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Evaluation Of Serum Levels Of Cyclooxygenase-1 (COX-1) Among Patients With Type Two Diabetes Mellitus (T2DM)

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ABSTRACT: Type 2 diabetes results from a combination of genetic variants associated with insulin resistance and decreased insulin secretion, as well as environmental factors such as obesity, overeating, lack of exercise, stress, and age. the study aims to explore the association between serum levels of COX1 and diabetes mellitus. The study included 40 patients with type2 DM(20 males and 20 females) and their age range between and 40-80 healthy individuals. The amounts of cyclooxygenase-1in serum were determined using the enzyme-linked immunosorbent assay (ELISA) method. As control group and their age range between40-80(10 males and 10 females). Blood samples were collected from patients and control groups. The sample was divided into two parts, the first part was subjected to Trizol preservation and the other part for serum separation. The results of this study showed a decrease in the concentration of cyclooxygenase-1 (COX-1) in the sera from patients with T2DM compared with the healthy participants. The level of the patients was (0.1029 ± 0.0233) compared to the control group (0.121 ± 0.0361), P = 0.047. There was no significant difference when comparing the concentration of COX-1 among males of the studied groups: patient group 0.099 ± 0.0215 versus control group 0.1023 ± 0.0157, P = 0.642. Females with T2DM revealed a decrease in the concentration of COX-1 with a significant difference compared to the females of the control group 0.1068 ± 0.0250 versus 0.1405 ± 0.0411, P = 0.034 of the two groups respectively. No significant difference in the concentration of COX-1 corresponds to males and females of the patient group. According to the results of the current study, we conclude that: COX-1 is a major contributor to the onset of type 2 diabetes and there may be an association between low levels of cyclooxygenase-1and type 2 diabetes.

Keywords: Cyclooxygenase-1, T2DM, ELISA

Introduction

Type 2 diabetes is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise, and stress, as well as aging. It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents(Kaneto, 2015). T2DM is accompanied by severe oxidative stress which is caused by increased oxygen-free radical production. Toxic oxygen free radicals have been implicated in the pathogenesis of Diabetes mellitus, and its micro and macrovascular complications. An imbalance that results from

increased production and/or the reduced scavenging of these free radicals leads to a metabolic state of oxidative stress, which consequently leads to tissue damage (Gupta et al., 2013). Cyclooxygenase (COX) also plays an important role in the induction of pain and inflammation as well as the analgesic actions of NSAIDs (Khan et al., 2007).Prostaglandins (PGs), including PGD2, PGE2, PGF2a, PGI2, and thromboxane (TX)A2 (collectively known also as prostanoids) are produced from arachidonic acid by sequential actions of cyclooxygenases (COX-1 or COX-2) and specific synthases, and they exert their effects in autocrine and/or paracrine manner mainly through G protein-coupled receptors (GPCRs) at the cell surface.(Pannunzio, and Coluccia, 2018). Prostanoids are produced when arachidonic acid is released from the plasma membrane employing phospholipases and metabolized by cyclooxygenase (Cox) and specific isomerases. Prostanoid production depends on the activation of the 2 Cox isoenzymes within cells. Cox-1 is present in most cells, and its expression is generally constitutive, whereas Cox-2 expression is low in most cells. In the present study, the expression levels of COX-1Inpatient with type2 DM were evaluated. (Mullol et al., 2002).

Materials and Methods

The number of participants in this study was 60 individuals. They are classified into two parts:

1. The patient group consisted of 40 cases with T2DM (20 males and 20 females). Data recorded for all samples included: name, gender, age, other diseases, smoking, treatment, weight, height, body mass index, residence, occupation, patient's disease history, family inheritance, and sample collection history. . All patients were diagnosed using the American Diabetes Association (ADA) criteria.
2. The control group included 20 healthy individuals (10 males and 10 females). Their data was recorded as with the patients above.(2.5 ml) of venous blood sample was taken from both studied groups, using plastic syringes, the blood was transferred to a gel tube and the sample was allowed to coagulate for a few minutes at room temperature, followed by separation of the serum from the clot by centrifugation for 10 minutes at 2000g. The serum was then divided into several aliquots in Eppendorf tubes, labeled, and stored at −20 °C until use.Serum amounts of cyclooxygenase-1were determined using the enzyme-linked immunosorbent assay (ELISA) method (My BioSource/USA) according to the manufacturer's recommendations. Data were collected and statistically analyzed.

RESULTS

The results of this study showed a decrease in the concentration of cyclooxygenase-1 (COX-1) in thesera from patients with T2DM compared with the healthy participants.The results indicated that there were significant differences, The level of the patients was**Mean+**SD for the patient's group (**0.1029 ± 0.0233**) compared to the control group **Mean+SD** (**0.121 ± 0.0361**), **P = 0.047**.

Table 1: COX1 Concentrations In The Sera From Patients and Control Groups.

Groups	Pg/ml Mean+SD
Control (N=20)	0.121 ± 0.0361
Diabetic Patients (N=40)	0.1029 ± 0.0233
P-value	0.047
Significance	*

*** Significant (P< 0.05)**

Groups	Elisa (Pg/ml)			
	Males	Females	P-value	Significant
Control	0.1023 ± 0.0157	0.1405 ±	0.019	*
Patient	0.099 ± 0.0215	0.1068 ±	0.303	N.S
P-value	0.642	0.034		
Significant	N.S	*		

Table 2: COX-1 concentrations In The Sera From Males and Females of Studied Groups.

Cyclooxygenase-1 (COX1) Concentrations Among Males and Females

patients group **0.099 ± 0.0215** versus control group **0.1023 ± 0.0157**,**P = 0.642** . The findings were contained in **Table (1)** that indicate the concentrations of COX-1 in the sera from patients and controls according to gender. There was no significant difference when compared the concentration of COX-1 among males of the studied groups:Females with T2DM revealed a decrease in the concentration of COX-1 with a significant difference compared to the females of the control group **0.1068 ± 0.0250**versus **0.1405 ± 0.0411,P = 0.034** of the two groups respectively. No significant difference in the concentration of COX-1 corresponds to males and females of the patient group.

N.S : Non- significant (P > 0.05) * significant (P < 0.05)

DISCUSSION

COX-1 has traditionally been regarded as a constitutively expressed enzyme that generates PGs forcell-cell signaling, blood clotting, and maintenance of renal function, tissue homeostasis, and gastrointestinal integrity (Vane, Bakhle, and Botting, 1998; Dubois et al., 1998). However, COX-1 is also thought to play a role in pathophysiological processes, including inflammation, arthritic disease, and cancer, and while there is evidence that COX-1 expression may be regulated, little is known about the mechanisms involved; Smith, Dewitt, and Garavito, 2000).

The results of this study showed a decrease in the concentration of cyclooxygenase-1 (COX-1) in the sera of T2DM patients compared to healthy subjects. There was a significant change in the level of cyclooxygenase-1 in the samples of the patient's group. These results are in agreement with previous studies, as results from similar studies of related ROS and COX1 levels at different periods showed that ROS production is directly proportional to COX1 levels (Verma, Chandra, and Banerjee, 2016).

The expression of The COX1 gene is induced by proinflammatory stimuli growth factors, cytokines, and mitogens in various cells (Choy and Milas, 2003). However, some workers suggested that it is unaffected by cytokines and inflammatory molecules (FitzGerald and Ricciotti, 2011).The COX1 expression level increases at the time of onset of diabetes and is associated with excess cardiovascular morbidity (Kiritoshi et al., 2003). Body fat excretes adipokines, which may be the most important factor in reactive oxygen species (ROS) production. Increased pro-inflammatory cytokines and activation of the inflammatory cascade are important factors in the development of insulin resistance and type 2 diabetes, so the new approach in the control of diabetes is modulating or inhibiting inflammation (King, 2008).

Studies have shown that prostaglandins are molecules of particular importance in the inflammatory response. The cyclooxygenase (COX) enzymes, COX1 and COX2 (also known as Prostaglandin combinations (PTGS), PTGS1, and PTGS2), are the rate-limiting enzymes in the production of Prostaglandins. PTGS2, which is induced in the inflammatory response, is responsible for the majority of prostaglandins present during the immune response to inflammation (Gupta and Dubois, 2001).

The higher enzyme level in females compared to males may be due to the increased energy expenditure associated with physical activity in males compared to females.Therefore, oxidative stress is higher in women with diabetes than in men due to increased fat and body mass.This study is consistent with what was concluded (Soleiman FA, Pahlavani N, Rasad, 2013) which confirmed that high triglycerides increased by 50% in women compared to men, which is the main cause of oxidative stress, which in turn stimulates the rise of cyclooxygenase.

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