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COMPARATIVE STUDY OF SERUM LEVELS OF TNF-A IN MAJOR DEPRESSION IN DIABETES MELLITUS AND NON-DIABETES MELLITUS PATIENTS IN CENTRAL INDIA

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Abstract:

Introduction*:* Depression is a psychiatric disorder characterized by depressed mood, loss of interest in activities and loss of energy that lasts for two weeks or more. Type 2 diabetes mellitus (T2DM) is a group of metabolic disorders that share common phenotype of chronic hyperglycaemia.

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine involved in cellular responses. This signalling molecule primarily acknowledged for its importance in immune responses and apoptosis.

High prevalence of depression and diabetes mellitus worldwide causes increased morbidity & mortality & have increased economic burden in the community. Pathogenesis of depression and diabetes may be associated with the destruction of brain cells and pancreatic cells resulting from immune and inflammatory mediators.

Studies about the role of inflammation in the pathogenesis of depression and diabetes mellitus, shown conflicting and non-conclusive results hence any reliable clue will be considered valuable.

Aims & Objective: To compare the serum levels of TNF-α in patients of depression with diabetes mellitus and in patients of depression without diabetes mellitus.

Materials and Methods: This cross-sectional study included 50 patients of depression with diabetes mellitus (case group) and 50 age and gender matched patients of depression without diabetes (control group). Serum TNF-α levels were measured for both the groups.

Results: The mean concentrations of TNF-α in the case group and the control group were 28.98 ± 16.47 pg/ml and 10.19 ± 5.05 pg/ml respectively. The difference was to be statistically significant ($P < 0.05$) Thus our study yielded higher levels of serum TNF-α in case group than in control group.

Conclusion: This study has shown that inflammation is more evident inpatients of depression with diabetes mellitus as compared to in patients of depression without diabetes.

Keywords: Depression, Diabetes, inflammation, TNF-α

INTRODUCTION:

Depression is a psychiatric disorder characterized by depressed mood, loss of interest in activities and loss of energy that lasts for two weeks or more. The Prevalence of depression worldwide is about 3.4% of the population. It is higher for women (4.1%) than for men (2.7%). [1]

The role of inflammation in the pathophysiology of depression comes from following factors - (a) Patients with inflammatory diseases show greater rates of Major depression. (b) In the absence of a medical illness a large number of people with major depression show elevated inflammatory biomarkers. [2]

Inflammatory cytokine hypothesis of depression suggesting that inflammatory cytokines (IL-2, IL-6, TNF-α, and IFN) stimulates enzyme indoleamine 2,3-dioxygenase (IDO) leads to depletion of plasma levels of tryptophan and therefore, decrease the synthesis of serotonin in the brain, [3] which may play a role in the development of depressive symptoms.

In the past few decades India has highest prevalence of depression with diabetes mellitus in the world. Type 2 diabetes mellitus (T2DM) is a group of metabolic disorders that share common phenotype of chronic hyperglycemia. In the pathogenesis of diabetes mellitus Chronic, systemic subclinical inflammation has been identified as a driving force. [4] Inflammation also plays important role in the development of insulin resistance. [5] Insulin therapy has a important role in control of chronic hyperglycaemia and also regulates inflammatory process due to its anti-inflammatory property. [6]

Tumor necrosis factor-alpha (TNF-α) is a principal regulator of inflammatory cytokine production and increases mediators of lipid signal transduction such as prostaglandins and platelet activating factor. [7] TNF-α play a critical role in the development of many chronic inflammatory diseases.

Development of insulin resistance and pathogenesis of T2DM are characterized by several stimulatory factors like generation of free radicals, epigenetic factors, stimulation of various transcriptional mediated pathways along with the production of various pro-inflammatory cytokines. TNF-α is one the most important immune

modulator that is involved in the development of insulin resistance and pathogenesis of T2DM.

TNF-α is primarily produced in adipocytes and induces tissue-specific inflammation through the involvement of generation of reactive oxygen species and activation of various transcriptional mediated pathways. The increased level of TNF-α induces insulin resistance in adipocytes and peripheral tissues by hampering the insulin signalling through the phosphorylation of serine that leads to the development of T2DM. [8]

AIMS AND OBJECTIVES:

The aim of our study is to compare the serum level of inflammatory marker TNF-α in patients of depression with diabetes mellitus and in patients of depression without diabetes mellitus.

MATERIAL & METHODS:

The study was conducted in Department of Biochemistry and Department of Psychiatry of M.G.M. Medical College and M.Y. Hospital Indore, after approval from institutional ethical committee from march 2019 to march 2020, includes 100 subjects of age group 45-65 years out of whom 50 were diagnosed patients of depression having diabetes mellitus (case group) and 50 were age and gender matched diagnosed patients of depression not having diabetes mellitus (control group).

Demographic characters like Age, height and weight were recorded and their BMI were calculated.

Patients were diagnosed by using ICD-10 criteria for depression and 2011 ADA criteria for diabetes mellitus. The written consent of patients was taken before starting the study.

Inclusion Criteria:

Patients with age group 45-65 years and both genders were taken. Cases include clinically diagnosed patients of depression with diabetes mellitus and controls included patients of depression without diabetes mellitus attending Psychiatric OPD in M.Y. Hospital.

Exclusion criteria:

Patients with atypical depression, recurrent depression, bipolar depression and any other psychiatric disorders, Subjects on antidepressant therapy, patients of diabetes mellitus on insulin therapy, previous history of any chronic kidney or liver disease or any inflammatory disorders, Patients with active bacterial, viral, fungal infection, Patients having dependence of alcohol or smoking, Patients having mental retardation, cancer, bed ridden patients.

Investigation Procedure:

Venous blood (5 ml) sample was withdrawn with aseptic precautions from the antecubital vein following overnight fasting. The blood sample was collected in clot activator tube and serum was separated. The serum was analysed for biochemical investigations on same day and remaining samples were preserved for further biochemical investigations at -20°C.

Measurement of Serum TNF-α is done by Enzyme Immunoassay (EIA) on Thermo-fisher ELISA reader in clinical Biochemistry laboratory of M.Y.Hospital Indore.

Data Collection and Statistics:

The data were expressed as mean ± standard deviation. SPSS version 20 software was used for statistical analysis. Unpaired Student t test was applied to compare TNF-α between two groups (control & cases). P values less than 0.05 was considered significant.

Table 1. Baseline Demographic characteristics between Case & Control

Characteristics	Control (n=50)	Case (n=50)	p value
Age	52.27 ± 5.06	52.31 ± 5.06	0.97
Gender (M : F)	26:24	19:31	0.159
Weight	63.2 ± 10.8	62.1 ± 7.8	> 0.05
Height	165.6 ± 6.5	164.8 ± 4.9	> 0.05
BMI (Kg/m^2)	22.8 ± 3.2	22.3 ± 2.4	> 0.05

Table 2. Comparison of Biochemical parameter between Case & Control

Biochemical parameter	Control (n=50)	Case (n=50)	p value
TNF-α (pg/ml)	10.19 ± 5.05	28.98 ± 16.47	<0.05

P value <0.05 was taken as statistically significant

RESULTS:

Baseline demographic and clinical characteristic of the participants are presented in Table1.The mean (± SD) concentrations of TNF-α in the case group and the control group were 28.98 ± 16.47 pg/ml and 10.19 ± 5.05 pg/ml respectively. The difference was statistically significant (P < 0.05) (Table 2).

DISCUSSION:

Many studies found effects of TNF-α has an important role in metabolism of serotonin and on the hypothalamic-pituitary-adrenal axis, which influences changes in the structure and function of the brain and leading to the development of depressive symptoms.

Infusion of TNF- α in lower animals responsible for some symptoms like: decreased social behaviour, decreased activity, decrease food intake, sleep abnormalities, fatigue, and alterations in cognition. These symptoms are similar to the symptoms of human depressive patients. These symptoms are blocked by co-administration of an anti-TNF-α antibody. [9]

Emanuele F et al., [10] in their study found that serum TNF-α levels were significantly higher in patients with depression (p< 0.0001). previous study by Wei Zou et al., [11] revealed that serum levels of TNF-α significantly correlated with severity of depression (p < 0.05) on HAMD rating scale of depression and higher TNF-α levels were associated with higher HAMD scores.

TNF-α induces insulin resistance by phosphorylation of serine residue of insulin receptor substrate-1 (IRS-1), which impairs insulin signalling. So, TNF-α is may be playing a major role in the pathophysiology of insulin resistance and development of diabetes mellitus. [12]

A study by Plomgaard P et al., [13] found that TNF- α plays a role in the metabolic syndrome and patients with diabetes show increase expression of TNF- α mRNA in skeletal muscle and increased TNF- α levels in plasma. The adipose tissue, which produces TNF- α, is likely the main source of the circulating TNF- α. Recently, it was revealed that TNF- α administration in healthy humans induces insulin resistance in skeletal muscle. TNF- α directly impaired glucose uptake and metabolism by altering insulin signal transduction. This information provides a molecular connection between low-grade systemic inflammation and insulin resistance. [13]

In our study, the levels of TNF-α in the patients of depression with diabetes mellitus (Case group) is found significantly higher than the levels of TNF-α in patients of depression without diabetes mellitus (control group) (p value <0.05). It is evident from many researches that inflammation plays an important role in pathophysiology of depression and diabetes mellitus. These results were consistent with various studies who revealed that higher level of serum TNF-α is seen in depression and diabetes mellitus.

Early assessment of TNF-α level in patients of depression and diabetes mellitus could modify the disease progression and limits their associated co-morbidities.

CONCLUSION:

This case-control study shows that greater elevation of inflammatory marker TNF-α level in patients of depression with diabetes mellitus (Case group) as compared to patients of depression without diabetes mellitus (control group). Inflammatory pathways playing pivotal roles in the development and progression of depression, diabetes & their complications. These pathogenic factors can be used as a prognostic tool for future new therapeutic approach in depression and diabetes mellitus. Further clinical studies with larger sample size are required to address the significance of inflammation in pathogenesis depression and diabetes.

Limitation of the Study

The limitation of this study lies in its relatively small sample size.

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Conflict of interest: Nil

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