Short Communication

Prediction of Protein Kinase A with Type 2 Diabetes Mellitus and Its Relation with Insulin and Homeostasis Model Assessment Insulin Resistance in Najaf Patients

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Abstract

Background: In the world, chronic disease represents the predominant illness. Autoimmune disease, β-cell dysfunction, and obesity are the main causes of type 2 diabetes mellitus (T2DM). The signal transducer for several external stimuli, which acts as a second messenger, is protein kinase A (PKA). It is accompanied by disease and controls several biological processes. **Objectives:** To study the amount of PKA in diabetic mellitus type 2 and its correlation with insulin and homeostasis model assessment insulin resistance (HOMA-IR) in Najaf patients province. **Materials and Methods:** In total, 120 subjects, 60 diagnosed with chronic diabetes mellitus type 2, and 60 healthy subjects were enrolled in the current study. Age ranged between 35 and 60 years for patients and healthy. PKA and insulin levels in serum were estimated by enzyme-linked immunosorbent assay technique, while HOMA-IR was calculated by the Tjokroprawiro method. **Results:** In T2DM, serum PKA levels significantly decreased in patients compared with control group ($P < 0.001$). On the other hand, this study observed a significant (P value < 0.001) negative, weak correlation for PKA with insulin and nonsignificant (P value > 0.05) no correlation with HOMA-IR in DM patients. **Conclusion:** Among T2DM patients in Najaf province, a decrease in the level of PKA, insulin, and HOMA-IR in patients; indicates a significant link with the progression of chronic T2DM.

Keywords: Diabetes mellitus, HOMA-IR, insulin, protein kinase A (PKA)

Introduction

A chronic condition (diabetes mellitus [DM]) happens during the inability of pancreas for the production of enough amount of insulin or when the insulin production is ineffective.[1,2] These effects might be balanced by regular medical checkups and adequate health management.[3]

Cardiovascular disease, chronic kidney failure, stroke, foot ulcers, and eye impairment are all serious long-term complications for untreated diabetes patients.[4] Type 2 diabetes mellitus (T2DM) represents about 90%–95% of patients who are obese or undiagnosed for several years because of the gradual development of hyperglycemia.[5]

The new strategies of the American Diabetic Association in 2019 revealed the importance of home health care for older adults with T2DM; they might need recurrent interference and home nursing.[6]

The International Diabetes Federation in 2009 reported that the prevalence of diabetes is noticeable in the developing counties of the world, and in 2030 about 438 million people will be living with diabetes.[7]

Insulin production is reduced or impaired when there is an autoimmune illness that affects pancreatic cells, so that is called type 1 DM, while decreased insulin secretion

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_369_23

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Submission: 28-Mar-2023 **Accepted:** 19-Apr-2023 **Published:** 23-Jan-2026

How to cite this article: Yousef TK, Al-Gazally ME, Bayati AA. Prediction of protein kinase A with type 2 diabetes mellitus and its relation with insulin and homeostasis model assessment insulin resistance in Najaf patients. Med J Babylon 2025;22:1539-43.

and insulin resistance are the main causes of type 2 DM, which impairs the utilization of insulin.[8]

T2DM is a combination of two factors: insufficient production of insulin and decreased sensitivity of tissues to reply to insulin.[9]

Pancreatic β-cells of Langerhans secreted the polypeptide hormone Insulin, which is comprised of 51 amino acids with a molecular weight of 5808 Da. The islets consist of four specific hormone-producing cells α, β, δ, and PP-cells that yield glucagon, insulin, somatostatin, and pancreatic polypeptide, respectively.[10]

A variety of external stimuli are activated by the second messenger cyclic adenosine 3′-5′ monophosphate (cyclic AMP [cAMP]). It is related to disease and regulates a variety of organic processes.[11]

cAMP activated the most important effector proteins, like cAMP-dependent protein kinase A (PKA). It is a wide-specific serine/threonine kinase that controls several biological processes, including cell proliferation, metabolism, cell division, and myocyte contraction. PKA is a heterotetramer composed of two catalytic subunits (Cα, Cβ, or Cγ) that are sustained inactive in the holoenzyme by two homodimers RI (RIα or RIβ) or RII (RIIα or RIIβ) subunits.[12]

When cAMP binds to the R subunits, it releases and activates C subunits, which produce substrate phosphorylation.[13]

Adenosine triphosphate (ATP) produces cyclic AMP by adenylyl cyclase (AC), which is started by stimulation of Gα protein (Gsα) after activating Gs protein-coupled receptors. This process leads to the cAMP signaling.[14]

The stimulation of G protein-coupled receptors (GPCRs) starts cAMP/PKA signaling, followed by stimulation of Gs α, AC, and the production of cAMP. It stimulates PKA by attaching to PKA regulation subunits. The PKA tetramer released PKA catalysis subunits (C) for the phosphorylation of targets in the plasma membrane, cytoplasm, and nucleus. PKA subcellular localization (AKAPs) required the attachment of R subunits to various A kinase anchoring proteins, and the ending of cAMP signaling required the breakdown of cAMP to AMP by phosphodiesterase.[15]

T2DM is characterized by the impairment in insulin secretion from β-cells of pancreas.[16] The levels of serum glucose is elevated after meal that causes elevated glucose intake into β cells by GLUT2 (the transporter of glucose). Higher level of glucose in cell leads to produce ATP, inhibition of the ATP-sensitive potassium channel (KATP) and cell depolarization. Cell depolarization motivates calcium channel on the plasma membrane and entry calcium to β cells. When Ca^{2+} increase in the cell stimulates insulin secretion. At that point, insulin flows and actions on different tissues to stimulate uptake of glucose and inhibition of production of glucose. This method is vital for the control of postprandial glycemic.[17]

cAMP/PKA controls the activities of molecules responsible for the secretion of insulin, including KATP, GLUT2, and Cav. GLUT2 is phosphorylated by PKA in the carboxyl-terminal after stimulation of β cells by either skolin or GLP1; suppression the action of GLUT2 leads to reduces glucose uptake into β cells by PKA-dependent phosphorylation.[18]

A constant amount of insulin is provided in the body to eliminate extra glucose from the blood. In hypoglycemia, the body starts to utilize fat as a source of energy by lipolysis (removal of lipids from adipose tissue to the liver).[19]

Materials and Methods

This study was done in private and government laboratories, and the samples were collected from Al-Sader Hospital, Diabetes and Endocrinology Center, Najaf during the period from the first of September until the first of January 2023. the serum glucose and hemoglobin A1c were measured by spectrophotometer, serum PKA and insulin were measured by enzyme-linked immunosorbent assay, while homeostasis model assessment insulin resistance (HOMA-IR) was used = [fasting plasma glucose (mg/dL) × fasting insulin(μU/mL)]/405.

Questionnaires were created to collect data from the control and patients group. In this case–control study, there are two groups: the first includes patients with DM, and the second includes those who appear to be healthy.

Ethical approval

All participants in this study were informed before collecting samples, and a verbal agreement was obtained from each of them. The protocol of the study and the information on the subject and agreement form were revised and accepted by a local ethics committee rendering to document number 14 on June 7, 2022.

Inclusion criteria

A patient who has been diagnosed with T2DM, patients without chronic complications of T2DM, all subscribers must be 30 years or more.

Exclusion criteria

Immune disease, pregnancy or lactation, patient with chronic liver disease, patient with a thyroid problem, patient with nephropathy, patient with hypertension, patient with cardiovascular disease, a patient who takes insulin as treatment, patient with DM type 1, history of ketoacidosis, cancer, patient on corticosteroid or thyroxin treatment.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS, IBM Company, Chicago, IL 60606, USA). Categorical variables were described by frequencies and percentages. Means ± SD were employed to represent continuous variables. To compare the means of the two groups, an independent *t*-test was applied. The Pearson correlation coefficient was used to assess the relationship between two continuous variables. A *P*-value of less than 0.05 was regarded as significant.

Results

The results showed that there was a significant difference in PKA level between T2DM and the control group ($P < 0.001$) [Tables 1 and 2; Figures 1 and 2].

The mean of HOMA-IR in T2DM patients and control groups was a significant difference at $P = 0.001$, as illustrated in Tables 3.

Table 1: Mean and standard deviation of protein kinase A in type 2 diabetic mellitus compared with control

Parameters	Patient ($n = 60$) Mean ± SD	Control ($n = 60$) Mean ± SD	*P*-value
PKA (pg/mL)	481.83 ± 19.76	641.22 ± 20.35	0.001

Table 2: Mean and standard deviation of insulin and FBG in type 2 diabetic mellitus compared with control

Parameters	Patient ($n = 60$) Mean ± SD	Control ($n = 60$) Mean ± SD	*P*-value
Insulin (µU/mL)	4.05 ± 0.07	2.14 ± 0.06	0.001
Fasting blood glucose (mg/dL)	213.65 ± 9.21	101.86 ± 5.84	0.001

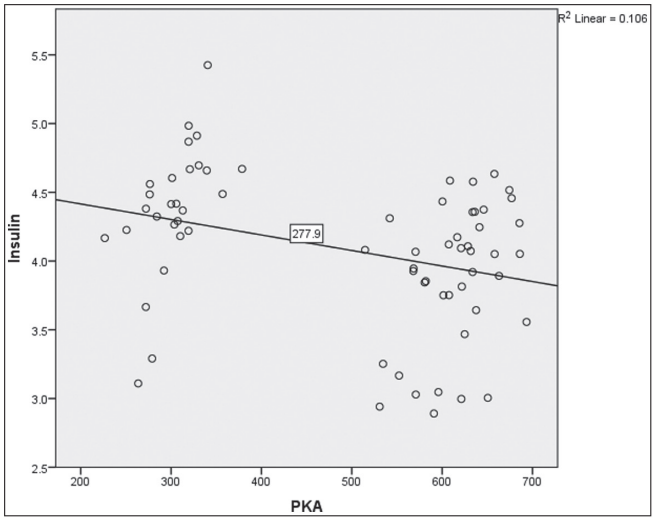

Figure 1: Correlation between PKA with insulin

Personal correlation between PKA, insulin, and HOMA in T2DM between patients and control [Table 4].

Discussion

In this study, the result revealed that there were significant differences in PKA levels between male patients and its control. We believe that the decrease in PKA level in diabetic patients is due to hyperglycemia, which leads to inhibition of the protein synthesis and as a result, decrement PKA level. In addition, hyperglycemia leads to the glycated of this enzyme molecule and a decrease in its activity. Our results are in agreement with the results of the study of Pernicova and Korbonits,[20] they concluded that metformin works by decreasing hepatic gluconeogenesis and blocking the action of glucagon to reduce blood glucose levels. Inhibition of mitochondrial complex I causes cAMP and PKA signaling to be disrupted in response to glucagon. On the same direction, cAMP/PKA signaling in different tissues has pleiotropic effects on whole-body glucose homeostasis and regulates glucose metabolism at multiple levels. Genetic and

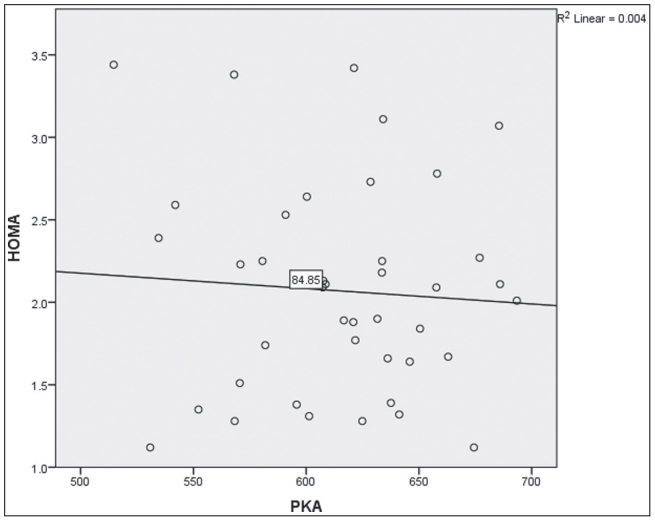

Figure 2: Correlation between PKA with HOMA

Table 3 Mean and standard deviation of HOMA-IR in type 2 diabetic mellitus compared with control group

Parameters	Patient ($n = 60$) Mean ± SD	Control ($n = 60$) Mean ± SD	*P*-value
HOMA-IR	2.13 ± 0.09	0.51 ± 0.02	0.001

Table 4: The correlation of PKA with other parameters in the patients' group with T2DM

Parameters	PKA	*P*-value
Insulin	-0.33**	0.007
HOMA	-0.09	0.514

**highly significant

pharmacological studies in animal models suggest that selective activation of cAMP/PKA pathway in pancreatic β cells or selective inhibition of cAMP/PKA pathway in liver can be safe and effective in improving glycemic control in T2DM.[21]

The current result revealed that there was a significant increase in insulin levels in the patient; the current study agreed with A-hakeim *et al.*,[22] which indicated that the obese diabetic patients had a higher insulin level than control group representing hyperinsulinemia in those obese patients.

The longer term of diabetes duration makes the body more resistance for insulin.[23]

Inconsistently, obese persons have a higher level of insulin, proposing that they might be "resistant" to these hormone effects. Previous studies displayed that lower levels of insulin motivate appetite and intake of energy and suppress expenditure of energy.[24]

The current result revealed significant elevated of HOMA-IR level in-patient, as shown in Table 3. The patient with type 2 have high level of insulin, which lead to insulin resistance and consequence to elevated the level of HOMA which followed by a complication such as cardiovascular disease, hypertension, nonalcoholic fatty liver disease and certain forms of cancer.[25]

In prediabetes or nondiabetic subjects, HOMA2 is more predictive than HOMA1 for the development to diabetes.[26]

Increased Insulin resistance accrued may be because of high adipose tissue. So, the patient has low lipolysis and has high lipogenesis. Adipose tissue elevated free fatty acids that contribute to insulin resistance.[27]

In overt T2DM patients, secretion of insulin seems to be the main factor of diabetic control. These patients treated with metformin alone or with a two-drug therapy metformin and glyburide.[28]

The results revealed that there was a significant increase in insulin levels in serum between patients and its control ($P < 0.001$).

The results of the present study are in accordance with those of (Ulfris and Lukshmy) based on the results of the present study, the HOMA method was concerned to select diabetics with insulin resistance. Two factors have strongly directed us for HOMA implication.[29]

First is the widespread use of HOMA-IR in previous studies. Second, more than 85% of the patients who participated were overweight or obese. Accordingly, the data of the HOMA technique is probably used for the selection of type 2 diabetic patients with insulin resistant.[30]

The T2DM group had the highest HOMA-IR index and lowest HOMA%S (QUIKI).[31] Also obesity, another important factor that trigger the progress of IR and T2DM. Besides, a sedentary lifestyle is another risk factors of T2DM and the value of exercise to increase insulin signaling and glucose metabolism cannot be overstated.[32] Abnormalities of lipid metabolism go with obesity and T2DM produced by IR. This disorder is characterized by hypertriglyceridemia and low HDLc levels.[33-35]

Conclusions

Mean PKA, insulin, and HOMA-IR levels high in diabetic patients. Insulin sensitivity is lower in diabetic patients than in control group. Obesity and T2DM are dangerous combinations of health and consequences according to the most measured parameters.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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