNF-α, IL-1β, IL-6, and cyclooxygenase-2(COX-2) gene expression and of secreted IL-6 and prostaglandin [32].Chronic treatment with curcumin in diabetic rats significantly reduced serum TNF-α level, attenuating oxidative stress and inflammation [33].

Certain types of statins should be used cautiously because they can impair glycemic control; however, statins have a potent cholesterol lowering effect [34]. Atorvastatin has been reported in some cases to disrupt glycemic control in patients with type 2 diabetes[35]. The mechanism by which atorvastatin disrupts glycemic control remains unknown; however, atorvastatin was shown to inhibit adipocyte maturation and glucose transporter 4 (Glut 4)

expressions by blocking isoprenoid biosynthesis, thus impairing glucose tolerance [36]. In addition, atorvastatin was reported to impair insulin secretion [37]; this suppressive effect occurs probably because atorvastatin and similar lipophilic statins cause β- cell cytotoxicity and sterol regulatory – element binding protein (SREBP) activation [35]. These statements agreed with the results obtained in the present study which shown an increment in the FBG and HbA1c levels after 12 week of treatment with atorvastatin [Table (1)]. Atorvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate limiting step in hepatic cholesterol biosynthesis. Unlike most other statin, however, it is a completely synthetic compound. Generally, statins (among them atorvastatin) are the most effective than other lipid lowering agents in reducing low-density lipoprotein cholesterol (LDL-C) [38]. Atorvastatin competitively inhibit this enzyme resulting in decreasing de novo cholesterol synthesis, and increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, resulting in decreasing the amount of LDL-cholesterol in the blood [39]. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of high-density lipoprotein cholesterol (HDL-C) [40, 41]. The present results in table (2) were compatible with the studies mentioned above about the effects of atorvastatin on serum levels of cholesterol; triglycerides and LDL. This may be particularly important in type 2 diabetes, given that there are data showing that atorvastatin does not consistently improve endothelial function in type 2 diabetes [42]. The findings of the current study were not agreed with findings of other studies that reported a reduction in serum TNF- α level in cases (acute pulmonary embolism) treated with atorvastatin [43] was associated with a potential beneficial increase of HDL (upon using TNF-α inhibitors) [44], and thereby a possible inverse relation between s.TNF-α and s.HDL level may be expected (table 3).

CONCLUSIONS

According to the results presented in this study it is easy to conclude that the administration of Curcumin, when used as adjunct therapy, could improve both glycemic control and lipid profile with consequent beneficial effects on oxidative stress and inflammatory markers in type 2 diabetic patients, may be through mechanisms of upregulating peripheral tissue responses to the available insulin at receptor levels in association with potent antioxidant effects. The results of this study can be summarized as: Atorvastatin was more effective on lipid profile than curcumin but Curcumin was more effective as inflammatory. There is opportunity to use these drugs for patients with diabetes mellitus; dyslipidemia; and cardiovascular diseases.

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