

# Role of Inflammatory Mediators in Pathogenesis of Type 2 Diabetes Mellitus

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## ABSTRACT

**Introduction:** Diabetes mellitus is one of the most common non-communicable diseases globally. Current research aimed to study inflammatory markers IL-6 & TNF- $\alpha$  in the newly diagnosed type II diabetics without hypertension in comparison with non-diabetic normotensive subjects.

**Material and Methods:** 50 patients of newly diagnosed Type 2 diabetes without hypertension of age more than 18 years were selected from the department of General Medicine. 25 age and sex matched healthy non-diabetic normotensive individuals were taken as controls. 5ml of blood was taken from each subject after informed consent. 3ml was used for serum extraction and 2ml was stored in EDTA vial. The levels of Interleukin -6 (IL-6) and Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured using the standardized ELISA kits as per standard laboratory guidelines.

**Results:** The levels of IL-6 and TNF- $\alpha$  were found to be elevated in cases as compared to the controls. The comparison between both the groups was found to be statistically significant.

**Conclusion:** There is a definite role of inflammatory markers in the pathogenesis of Type-2 diabetes. In future we can target these inflammatory mediators in the treatment or even prevention of this modern day epidemic. Yet it is difficult to come to a definite conclusion whether the altered levels of inflammatory markers are cause or the effect of diabetes mellitus. But proper results and generalization of results can only be achieved after large cohort studies.

**Keywords:** Inflammatory Mediators, Type 2 Diabetes Mellitus, ELISA

## INTRODUCTION

About 382 million people or 8.3% adults worldwide have diabetes. Among them, 316 million have impaired glucose tolerance. About 80% live in low and middle income countries. About 366 million people in the world were estimated to have Diabetes Mellitus in 2001. It is estimated that this number will rise up to 522 million by 2030.<sup>1,2</sup>

Current researches and observations revealed a new concept of chronic low grade inflammation into the pathogenesis of type 2 diabetes mellitus. Some known non-communicable diseases like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease etc. are proven inflammatory diseases. On similar lines, there are chances that diabetes mellitus may prove to be a new entrant in this list.

Current research aimed to study inflammatory markers IL-6 & TNF- $\alpha$  in the newly diagnosed type II diabetics without hypertension in comparison with non-diabetic normotensive

subjects.

## MATERIAL AND METHODS

This observational case control study was carried out in the department of General Medicine in a tertiary health care establishment in Central India. 50 patients of newly diagnosed Type 2 diabetes without hypertension of age > 18 years were randomly selected from the department of General Medicine. 25 age and sex matched healthy non-diabetic normotensive individuals were taken as controls. Subsequently, an informed consent was taken from each patient. Detailed history taking and clinical examination (including fundoscopy by ophthalmologist) was done in all the selected cases and controls. 5ml of blood was taken from each subject - 3ml was used for serum extraction and 2ml was stored in EDTA vial. The levels of Interleukin -6 (IL-6) and Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured using the standardized ELISA kits as per standard laboratory guidelines. HbA1C, blood sugar levels and other relevant investigations were performed. Results of the above parameters were analyzed for correlation.

### Inclusion criteria

[a] Newly diagnosed diabetics (according to ADA 2019 guidelines)<sup>3</sup>

-Fasting Plasma Glucose (FPG)  $\geq$  126 mg/dL (7.0 mmol/L)

-2-hours plasma glucose  $\geq$  200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT).

-HbA1c > 6.5%.

[b] Blood pressure values below 140/90 mm of hg, without antihypertensive medication

[c] Age > 18 years

### Exclusion criteria

[a] History of smoking

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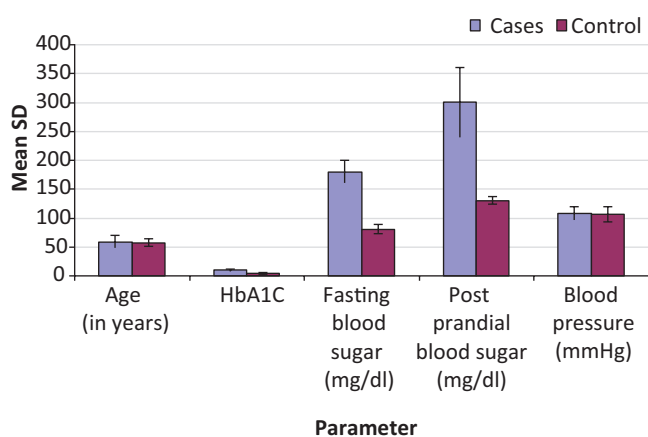
- [b] Patients with active infection
- [c] Patients who were working in chemical / asbestos / metal factories
- [d] Patients receiving chemotherapy
- [e] Patients with hypertension
- [f] Patients with chronic diseases like RA, SLE, IBD etc.

## RESULTS

50 cases and 25 controls were selected during this study period. There were 43 males and 32 females in the study.

The present study consisted of middle aged cases and similarly matched controls (mean age  $56 \pm 9.038$ ). There were slightly higher number of males in the study compared to female participants in both cases as well as controls. The clinical parameters of cases were in consistence with the diagnostic criteria for type 2 diabetes mellitus (ADA 2019 guidelines) with HbA1C varying between  $10.2 \pm 2.002$  for cases, Fasting sugar above 126 mg/dl (range 163.75-28.20) as well as post prandial sugar above 200 mg/dl (range 227-48) (table-1, graph-1).

In the present study, mean serum IL-6 level in the age & sex matched healthy controls was  $6.285 \pm 4.0084$  pg/ml, while in Normotensive diabetic group it was  $12.790 \pm 3.1767$  pg/ml. The mean serum IL-6 level in the Normotensive diabetic



Graph-1: Clinical parameters of cases and controls

Parameter	Cases	Controls
Age (in years)	56.01±9.038	57.56±6.76
Male / Female	28 / 22	15 / 10
HbA1C(in%)	10.2±2.002	5.5±0.51
Fasting blood sugar (mg/dl)	163.75±28.20	89.45±8.47
Post Prandial blood sugar (mg/dl)	227.45±48	125.6±9.13

Table-1: Clinical parameters of cases and controls

Parameter	Case	Control	p-value
IL-6 (pg/ml)	12.790±3.1767	6.285±4.0084	<0.0001

Table-2: IL-6 results

Parameter	Case	Control	p-value
TNFα(pg/ml)	21.725±4.9430	6.645±2.9584	<0.0001

Table-3: TNFα results

group was elevated as compared to the mean IL-6 level in control group. The difference between the both groups was statistically significant ( $P < 0.0001$ ) (table-2).

In the present study, mean serum TNF-α level in the age & sex matched healthy controls was  $6.645 \pm 2.9584$  pg/ml, while in Normotensive diabetic group it was  $21.725 \pm 4.9430$  pg/ml. The mean serum level of TNF-α in the Normotensive diabetic group was elevated as compared to the mean TNF-α level in control group. The difference between the both groups was statistically significant ( $P < 0.0001$ ) (table-3).

## DISCUSSION

The values of IL6 were significantly higher (p value  $< 0.0001$ ) in cases as compared to controls. The results of our study are somewhat similar to other studies.<sup>4,5,6,7,8</sup>

In our study the levels of TNF-α in the diabetic patients was considerably higher ( $21.725 \pm 4.9430$  pg/ml) as compared to healthy controls ( $6.645 \pm 2.9584$  pg/ml) with p value  $< 0.0001$ . This result matches with few other studies too, where a significant correlation was found between per cent β cell function and TNF-α ( $P = 0.008$ ).<sup>9,10</sup>

Type 2 diabetes mellitus (T2DM) has emerged as a pandemic and India, with  $> 60$  million people with diabetes, has the second largest diabetic kingdom in terms of population of the world. The projection shows that this number will increase to 100 million by 2030.

Diabetes is a disease of multifactorial origin. There are several lines of evidence that inflammation causes diabetes. Inflammation begins in the fat cells and it causes insulin resistance which is the primary feature of type 2 DM. When fat cells become insensitive to insulin, they cannot store any more glucose and hyperglycemia results. One mechanism for this may be dysfunction of mitochondria (powerhouse of the cell) and another mechanism may be oxidative stress. As more glucose is delivered to fat cells they produce an excess of reactive oxygen species, which in turn start an inflammatory cascade within the cells. Presence of chronic low grade inflammation is a new concept in the pathogenesis of DM. So our present study is based on the above hypothesis, to find an association inflammatory markers in normotensive diabetics in comparison with non-diabetic normotensive controls.

As we target pathophysiological mechanisms in treatment of DM this study would help in creating a new paradigm in treatment of DM. Diabetes mellitus is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (Vinay, K *et al.*, 2005). Individuals who progress to type 2 DM show chronic low grade inflammation years in advance of disease onset. Mediators of inflammation such as TNFα, IL6, IL18 and certain chemokines have been proposed to be involved in the events causing both forms of diabetes. IL-6 has been proposed to affect glucose homeostasis and metabolism directly and indirectly by action on skeletal muscle cells, adipocytes, hepatocytes, pancreatic β-cells and neuroendocrine cells.

Various immunological changes occur in DMT2 which

include-altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocyte populations and increased apoptosis and tissue fibrosis. Consequently, these changes suggest that inflammation participates in the pathogenesis of Type 2 Diabetes.

## CONCLUSION

IL-6 and TNF- $\alpha$  measured were significantly higher in cases i.e. newly diagnosed normotensive type II diabetics as compared to the healthy subjects. This supports the view that Chronic inflammation plays a crucial role in the pathogenesis of Type-2 Diabetes. Future development of therapies directed against these inflammatory mediators might be helpful in prevention or slowing up the speed of progression of this disease. Low-grade inflammation has been shown to precede and be a risk factor of future development of type 2 diabetes. Lifestyle modifications and medical treatment lowering the inflammatory state reduce risk of future development of type 2 diabetes. Studies regarding the levels of these inflammatory mediators namely IL-6 and TNF- $\alpha$  in diabetes with various complications (Micro and Macrovascular) will further support their role in the progression and severity of Diabetes. In future better funded and larger population studies will help to validate this study. Proper results and generalization of results can only be achieved after large cohort studies.

## REFERENCES

1. Whiting, D.R., Guariguata, L., Weil, C., Shaw, J. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract.* 2011;94:311–321
2. International Diabetic Federation, diabetic atlas, global burden, 5th ed.
3. American diabetes association diabetes care 2019;42:S13-S28
4. Senn JJ, Klover PJ, Nowak IA, Mooney RA: Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes* 2002;51:3391–3399.
5. Monnier, V. M., Bautista, O., Kenny, D., Sell, D. R., Fogarty, J., Dahms, W., Cleary, P. A., Lachin, J. & Genuth, S. (1999). Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. DCCT Skin Collagen Ancillary Study Group.
6. Thomas mandrup Paulson and Ole P. Kristianson: inflammation and diabetes; ‘the good, the bad or the indifferent?’
7. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P: The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest* 1998;102:1369–1376.
8. Senn JJ, Klover PJ, Nowak IA, Zimmers TA, Koniaris LG, Furlanetto RW, Mooney RA: Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in

hepatocytes. *J Biol Chem* 2003;278:13740–13746.

9. Klover PJ, Zimmers TA, Koniaris LG, Mooney RA: Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. *Diabetes.* 2003;52:2784-9.
10. Jatla Jyothi Swaroop, duggirawala rajarajeshwari, JN Naidu: Association of TNFa with insulin resistance in type 2 diabetes mellitus. *Indian J Med Res.* 2012;135: 127–130.

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