Curcumin/Irbesartan Combination Improves Insulin Sensitivity and Ameliorates Serum Pro-inflammatory Cytokines levels in Diabetes Rat model

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Abstract: To evaluate the impact of chronic administration of an angiotensin II receptor antagonist (Irbesartan) and/or curcumin on fasting blood glucose level (FBG), insulin sensitivity, and proinflammatory cytokines in experimentally-induced diabetes in albino rats. Materials and Methods: The study included 80 (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 (30 rats) for induction of non-insulin dependent DM (NIDDM) or without dieting regimen (30 rats) for induction of IDDM. One-week later, rats received oral irbesartan (2.5 mg/kg/day), oral curcumin (200 mg/kg) or both lines for 6 weeks. 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 prior to initiation and at 6-wks after treatment for estimation of FBG and ELISA estimation of fasting plasma insulin (FPI), serum interleukin (IL)-1β and -6 and tumor necrosis factor-α (TNF-α). Results: Both lines of treatment induced significant reduction of FBG and FPI levels compared to pre-treatment levels with significant reduction of FBG on using curcumin compared to irbesartan, but combination therapy significantly lowered FPI levels compared to either drug alone. Post-treatment serum levels of studied cytokines in all groups were significantly lower compared to pre-treatment levels, but curcumin alone significantly reduced serum levels of IL-6 and TNF-α compared to irbesartan alone. Post-treatment HOMA-IR and RIST indices were significantly improved compared to pre-treatment levels. Conclusion: Chronic administration of irbesartan/curcumin combination showed anti-diabetic effect manifested as decreased FBG and FPI levels and ameliorated the increased serum levels of pro-inflammatory cytokines. The use of such combination could be recommended for clinical trials so as to document its use for control of both types diabetes.

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1. Introduction

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, (Muniyappa et al., 2008). Cross-talk between inflammatory signaling pathways and insulin signaling pathways causes metabolic insulin resistance and endothelial dysfunction, (Kim et al., 2006).

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, (Petersen et al., 2007). 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, (Salmennienmi et al., 2008). Therefore, improvement of insulin sensitivity is an important therapeutic goal.

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, (Weisberg et al., 2008). 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,

chemopreventive and chemotherapeutic actions, (Hatcher et al., 2008, Bengmark et al., 2009).

Angiotensin II (Ang II), the main effector peptide of the renin–angiotensin system (RAS), is implicated in the development of vascular, cardiac, and renal pathologies. Several lines of evidence suggest that Ang II impairs insulin sensitivity and provoke glucose intolerance, (Ogihara et al., 2002). Furthermore, angiotensin type-1 receptor (AT1R) blockers (ARBs) have recently been demonstrated to exert beneficial effects on glucose and lipid metabolism in adipocytes and adipose tissue, (Clasen et al., 2005). The RAS by blockade of the AT1R substantially lowers the risk for type 2 diabetes, (Dahlof et al., 2002). Additionally, blockade of the AT1R has been shown to improve insulin sensitivity in animal models of insulin resistance, (Henriksen et al., 2001). However, the mechanisms underlying the insulin-sensitizing and antidiabetic effects of the ARBs have not been defined. Findings from in vitro and in vivo studies have revealed that two newer ARBs, telmisartan and irbesartan, have the potential to improve insulin sensitivity and beta- cell responsiveness, (Schupp et al., 2005).

The present study was designed to evaluate the impact of chronic administration of an angiotensin II receptor antagonist (Irbesartan) and/or curcumin on blood glucose level, insulin sensitivity, and pro-inflammatory cytokines in experimentally-induced diabetes in albino rats.

2. Materials and Methods

Animals: The present study comprised 80 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), (Islam and Choi, 2007) 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), (Islam and Choi, 2007).

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 FBG of ≥200 mg/dl were considered diabetic, (Islam and Choi, 2007).

Drugs: Irbesartan (Sanofi-Aventis) and curcumin (Sigma chemicals) were dissolved in 1% gum acacia so that 0.5 to 1 ml contained the desired dose. The therapeutic human dose of irbesartan was converted to rat dose according to Paget converting table, (Paget and Barnes, 1964) and about half of the therapeutic dose was used in this study.

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 30 rats had induced IDDM and were subdivided into 3 equal subgroups:

a) Group II-A: 10 rats were administered irbesartan in a dose of 5 mg/kg/day, (Richer et al., 1999) in the drinking water for a period of 6 weeks, (O'Donnell et., 1997).
b) Group II-B: 10 rats were administered 200 mg/kg body weight of curcumin in 1% gum acacia, orally/day for a period of 6 weeks
c) Group II-A/B: 10 rats were administered both irbesartan in a dose of 5 mg/ kg body weight in the drinking water and curcumin in a dose of 200 mg/kg body weight in 1% gum acacia; orally/day for a period of 6 weeks.

Group III: included 30 rats had induced NIDDM and were subdivided into 3 equal subgroups:

a) Group III-A: 10 rats were administered irbesartan in a dose of 5 mg/kg/day in the drinking water for a period of 6 weeks.
b) Group III-B: 10 rats were administered 200 mg/kg body weight of curcumin in 1% gum acacia, orally/day for a period of 6 weeks.
c) Group III-A/B: 10 rats were administered both irbesartan in a dose of 5 mg/ kg body weight in the drinking water and curcumin in a dose of 200 mg/kg body weight 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 estimation of glucose by glucose oxidase method, (Tinder, 1969).
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: the first for RIA determination of serum level of insulin, (Gordon et al., 1985) and 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, (Dinarello et al., 1992), IL-6, (Engvall et al., 1972) and TNF-α, (Beutler et al., 1985) using Quantikine ELISA kits from R & D Systems, Inc., (Minneapolis, MN).

Insulin sensitivity Evaluation: Insulin sensitivity of control and studied 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) (Matthews et al., 1985) 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 >2, (Ascaso et al., 2001).
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) (Lautt et al., 1998).

Statistical analysis: obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using one-way ANOVA test and Chi-square test. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

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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 control group I-A that arbitrary named control group.

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

Variable	Group I-A	Group I-B
FBG (mg/dl)	77.4±9.1	81±9.3
FPI(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

Fasting blood glucose levels estimated either prior to or at end of therapy, were significantly higher in all studied animals compared to control levels. Both lines of treatment either alone or in combination induced significant reduction of FBG levels in both study groups, irrespective of type of diabetes. However, administration of curcumin either alone or in combination with irbesartan induced significant

reduction of FBG, irrespective of type of diabetes, compared to irbesartan alone with non-significant difference between animals received curcumin, (Table 2).

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

		Pre-ttt	Post-ttt
Control		77.4±9.1	
Group II (IDDM)	Irb	164.8±30.7*	145.4±9.6*†
	Cur	166.9±37.5*	134.4±6.9*†#
	Irb/Cur	173.4±28*	127.7±6.5*†#
Group III (NIDDM)	Irb	176.3±24.9*	144.9±17.8*†
	Cur	167.7±23*	126.9±9.2*†#
	Irb/Cur	176.3±24.9*	124.5±6.4*†#

Pre: before start of therapy Post: at 6-wks of therapy
*: significant difference versus control group
†: significant difference versus pre levels
‡: significant difference versus counterpart IDDM group
#: significant difference versus Irb subgroup
∫: significant difference versus Cur subgroup

Fasting plasma insulin (FPI) levels estimated either prior to or at end of therapy, were significantly higher in group III animals compared to both control and group II animals that had significantly lower FPI levels compared to control animals. As regard treatment subgroups, there was non-significant difference between group II subgroups with non-significant difference between pre and post-treatment levels. However, group III animals administered combination therapy showed significantly lower FPI levels compared to animals received either irbesartan or curcumin alone with a non-significant difference of FPI levels in animals received irbesartan compared to those received curcumin alone, (Table 3).

Table (3): Mean (±SD) of FPI levels estimated in studied animals pre- and post-treatment compared to control levels

		Pre-ttt	Post-ttt
Control		0.9±0.2	
Group II (IDDM)	Irb	0.22±0.08*	0.23±0.08*
	Cur	0.25±0.1*	0.26±0.1*
	Irb/Cur	0.28±0.1*	0.29±0.1*
Group III (NIDDM)	Irb	5.1±1.3*‡	3.61±0.35*†‡
	Cur	4.9±1*‡	3.14±0.41*†‡
	Irb/Cur	5.3±1.2*‡	2.55±0.54*†‡#∫

Pre: before start of therapy Post: at 6-wks of therapy
*: significant difference versus control group
†: significant difference versus pre levels
‡: significant difference versus counterpart IDDM group
#: significant difference versus Irb subgroup
∫: significant difference versus Cur subgroup

Pre- and post-treatment estimated levels of studied pro-inflammatory cytokines were significantly higher in groups II and III compared to control level, irrespective of type of induced diabetes or line of treatment used. However, post-treatment serum levels of studied cytokines were significantly lower compared to pre-treatment levels, irrespective of line of treatment applied. Post-treatment serum levels of IL-1β were significantly lower in group III animals compared to group II animals, irrespective of line of treatment, (Table 4, Figure 1).

Table (4): Mean (±SD) of serum levels of IL-1β estimated in studied animals pre- and post-treatment compared to control levels

		Pre	Post
Control group		1.28±0.23	
Group II (IDDM)	Irb	2.62±0.42*	2.07±0.56*†
	Cur	2.82±0.41*	1.92±0.58*†
	Irb/Cur	2.57±0.36*	1.75±0.4*†
Group III (NIDDM)	Irb	2.29±0.3*‡	1.7±0.41*†
	Cur	2.14±0.51*‡	1.58±0.4*†‡
	Irb/Cur	2.22±0.46*‡	1.4±0.32†‡

Pre: before start of therapy Post: at 6-wks of therapy
*: significant difference versus control group
†: significant difference versus pre levels
‡: significant difference versus counterpart IDDM group

On contrary, there was non-significant difference between post-treatment serum levels of IL-6 and TNF-α between studied animals, irrespective of type of diabetes. However, administration of curcumin, either alone or in combination with irbesartan significantly reduced serum IL-6 in comparison to irbesartan alone, irrespective of type of diabetes and in IDDM animals, combination therapy significantly reduced serum IL-6 compared to curcumin alone and significantly reduced serum TNF-α compared to irbesartan alone, but non-significantly compared to curcumin alone, (Tables 5 & 6, Figures 2 & 3).

In group III, HOMA-IR index calculated prior to initiation of therapy was significantly higher in studied subgroups compared to control index with non-significant difference among studied subgroups. Post-treatment HOMA-IR index was significantly decreased in the three subgroups compared to pre-treatment levels, despite still being significantly higher compared to control group. Combination therapy significantly reduced HOMA-IR index compared to either irbesartan or curcumin alone with a significant difference in favor of irbesartan, (Table 7).

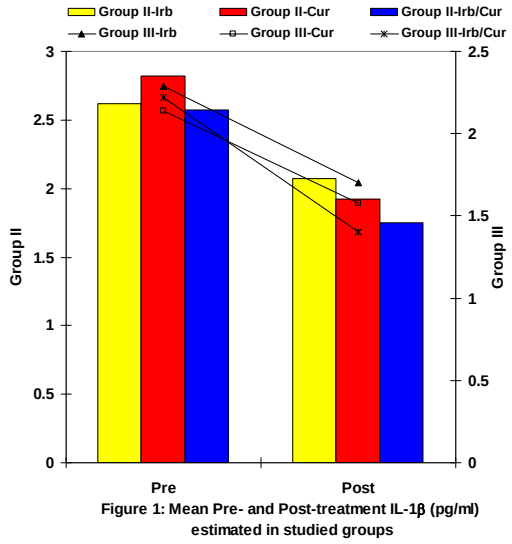

Figure 1: Mean Pre- and Post-treatment IL-1β (pg/ml) estimated in studied groups

Table (5): Mean (±SD) of serum levels of IL-6 estimated in studied animals pre- and post-treatment compared to control levels

		Pre	Post
Control group		12.2±3.3	
Group II (IDDM)	Irb	54.8±9.1*	30.5±4*†
	Cur	49.6±8.8*	26.4±2.1*†#
	Irb/Cur	50.2±7.5*	23.5±1.7*†#∫
Group III (NIDDM)	Irb	40.7±14.1*	28.5±1.9*†
	Cur	43.9±11.6*	24±2.3*†#
	Irb/Cur	43.2±9.3*	21.9±2.3*†#

Pre: before start of therapy Post: at 6-wks of therapy
*: significant difference versus control group
†: significant difference versus pre levels
#: significant difference versus Irb subgroup
∫: significant difference versus Cur subgroup

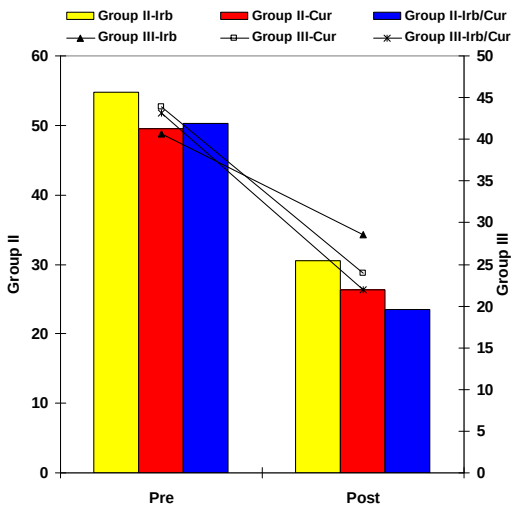

Figure 2: Mean Pre- and Post-treatment IL-6 (pg/ml) estimated in studied groups

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

		Pre	Post
Control group		1.82±0.6	
Group II (IDDM)	Irb	6.36±1.7*	4±1*†
	Cur	6.51±1.4*	3.5±0.7*†
	Irb/Cur	6.54±1.7*	3.1±0.5*†#
Group III (NIDDM)	Irb	6.86±1.8*	3.82±0.7*†
	Cur	6.4±1.9*	3.6±0.8*†
	Irb/Cur	6.7±2*	3.4±0.6*†

Pre: before start of therapy Post: at 6-wks of therapy
*: significant difference versus control group
†: significant difference versus pre levels
#: significant difference versus Irb subgroup

In group II, post-treatment RIST index was significantly lower (p=0.009) in animals pre-treated with irbesartan (17.5±3.9) compared to control index (30.6±7.8) with non-significant difference between both other subgroups compared to control index. Moreover, RIST index calculated in animals pre-treated with either curcumin alone (28.8±6.6) or in combination with irbesartan (34.5±3.9) was significantly higher (p=0.005, respectively) compared to those pre-treated with irbesartan only with significantly higher (p=0.028) RIST index in animals received combination therapy compared to those pre-treated with curcumin alone.

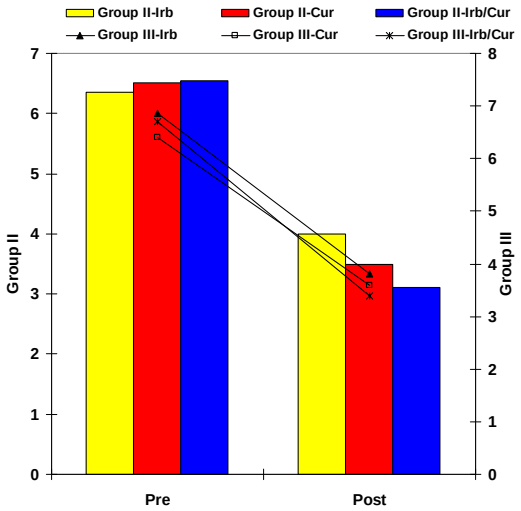

Figure 3: Mean Pre- and Post-treatment TNF-α (pg/ml) ureestimated in studied groups

Table (7): Mean (±SD) of HOMA-IR index calculated in Group III compared to control levels

		Pre-ttt	Post-ttt
Control		0.17±0.03	
Group III (NIDDM)	Irb	1.98±0.54*	1.04±0.14*†
	Cur	2.11±0.6*	1.29±0.14*†#
	Irb/Cur	2.3±0.08*	0.81±0.19*†#∫

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 Irb subgroup
∫: significant difference versus Cur subgroup

4. Discussion

Both applied lines of treatment either alone or in combination induced significant reduction of FBG levels in both study groups, irrespective of type of diabetes. However, administration of curcumin either alone or in combination with irbesartan induced significant reduction of FBG, irrespective of type of diabetes, compared to irbesartan. These findings spotlight on the fact that both of curcumin and irbesartan induced lowering of FBG by a different mode of action towards one target, i.e. lowering FBG and both could act synergistically and that the response for either curcumin or irbesartan differed between both types of diabetes.

In NIDDM animals, FPI levels estimated at end of therapy despite being still significantly higher compared to control levels, were significantly lower compared to their pre-treatment levels and animals administered combination therapy showed significantly lower FPI levels compared to animals received either irbesartan or curcumin alone. These finding indicated that the effect of the studied drugs on diabetic animals was conducted 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 and Murugan, (2005), 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 streptozotocin-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. Also, Murugan and Pari, (2006), 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.

Thereafter, Murugan and Pari, (2007), and Suryanarayana et al., (2007) 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 subgroups compared to pre-treatment levels, with the effect was more significantly pronounced with combination therapy. Such clinical implication of the obtained results goes in hand with various clinical studies; Huang et al., (2007) suggested

that a local pancreatic renin-angiotensin system and pravastatin, captopril and irbesartan treatment may be selectively controlling pancreatic islet blood flow, augmenting insulin secretion and thereby improving glucose tolerance and concluded that the antidiabetic actions of renin-angiotensin system inhibitors might occur, in part, through this beneficial direct islet effects. Cetinkalp et al., (2008), found the short-term treatment of irbesartan is effective to decrease microalbuminuria in normotensive type-2 diabetes patients independent of its antihypertensive effect and such decrease was associated with significantly decreased fasting and non-fasting blood glucose, and HbA1c compared to pre-treatment values.

Furthermore, post-treatment serum levels of studied cytokines were significantly lower compared to pre-treatment levels, irrespective of line of treatment applied; such ameliorative effect of curcumin and irbesartan administered separately or in combination 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 or the drug used.

These data go in hand with Ceriello et al., (2005), who reported an independent and cumulative effect of postprandial hyper-triglyceridemia and hyperglycemia on endothelial function and inflammation, suggesting oxidative stress as a common mediator of such an effect and short-term treatment with irbesartan may counterbalance this phenomenon. Also, Persson et al., (2006), evaluated the impact of irbesartan treatment on biomarkers of low-grade inflammation in patients with Type 2 diabetes and microalbuminuria and found irbesartan treatment yielded significant changes in CRP with a 5.4% decrease per year versus a 10% increase per year in the placebo group, IL-6 showed a 1.8% increase per year compared with placebo's 6.5% increase per year and changes in IL-6 were associated with changes in albumin excretion and concluded that irbesartan reduces low-grade inflammation in this high-risk population. Vieitez et al., (2008), found systemic and local administration of irbesartan lowers glomerular expression of growth factors and TNF-α and concluded that part of the effect of lowering the expression of these growth factors and cytokines is due to a direct blockade of glomerular renin-angiotensin system.

The reported beneficial effects of curcumin alone or combination on IDDM could be attributed to the anti-oxidant and anti-inflammatory effects of curcumin and go in hand with Tikoo et al., (2008), 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., (2008), demonstrated that curcumin in vitro protects pancreatic islets against cytokine-induced death and dysfunction by scavenging ROS and normalized cytokine-induced NF-kappaB translocation by inhibiting phosphorylation of inhibitor of kappa B alpha (IkappaBalpha) and in vivo curcumin prevents STZ-induced diabetes.

Kang and Chen, (2009) 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., (2009) 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

It could be concluded that chronic administration of irbesartan/curcumin combination showed 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. The use of such combination could be recommended for clinical trials so as to document its use for control of both types diabetes.

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