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Short Report

Effect of *rosiglitazone* on inflammatory mediators in type 2 diabetes

Aruliah Sohna Chandra Packiavathy [a], Marimuthu Ramalingam [b] , Chenniappan Anchana Devi [c]

[a] *Department of Biochemistry, PRIST University, Thanjavur-04, Tamil Nadu, India*

[b] *Center for Research and Development, PRIST University, Thanjavur-03, Tamil Nadu, India.*

[c] *Department of Microbiology, Bharathidasan University, Trichy-24 Tamil Nadu, India.*

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ABSTRACT

Type 2 diabetes is a heterogenous disorder involving impairment of both insulin secretion and insulin action. Inflammation is predominantly seen in type 2 diabetes. The effect of *rosiglitazone* on inflammatory mediators was analysed in the present study. The study groups consisted of 220 type 2 diabetic patients (110 Males, 110 Females) and 220 age and sex matched *rosiglitazone* treated type 2 diabetic subjects (110 Males, 110 Females). The values of C-reactive protein (CRP), Complement 3 (C3), ceruloplasmin, cortisol, alpha 1 antitrypsin and haptoglobin were found to be significantly decreased by *rosiglitazone* when compared to type 2 diabetic subjects. The levels of tumour necrosis factor α (TNF-α), interleukin-6 (IL-6) and adiponectin were found to be remarkably reduced in *rosiglitazone* treated type 2 diabetic subjects as compared to type 2 diabetic patients. Hence rosiglitazone therapy serves as an effective approach in restoring immune status in type 2 diabetes mellitus.

1. Introduction

Type 2 diabetes is an incurable chronic endocrine disorder that affects the body's ability to convert food into energy. Hyperglycemia is the hallmark of diabetes mellitus. Diabetics are likely to experience acute metabolic complications. They are prone to develop micro and macrovascular complications compared to non-diabetics. Type 2 diabetes is characterized by insulin resistance, decreased pancreatic- cell function and elevated hepatic glucose output [1].

Rosiglitazone is a potent member of the thiazolidinedione class with a binding affinity for PPAR Y that is ~ 100 fold greater than that of pioglitazone and 190-fold greater than that of *Troglitazone* [2]. *Rosiglitazone* therapy is not associated with either hypoglycemia or GIT intolerance. The benefits of rosiglitazone in reducing glucose levels apply to wide spectrum of patients with type 2 diabetes. In addition to the effects on glucose metabolism, *rosiglitazone* has effects on lipid metabolism, inflammatory responses and cellular proliferation [3].

* Corresponding Author : A. Sohna Chandra Packiavathy,
Head of the Department, Department of Biochemistry,
PRIST University, Thanjavur 614904,
Tamilnadu, India.
Phone: +91 9443338348
E-mail: sohnachandra@gmail.com

2. Materials and Methods

The study groups consisted of uncontrolled type 2 diabetes mellitus patients (n=220, 110 Males, 110 Females) attending Samuel Clinic, Thanjavur. They were freshly diagnosed diabetics and were not under medication for the disease previously. Age and sex matched *rosiglitazone* treated type 2 diabetic subjects (n=220, 110 Males, 110 Females) were also selected and analysed as given below.

Serum, plasma and whole blood were utilized for immunological studies. CRP was assayed by Singer method [4]. C3 was estimated by radial immuno diffusion [5]. Serum haptoglobin was determined by sandwich ELISA technique [6]. Cortisol was estimated by immuno enzymatic method [7]. Plasma ceruloplasmin was estimated by the Ravin method [8]. The concentration of alpha 1 anti-trypsin was measured by double antibody sandwich enzyme linked immunosorbent assay [9].

Enzyme linked immunosorbent assay was used for the invitro quantitative determination of IL-6 and TNF-α in human serum [10]. The amount of plasma adiponectin was estimated by ELISA method [11].

Table 1. The levels of inflammatory markers in type 2 diabetic and *rosiglitazone* treated subjects

GROUPS	Treatment	CRP (mg/m	C_3 (g/l)	Ceruloplasmin (mg/dl)	Cortisol (mg/dl	Haptoglobin (g/l)	Alpha 1 anti-trypsin (mg/dl
I.	Type 2 diabetic subjects	2.14± 0.89[b]	3.355± 0.709[b]	55.38±9.34 [b]	25.63± 6.88 [b]	2.93±2.083 [b]	257.83± 21.37 [b]
II.	Rosiglitazone treated type 2 diabetic subjects	0.24± 0.074[c]	1.74± 0.370 [c]	36.86±5.44 [c]	14.70± 3.44 [c]	1.936±0.318 [c]	188.98± 19.132 [c]

Values were expressed in mean ± SD (n =220). Values not sharing a commonsuperscript significantly differ at $P < 0.01$ (paired sample t test)

Table 2. Levels of IL-6, TNF- and Adiponectin in type 2 diabetic and *rosiglitazone* treated subjects

GROUPS	Treatment	IL-6 (pg/ml)	TNF -α (pg/ml)	Adiponectin (pg/ml)
I.	Type 2 diabetic subjects	51.47 ± 24.20 [b]	26.39 ± 11.68 [b]	4.928 ± 0.966 [b]
II.	Rosiglitazone treated type 2 diabetic subjects	1.98 ± 0.458[c]	5.92 ± 1.34 [c]	112.59 ± 17.187 [c]

Values were expressed in mean ± SD (n =220). Values not sharing a commonSuperscript significantly differ at $P < 0.01$ (paired sample t test)

3. Results and Discussion

There is an intricate network of apparent links between cytokines, inflammation, macrovascular disease and type 2 diabetes. The study of [12] clearly emphasizes the potential role of IL-6 since robust correlations were found between IL-6 levels and the various markers of inflammation. Patients with type 2 diabetes and insulin resistance have elevated levels of TNF-α also. CRP production by hepatocytes is stimulated by TNF-α and IL-6 and increased CRP levels have been described in people with type 2 diabetes [13].

In type 2 diabetic subjects hypothalamic pituitary adrenal activity is enhanced in patients with diabetic complications and the degree of cortisol secretion is related to the presence and the number of diabetic complications. C_3 is mainly produced in the liver in response to proinflammatory cytokines such as IL-6 [14]. The relation between C_3 and incidence of diabetes could reflect a systemic low-grade inflammation and the actions of IL-6 and TNF-α.

An increase in serum ceruloplasmin levels has been reported in type 2 diabetes [15]. The increase is due to hyperglycemia in type 2 diabetic patients. α 1AT is an acute phase reactant. It is upregulated during acute phase response to tissue necrosis and inflammation. Haptoglobin is synthesized in liver and IL-6 is thought to be the main cytokine that induces the synthesis of haptoglobin in the liver [16].

The present study deals with the effect of *rosiglitazone* on the inflammatory mediators in type 2 diabetes mellitus. With *rosiglitazone* treatment, fasting C3 level was decreased, producing a little change in fasting ASP with the most striking change being a loss of postprandial ASP production.

In the present study, the levels of ceruloplasmin, haptoglobin and α 1 antitrypsin were also brought to normal range by *rosiglitazone* treatment in group II subjects. This may be attributed to improvement of inflammatory status in type 2 diabetic subjects by *rosiglitazone* therapy.

The levels of CRP, IL-6 and TNF-α were found to be within the normal range in group II subjects. This is due to the anti-inflammatory action of *rosiglitazone*. The present study clearly demonstrated that treatment with *rosiglitazone* in type 2 diabetic patients increased plasma adiponectin levels. This effect may potentially protect diabetic patients from macro vascular complications and may improve their insulin sensitivity and glycemic control.

4. Conclusion

Thus it is concluded that *rosiglitazone* may serve as an effective hypoglycemic agent in restoring normal immune status in type 2 diabetes mellitus.

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