



# IL-6, TNF- $\alpha$ and Incidence of Delirium After Femur Fracture in Diabetes Patients

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## ABSTRACT

This study aimed at investigating Comparison Interleukin 6 and TNF- $\alpha$  and Incidence of Delirium before and after femur fracture in Patients with Type 2 Diabetes. In order to reach the research goals, 30 patients who were referred to Taleghani Hospital were selected by available sampling method. In order to measure the variables of study, the CAM tool and the measurement of IL-6 and TNF- $\alpha$  were used before and after surgery. The correlated T-test was used to analyze the data. The findings indicated that 5 diabetic patients who were taking part in study after the operation had delirium. The findings indicated that IL-6 and TNF- $\alpha$  levels were different before and after surgery. Comparison of means showed that these indices were significantly increased after surgery. Generally, it can be stated that delirium is a common problem among the diabetic patients and we face it after surgery days. It is suggested that hospital staff receive the essential trainings to prevent, diagnose and treat it on time.

**Key Words:** Delirium, Diabetes type 2, IL-6, TNF  $\alpha$ , Surgery, Fractures

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## INTRODUCTION

According to the World Health Organization (WHO), the prevalence of diabetes is risen from 4% in 1995 to 5.4% in 2025, hence about 140 million patients at the end of the 20<sup>th</sup> century will reach to 300 million in 2025. The amount of increase is higher in the developing countries. Type 2 diabetes is the most common metabolic disease in the world, and the World Health Organization has predicted that mortality will double from type 2 diabetes between the years 2005-2030 [1].

Surgery and anesthesia are accompanied with serious effects on the body metabolism so that the further knowledge of carbohydrate metabolism, insulin therapy, proper management of this disease, and the mortality rate and subsequent pathogenesis decrease significantly. In fact, the correct treatment of these patients during the operation reduces acute metabolic events and, consequently, decreases mortality and disability, accelerates the process of wound healing, decreases infections, and shortens the length of hospitalization in patients. Stress and trauma which is caused during surgery and also induction of anesthesia,

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increase the level of counter-regulatory hormones (catecholamine, glucagon, cortisol and growth hormone) and also decrease secretion of insulin. Moreover, the insulin efficiency is reduced due to the increased level of these hormones. Metabolic effects can be expected in such a setting of hormonal changes [2,3,4]; including: 1- hyperglycemia, 2- reduction in glucose consumption (via containment of glycogenesis and glucose uptake), 3- increase in glucose production (due to increased gluconeogenesis and glycogenesis), 4- increase in protein catabolism, 5- increase in lipolysis and production of Keton bodies, 6- On the other hand, it will cause in short or long-term effects such as dehydration and hemodynamic instability (due to osmotic diuresis, negative nitrogen balance) which in turn leads to disorders of wound healing and muscle mass loss, fat tissue loss and energy stores, and finally leads to the loss of amino acids, vitamins and minerals. It should be noted that neuroaxial anesthesia compared to general anesthesia is associated with lower levels of glucose metabolism. In general, the severity of these metabolic responses during the procedure depends on the duration of surgery, the severity of the underlying disease, the type of diabetes, the presence of infection and the type of anesthesia [5].

One of the consequences of surgery is Delirium. Delirium can cause events and complications that, in general, lead to an increase in the length of hospitalization time, reduction in patients' independent operation, reduction in cognitive operation of patients, and even increase in mortality and death, which ultimately result in worsening the surgical outcomes [6]. Each year, \$ 150 billion is spent in the United States regarding the delirium, and since about 40% of the patients are preventable, recognizing and evaluating the factors involved in it in order to reduce the incidence, in addition to reducing the cost of treatment, cause reduction of healthcare costs [6].

So far, various studies have been conducted to investigate the cause and pathophysiology of delirium, and contrary to the high number of studies, in order to identify the risk factors of delirium, investigations for finding molecular mechanisms out are inadequate [7]. However, several hypotheses have been proposed for the pathology of this disorder, in which the hypothesis of Imbalance Neurotransmitter and Impairment Inflammatory are more frequent than others [8]. Increasing the age can increase inflammatory factors, which in some studies is called in short inflammaging, and this phenomenon has local and systemic effects in

the body and can directly affect certain incidence of diseases, including delirium [9, 10].

Several studies have been conducted to identify the risk factors associated with the type of disease or surgery (duration of surgery, the amount of bleeding, duration of the tourniquet time, etc.) that have been implicated in the incidence of POD or POCD. However, diabetes as an inflammatory factor and the incidence of POD or POCD, and the level of blood and serum inflammatory factors such as IL-6 and TNF- $\alpha$  have not been studied. Therefore, the aim of this study was to investigate the relationship between incidence of delirium after operation of intertrochanteric fracture surgery with level of Cerebrospinal and blood fluid before operation of IL-6 and TNF- $\alpha$  in patients with type 2 diabetes under spinal anesthesia.

## METHODOLOGY

The study was a single-blind clinical trial. The research population was all diabetic patients over 60 years old with intertrochanteric fracture, under spinal anesthesia, which was selected through available sampling method for 30 patients who referred to Taleghani Hospital. All referred diabetic patients were included in the study to complete the sample size.

## METHOD

Patients aged 60 or above 60 with type 2 diabetes that were referred to Taleghani Hospital due to acute proximal lower-extremity fractures were candidates of the orthopedic surgery, and were first asked about diabetes. Then for diabetic patients, a questionnaire was filled including demographic information such as age, sex, background of smoking, medical background such as the duration of diabetes, background of blood pressure, background of cardiovascular disease, background of cerebrovascular abnormalities such as stroke, transient ischemic attacks, and background of environmental vascular diseases. Patients with drug addiction, pathologic fracture, THA operation, more than 3-hour length of surgery or contraindication, or failure to perform spinal anesthesia or patient who are not pleased to participate in the study were excluded. Before and during operation in order to get the best metabolic status, blood glucose levels were controlled in the range of 120-180 mg / dl. After filling out the questionnaire and assessing the cognitive status of patients by CAM and then performing the femoral block in Quincke 25 G needles under sterile conditions, they were subjected to PL under and 1 cc samples of CSF were sent to the laboratory and were subjected to

anesthesia of the spinal cord by injection of Local Anesthetic in the intrathecal space. At the same time, a blood sample was sent to the laboratory to measure IL-6 and TNF- $\alpha$ . Duration of surgery was recorded according to the anesthetic sheet and the amount of bleeding was recorded by counting blood gases and estimating amount of blood in suction. After surgery, POD was evaluated by MCA on the first and third day after surgery. The CAM tool was used to measure the delirium.

**CAM:** The CAM tool is set up based on DSM-III criteria and has 9 main items, including sudden and volatile initiation, thought disorder, change in level of consciousness, memory impairment, perception disorder, behavioral disorder such as restlessness or slow motion, and sleep disturbance. Data is collected on the basis of an open question and requires the ability to speak in patients. After psychosocial assessment by MMSE<sup>1</sup>, the physician will be able to assess the patient's delirium using the CAM<sup>2</sup> tool. Completion of this tool takes 20 minutes and should be filled by experienced people. If it is used by non-physicians, its sensitivity decreases. The tool has a sensitivity of 92.8% [11, 12]. In analyzing data, the meanings, standard deviations, frequency, tables and charts were used to categorize and summarize the collected data. In examining statistical pre-requisites according to the number of observations in each distribution, the Kolmogorov-Smirnov test was used to verify the natural distribution of the data. According to statistical assumptions, correlated T-test at 95% confidence level to compare the variables before and after the operation and the version 22 statistical package were used.

## RESULTS

At the beginning of the study, out of 38 volunteers, 30 patients were selected to participate in the study. The participants in the study consisted of 18 (60%) women and 12 (40%) men. The age range was 60-75 years old and the mean age was 68.5 years. Delirium evaluation was performed by the anesthetist on the first and third days after surgery. The results of the study indicated that on the first day, delirium symptoms were observed in 5 patients. The other two had symptoms but were not diagnosed by Delirium anesthetist. On the third day, two patients remained in this condition, and the rest of the patients returned to normal status. The results of Kolmogorov's test represented that the distribution of data was normal ( $P > 0.05$ ). The

evaluation of blood parameters before and after the operation indicated that IL-6 and TNF- $\alpha$  levels were different before and after surgery (Table 1). The compared means indicated that these indices were significantly increased after surgery.

Variable	Average and Standard Deviations		Degrees of Freedom	t	P
	Before surgery	After surgery			
IL-6	Before surgery	1.54±0.74	29	1.22	0.015
	After surgery	1.95±0.87			
TNF $\alpha$ (g / L)	Before surgery	13.12±4.32	29	1.38	0.000
	After surgery	15.57±5.11			

**Table 1.** The Results of Correlated T-Test Analysis before and after the Operation of IL-6 and TNF- $\alpha$  Indices

## DISCUSSION AND CONCLUSION

This study aimed to investigate Comparison Interleukin 6 and TNF- $\alpha$  and Incidence of Delirium before and after femur fracture in Patients with Type 2 Diabetes.

The findings indicated that 5 diabetic patients had delirium after the surgery. Other findings indicated that IL-6 and TNF- $\alpha$  levels were different before and after surgery in a way that the comparison of means indicated that these indices were significantly increased after surgery. These findings are consistent with the results of [13,6]. For example, [13] conducted a study on patients undergoing major knee surgery. In this study, patients underwent spinal anesthesia after femoral block. Significant results were found between the incidence of POD and POCD with levels of IL-5, IL-6, IL-8, MCP-1 and other inflammatory factors in plasma, as well as IL-6, TNF- $\alpha$  and interferon gamma in CSF. [6] measured the inflammatory cytokines in pre-operative samples with ELISA method, and in addition to the incidence of POD, the serum levels of these cytokines were examined for cognitive status and mortality in the hospital. As a result, in this study, the increase in IL-6 and decrease in IL-12 was associated with the incidence of POD; and high level of IL-6 before surgery was significantly associated with POD. Also, the high level of this inflammatory factor was associated with poor functional status, cognitive impairment, emergency admission and the burden of accompanying illnesses. Therefore, the serum level of IL-6 greater

<sup>1</sup> Mini Mental Status Examination

<sup>2</sup> confusion assessment method

than 9 pg / ml in this paper were presented as a risk factor in addition to the known risk factors of POD. Studies have indicated that the incidence of delirium varies depending on the severity of the disease, the used scale and the reasons for Hospitalization [14]. Studies have also indicated that the relative frequency of delirium is higher in patients with diabetes, hypertension and heart disease [15]. It seems that in the present study, diabetes had an important role in incidence of this disorder in subjects. In some other studies, the subjects with more than 65-year-old were considered to be in a risk factor of delirium [16, 17, 18]. In the present study, the mean age of patients was 68 years old, which could have an important role in the incidence of delirium in the subjects. Other findings indicated that levels of IL-6 and TNF- $\alpha$  in the postoperative period were significantly higher before the operation. In diabetic patients, it has been represented that expression of TNF- $\alpha$  gene, its protein content in the skeletal muscle and its serum concentration levels increase, which seems to be the main source of elevated serum levels of these cytokines in adipose tissue [19]. It can be said that surgery in the patients of the present study leads to an increase in inflammatory factors of IL-6 and TNF- $\alpha$ . Generally speaking, delirium is a common problem in diabetic patients and is evident during the post-operative days. It is suggested that hospital staff receive the necessary training to prevent, diagnose and treat it on time.

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