# Curcumin Improves Insulin Sensitivity and Ameliorates Serum Pro-inflammatory Cytokines Levels in Diabetes Rat model Irrespective of type of Diabetes

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**Abstract:** Objectives: To evaluate the impact of type of diabetes on serum levels of pro-inflammatory cytokines and the effect of chronic administration of curcumin on their levels in experimentally-induced diabetes in albino rats. The study included 60 (20 as control group) male albino rats; diabetes mellitus (DM) was induced using intraperitoneal injection of a single dose of 50 mg/kg of streptozotocin (STZ) after animals were maintained on high-fat diet for 2-weeks (20 rats) for induction of non-insulin dependent DM (NIDDM) or without dieting regimen for induction of IDDM (20 rats). One-week later, rats received oral curcumin (200 mg/kg). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and rapid insulin sensitivity test (RIST) were used for clinical assessment. Two fasting venous blood samples were obtained after induction of diabetes and prior to initiation of therapy and at 6-wks after treatment for calorimetric estimation of fasting blood glucose (FBG) and ELISA estimation of fasting plasma insulin (FPI), serum interleukin (IL)-1β and -6 and tumor necrosis factor-α (TNF-α). Results: Curcumin induced significant reduction of FBG levels, irrespective of type of diabetes and in NIDDM animals, post-treatment FPI levels were significantly lower compared to their pre-treatment levels. Diabetes, irrespective of its type, induced significantly higher pre-treatment serum levels of pro-inflammatory cytokines in both study groups compared to control group. However, curcumin significantly lowered serum levels of estimated cytokines at 6-weeks after treatment compared to pre-treatment levels. In group II, post-treatment RIST index was non-significantly higher compared to control index. In group III, pre-treatment HOMA-IR index was significantly higher compared to control index, while post-treatment HOMA-IR index was significantly lower compared to pre-treatment levels, despite still being significantly higher compared to control group. It is concluded that chronic administration of curcumin improves insulin sensitivity and thus imposing an anti-diabetic effect manifested as decreased FBG levels with concomitant decreased FPI and ameliorated the increased serum levels of pro-inflammatory cytokines and such effects are manifested in both types of diabetes.
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**Keywords:** Diabetes mellitus, Curcumin, pro-inflammatory cytokines.

## 1. Introduction

Diabetes and inflammation form a vicious circle, where diabetes is usually associated with inflammation and inflammation contributes to the development of diabetes. Glucose is proinflammatory and even a 75-g glucose load given orally to normal subject results in profound oxidative stress and inflammatory changes at the cellular and molecular level. This occurs even without an increase in plasma glucose concentrations into the pathological range and in spite of endogenous insulin secretion. Therefore, if high plasma glucose concentrations are maintained, they can be expected to be profoundly pro-inflammatory; this is indeed the case, especially if endogenous insulin secretion is inhibited [1, 2, 3].

Insulin resistance is typically defined as decreased sensitivity or responsiveness to metabolic actions of insulin, such as insulin-mediated glucose disposal in skeletal muscle and adipose tissue and inhibition of hepatic glucose production [4]**.** Cross-talk between inflammatory signaling pathways and insulin signaling pathways causes metabolic insulin resistance and endothelial dysfunction [5]**.**

Insulin resistance plays a major pathophysiological role in type 2 diabetes and is tightly associated with major public health problems, including obesity, hypertension, coronary artery disease, dyslipidemias, and a cluster of metabolic and cardiovascular abnormalities that define the metabolic syndrome [6]. The metabolic syndrome is considered to be a pro-inflammatory state because it is associated with elevated levels of high-sensitivity C-reactive protein, IL-6, fibrinogen, and plasminogen activator inhibitor-1, all of which promote the development of atherosclerotic cardiovascular disease [7].

Improvement of insulin sensitivity has been suggested in many reports to be feasible by certain herbs and drugs. For instance, it was reported that curcumin improve blood glucose and insulin sensitivity in rat models of diabetes. Curcumin, a polyphenolic compound, is the major yellow-colored

pigment found in the spice, turmeric. It has been used in traditional Indian medicine for centuries, and has numerous pharmacological activities, including potent anti-inflammatory, antioxidant, chemo-preventive and chemotherapeutic actions [8, 9, 10].

The present study aimed to evaluate the impact of type of diabetes on serum levels of pro-inflammatory cytokines and the effect of chronic administration of curcumin on their levels in experimentally-induced diabetes in albino rats.

## 2. Materials and Methods

### Animals

The present study comprised 60 male albino rats with weight range of 250-300 grams. Rats were grouped and kept in separate animal cages, under the prevailing atmospheric conditions and maintained on a balanced diet (bread, barely, carrots, lettuce, milk) and fresh-water supply.

### Induction of diabetes

A) Type 1 diabetes mellitus (IDDM group) was induced by injecting rats intraperitoneally with a single dose of streptozotocin (STZ) (Sigma) in a dose of 50 mg/kg body weight dissolved in 0.2 ml of citrate buffer (pH 4.5) [11] without dieting regimen.

B) Type 2 diabetes mellitus (NIDDM group) was induced by feeding rats with high-fat diet (HFD) consisting of 22% fat, 48% carbohydrate and 20% protein. After two weeks, rats were injected intraperitoneally with a single dose of streptozotocin (STZ) (Sigma) in a dose of 50 mg/kg body weight dissolved in 0.2 ml of citrate buffer (pH 4.5) [11].

### Diagnosis of diabetes

On the third day of injection, the animals were checked for the presence of glucose in the urine using enzymatic test strips as STZ induces diabetes within 3 days by destroying the beta cells, ***(Karunanayake et al., 1975)***. Confirmation was done by measuring fasting blood glucose levels by taking a drop of blood from the rat-tail using a glucose-measuring device (Glucocheck). Rats had blood glucose levels of ≥200 mg/dl were considered diabetic [11].

### Grouping & Dosing:

- Group I (Control group): 20 animals were considered as a control group for estimated parameters and were divided into 2 subgroups:

a) Group I-A: included 10 rats received no medications and kept under the same conditions as prior to start of the study.

b) Group I-B: included 10 rats were injected intraperitoneally with one injection of citrate buffer and received 1ml/rat of 1% gum acacia orally for 6 weeks.

- Group II: included 20 rats had induced IDDM and were administered 200 mg/kg body weight of curcumin in 1% gum acacia, orally/day for a period of 6 weeks
- Group III: included 20 rats had induced NIDDM and were administered 200 mg/kg body weight of curcumin in 1% gum acacia, orally/day for a period of 6 weeks.

### Biochemical Evaluation

Two fasting venous blood samples, withdrawn from the tail vein, were obtained, the 1st after induction of diabetes and prior to initiation of therapy and the 2nd at the end of the 6-wks treatment period. Blood samples were divided into 2 parts:

A) The first was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis. Plasma was separated by centrifugation and used for calorimetric estimation of glucose by glucose oxidase method [12].

B) The second part was allowed to clot then serum was separated by centrifugation at 3000 rpm for 10 min. Serum was removed, divided into 2 parts:

1. The first part was used for RIA determination of serum level of insulin [13].
2. The second part was placed in pyrogen-free Eppendorf tubes and stored at -80°C until ELISA assayed (within one month) for estimation of serum levels of IL-1β [14], IL-6 [15] and TNF-α [16] using Quantikine ELISA kits from R & D Systems, Inc., (Minneapolis, MN).

### Insulin sensitivity Evaluation

Insulin sensitivity of control animals was evaluated by both tests, for comparison with IDDM using RIST and NIDDM using HOMA-IR test

a. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) [17] on the basis of fasting insulin and glucose levels and according to the formula HOMA-IR= I x G/22.5, where I is fasting plasma insulin level (μIU/ml) and G is fasting blood glucose in mg/dl divided by 18, considering an abnormal HOMA-index >3.8 [18].

b. Rapid insulin sensitivity test (RIST): The RIST starts with the administration of an insulin bolus (50mU/kg i.v.), over 5 min. At 1 min after initiating the insulin infusion, arterial blood glucose was measured and glucose infusion (D-Glucose/saline, 100 mg/ml, i.v.) was started at a

rate of 5mg/kg/min. According to arterial glucose concentrations measured at 2 min intervals, the infusion rate of the glucose was readjusted to maintain euglycemia. When no further glucose infusion was required, usually within 35 min, the test was concluded. The amount of glucose necessary to maintain euglycemia along the test quantifies insulin sensitivity and is referred to as the RIST index (mg glucose/kg) [19].

**Statistical analysis**

Data are presented as mean±SD and compared using Wilcoxon ranked test for unrelated data (Z test) using SPSS program (Version 10, 2002). P value at <0.05 was considered significant.

**3. Results:**

Estimated variables showed a non-significant (p>0.05) difference between both subgroups of control rats, (Table 1), so all statistical analyses of study groups were compared versus the total number of control rats and arbitrary named control group.

Fasting blood glucose (FBG) levels estimated either prior to or at end of therapy, were significantly (p<0.05) higher in all studied animals compared to control group. Administration of curcumin induced significant (p<0.05) reduction of FBG despite still being significantly (p<0.05) higher compared to control group. Curcumin induced reduction of FBG, irrespective of type of diabetes, as judged by the non-significant (p>0.05) difference of post-treatment FBG levels in both groups. The impact of type of diabetes was evident on fasting plasma insulin (FPI) levels which were significantly (p<0.05) lower in Group II compared to both control group and group III at pre- and post-treatment estimates. On contrary to FBG, curcumin has no impact on FPI in group II, while significantly reduced FPI levels in group III at 6-weeks after initiation of administration compared to prior to administration, despite being still significantly (p<0.05) higher compared to control levels, (Table 2).

Induced diabetes, irrespective of its type, significantly induced release of pro-inflammatory cytokines as evidenced by significantly (p<0.05) higher pre-treatment serum levels of pro-inflammatory cytokines in both study groups compared to control group. However, the ameliorative effect of curcumin was also evident as manifested by the significantly (p<0.05) lower serum levels of estimated cytokines at 6-weeks after treatment compared to pre-treatment levels, despite still being significantly (p<0.05) higher compared to control levels

In group II, post-treatment RIST index (34.5±3.9) was non-significantly higher (p>0.05) compared to control index (30.6±7.8). In group III, HOMA-IR index calculated prior to initiation of therapy (2.3±0.08) was significantly (p<0.05) higher compared to control index (0.17±0.03), while post-treatment HOMA-IR index (0.81±0.19) was significantly (p<0.05) decreased compared to pre-treatment levels, despite still being significantly (p<0.05) higher compared to control group.

**Table (1): Mean values of estimated parameters in both control subgroups**

| Variable | Group I-A | Group I-B |
|---|---|---|
| Fasting blood glucose (mg/dl) | 77.4±9.1 | 81±9.3 |
| Fasting insulin (µIU/ml) | 0.9±0.2 | 0.82±0.21 |
| HOMA-IR index | 0.17±0.03 | 0.16±0.05 |
| IL-1β (pg/ml) | 1.28±0.23 | 1.19±0.31 |
| IL-6 (pg/ml) | 12.2±3.3 | 11.9±4.2 |
| TNF-α (pg/ml) | 1.82±0.6 | 1.86±0.52 |

Data are presented as mean±SD

**Table (2): Mean (±SD) of FBG and FPI levels estimated in studied animals pre- and post-treatment compared to control levels**

| | Fasting blood glucose (mg/dl) | | Fasting plasma insulin (µIU/ml) | |
|---|---|---|---|---|
| | Pre-ttt | Post-ttt | Pre-ttt | Post-ttt |
| Control | 77.4±9.1 | | 0.9±0.2 | |
| Group II (IDDM) | 173.4±28* | 127.7±6.5*† | 0.28±0.1* | 0.29±0.1* |
| Group III (NIDDM) | 176.3±24.9* | 124.5±6.4*† | 5.3±1.2*‡ | 2.55±0.54*†‡ |

Data are presented as mean±SD Pre: prior to initiation of therapy Post: at end of 6-wks therapy
*: significant difference versus control group †: significant difference versus pre levels
‡: significant difference versus Group II

**Table (3): Mean (±SD) of serum levels of IL-1β, IL-6 and TNF-α estimated in studied animals pre- and post-treatment compared to control levels**

| | | Control | Group II (IDDM) | Group III (NIDDM) |
|---|---|---|---|---|
| IL-1β (pg/ml) | Pre | 1.28±0.23 | 2.57±0.36* | 2.22±0.46*‡ |
| | Post | | 1.75±0.4*† | 1.4±0.32†‡ |
| IL-6 (pg/ml) | Pre | 12.2±3.3 | 50.2±7.5* | 43.2±9.3* |
| | Post | | 23.5±1.7*†#∫ | 21.9±2.3*†# |
| TNF-α (pg/ml) | Pre | 1.82±0.6 | 6.54±1.7* | 6.7±2* |
| | Post | | 3.1±0.5*†# | 3.4±0.6*† |

Data are presented as mean±SD Pre: prior to initiation of therapy Post: at end of 6-wks therapy
*: significant difference versus control group †: significant difference versus pre levels
‡: significant difference versus Group II

## 4. Discussion

Curcumin induced significant reduction of FBG levels in both diabetic groups, irrespective of type of diabetes. Moreover, in NIDDM animals, FPI levels estimated at end of therapy despite being still significantly higher compared to control levels, but were significantly lower compared to their pre-treatment levels. These findings indicated that the effect of curcumin was mediated through increasing the sensitivity of insulin receptor to the available secreted amount of insulin and consequently increased glucose metabolism with lowering FBG without any impact on insulin secretion.

The obtained results coincided with and supported that previously reported by Pari & Murugan(2005) [20] who investigated the effect of tetrahydrocurcumin (THC), one of the active metabolites in curcumin, on the key hepatic metabolic enzymes involved in carbohydrate metabolism in STZ-induced diabetic rats and found that in untreated diabetic control rats, the activities of the gluconeogenic enzymes were significantly increased, whereas hexokinase and G6PD activity and glycogen levels were significantly decreased, while both THC and curcumin were able to restore the altered enzyme activities to near normal levels and normalize blood glucose in diabetic rats. Thereafter, Murugan & Pari [21] investigated the effect of THC on lipid profile and lipid peroxidation in type-2 diabetic rats and reported a significant reduction in blood glucose, which proved its antidiabetic effect and caused a significant reduction in lipid peroxidation and lipids in serum and tissues, suggesting its role in protection against lipid peroxidation and its antihyperlipidemic effect.

Murugan & Pari [22] and Suryanarayana et al. [23] examined the effect of THC and curcumin on erythrocyte membrane bound enzymes and antioxidants activity in type-2 diabetic model and reported that administration of THC and curcumin induced increased levels erythrocyte antioxidants and the activities of membrane bound enzymes and concluded that these biochemical observations indicate that the THC and curcumin possess a significant beneficial effect on erythrocyte membrane bound enzymes and antioxidants defense in addition to its antidiabetic effect. In support of the reported data, post-treatment HOMA-IR and RIST indices were significantly improved in the studied animals compared to pre-treatment levels.

Furthermore, post-treatment serum levels of studied cytokines were significantly lower compared to pre-treatment levels, such ameliorative effect of curcumin on pro-inflammatory cytokines could be a possible mechanism for the reported effects on insulin sensitivity that proved to be improved irrespective of type of diabetes.

The reported beneficial effects of curcumin especially on IDDM could be attributed to its anti-oxidant and anti-inflammatory effects and go in hand with Tikoo et al. [24] who reported that treatment of type-1 diabetic rats with curcumin significantly decreased blood urea nitrogen and creatinine and increased albumin; variables associated with the development of diabetic nephropathy and prevented the increased levels of HSP-27 and MAP kinase (p38) in diabetic kidney and at nuclear level curcumin prevented the decrease in dephosphorylation and increases acetylation of histone H3. Moreover, Kanitkar et al. [25] demonstrated that curcumin in vitro protects pancreatic islets against cytokine-induced death and dysfunction by scavenging reactive oxygen species (ROS) and normalized cytokine-induced NF-kappaB translocation by inhibiting phosphorylation of inhibitor of kappa B alpha and in vivo curcumin prevents STZ-induced diabetes.

Kang & Chen [26] found curcumin dose-dependently eliminates insulin-induced hepatic stellate cells (HSC) activation by suppressing expression of type I collagen gene, interrupts insulin signaling in HSC by reducing the phosphorylation level of insulin receptor and suppressing its gene expression. Furthermore, curcumin attenuates insulin-induced oxidative stress in HSC by inducing gene expression of glutamate-cysteine ligase leading

to de novo synthesis of glutathione. Also, Lin et al. [27] found curcumin suppresses gene expression of lectin-like oxidized LDL receptor-1, leading to the blockade of the transport of extracellular oxidized LDL into cells through interruption of Wnt signaling and the activation of peroxisome proliferator-activated receptor-gamma

Recently, El-Moselhy et al. [28] found curcumin showed an anti-hyperglycemic effect and improved insulin sensitivity, and this action may be attributed at least in part to its anti-inflammatory properties as evident by attenuating TNF-α levels in high fat diet (HFD) fed rats, and its anti-lipolytic effect as evident by attenuating plasma free fatty acids and concluded that curcumin could be a beneficial adjuvant therapy in patients with T2DM. El-Azab et al. [29], (2011), reported that treatment with curcumin significantly reversed STZ-induced hyperglycemia/glucose intolerance, hypoinsulinemia, and damage of pancreatic islets. Moreover, El-Azab et al., [29] found curcumin blunted the pancreatic lipid-peroxidation, up-regulated activities of the antioxidant enzymes, and suppressed serum levels of TNF-α and IL-1β. Lin & Chen [30], (2011), observed that high levels of glucose induced cell proliferation, type I collagen production and expression of genes relevant to HSC activation, and elevated intracellular glucose levels in cultured HSC, but curcumin eliminated such stimulatory impacts, abrogated the membrane translocation of GLUT2 by interrupting the p38 MAPK signaling pathway, suppressed Glut2 expression by stimulating the activity of peroxisome proliferator-activated receptor-gamma and de novo synthesis of glutathione.

The obtained results and data extracted from literature allow concluding that chronic administration of curcumin improves insulin sensitivity and thus imposing an anti-diabetic effect manifested as decreased FBG levels with concomitant decreased FPI and ameliorated the increased serum levels of pro-inflammatory cytokines and such effects are manifested in both types of diabetes.

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