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Assessment the role of Kidney injury molecule- 1 , Endostatin, and Insulin resistance in patients with Diabetic nephropathy in Kirkuk /Iraq

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Abstract:

The current study aims to determine the levels of kidney injury molecule KIM-1, endostatin, insulin, glucose and insulin resistance in patients with diabetic nephropathy, the experiment was conducted for the period from the beginning of July 2023 until the end of October 2023 Blood samples were collected from patients visiting Kirkuk General Hospital and specialized medical clinics in Kirkuk City, and included (70) male patients with diabetic nephropathy with ages of (35-75) years and an average weight of (79) kg, as well as a number of healthy people with the same average age and weight of patients, the study samples were distributed as follows: The first group of control group included (20) healthy males and the second set of patients was divided into four subgroups according to age groups, The patients in the study were categorized based on age as follows: 16 patients in the 35-45 age group, 17 patients in the 46-55 age group, 20 patients in the 56-65 age group, and 17 patients in the 66-75 age group. The study's findings indicated a noteworthy rise ($P \leq 0.05$) in the levels of kidney injury molecule KIM-1, and endostatin, insulin, glucose, and insulin resistance in patients with diabetes compared to the control group, either by age groups, the results showed no significant differences in the concentrations of kidney injury molecule KIM-1, endostatin, glucose and insulin resistance in patients with diabetes. In contrast, insulin concentration by age groups showed significant differences in patients with diabetes, as the first group showed a significant increase compared to the rest of the groups.

1. Introduction:

Diabetes Mellitus is a chronic metabolic disorder characterized by hyperglycemia, which appears as a result of impaired insulin production or secretion or the inability of cells to respond to insulin; most of the diagnosed cases fall into type 1 diabetes and type 2 diabetes (1). The prevalence of diabetes worldwide is increasing for adults aged 20-79 years and is expected to rise from 10.5% in 2021 to 12.2% by 2045 (2). Diabetes risk is linked to various genetic and metabolic elements, in addition to factors such as genetics, ethnicity, family medical history, and a prior history of gestational diabetes, as well as increasing age, overweight, and obesity, the risk of developing the disease as unhealthy diet and lack of exercise and smoking contribute to the increased risk of diabetes, there are also social and demographic risk factors associated with diabetes (3). Nephropathy is an indicator of kidney dysfunction, and kidney damage caused by diabetes can be severe once the kidney becomes unable to perform its functions regularly, including blood filtration. Then it is the result of kidney failure (4) Early diagnosis is essential to regulate risks and slow the progression of the disease, so it requires the identification of early and reliable physiological indicators to detect kidney damage associated with diabetes, and many physiological indicators were used on Recent global level for prediction and diagnosis in cases of kidney disorder are the kidney injury molecule-1 (KIM-1) and endostatin protein (ESP) (5, 6). Kidney injury molecule-1 (KIM-1) is a glycoprotein of type 1 that is produced by epithelial cells in the adjacent renal tubules, serving as a novel early indicator of renal impairment. (7); endostatin is a protein associated with the C-end of collagen found in the basement membrane of endothelial cells and acts as an antiangiogenesis protein that prevents vascular endothelial spread, migration and tube formation (8). Insulin is a hormone synthesized by the beta cells within the pancreas, playing a vital role in enabling the body to utilize glucose obtained from the digestion of food as its primary energy source. (9). Insulin resistance (IR) is a low physiological response to insulin stimulation or an imbalance in insulin control of glucose metabolism in target tissues in the muscles and liver (10). The current study aimed to test recent indicators as predictors of disease progression and diagnostic markers of diabetic nephropathy, which included both Kidney injury molecule and Endostatin and knowledge of insulin concentrations, glucose, and resistance insulin in people with diabetic nephropathy.

2. Materials and methods:

Study Design:

The research took place from July 2023 inception through October 2023 conclusion.at Kirkuk General Hospital and specialized medical clinics in Kirkuk City. It included (70) male patients with diabetic nephropathy at the ages of (35-75) years, and an average of weights (79) kg, as well as a number of healthy people with the same average age and weight of patients, and the study samples were distributed into two groups. The first group, the control group, included (20) healthy males, and the second group, the patient group, were distributed into four groups according to age groups: there were 16 patients in the 35-45 age group, 17 patients in the 46-55 age group, 20 patients in the 56-65 age group, and 17 patients in the 66-75 age group.

Blood samples

Blood samples were obtained from patients via a 5 ml venous draw and were then transferred into glass tubes that contained gel, as well as into vacuum tubes with gel and clot activator but no anticoagulant. The sample was left at room temperature for 30 minutes to coagulate, and the tubes were placed in a centrifuge for a duration of 15 minutes, rotating at a speed of 3000 rpm to acquire serum.

Physiological and biochemical tests:

Estimation of concentrations of a set of physiological and biochemical indicators for the studied groups, including estimating the concentration of kidney injury molecule, endostatin and insulin through the use of ready-made analysis kits (Kits) from the manufacturer Sunlong of origin using the ELISA type Sandwich-ELISA technology as a method, and determining the serum glucose concentration was carried out utilizing a specialized, pre-made kit of French origin from Biolabo. according to method (11), an enzymatic method in which oxidation occurs. For glucose, insulin resistance (IR) was calculated by knowing the concentration of glucose and insulin in blood serum and was performed via the HOMA2 calculator.(12)

Statistical Analysis:

Statistical analysis of the results was performed using the SPSS software program based on the T-test test, where the averages of patients and healthy people were compared at a significant level ($P \leq 0.05$). The ANOVA test was used to compare between age groups and at a significant level ($P \leq 0.05$), and the values of the variables were described as a standard deviation ± Mean (13).

3. Results and discussion:

Levels of the kidney injury molecule KIM-1 in individuals with diabetes compared to a control group.

The findings in Table (1) reveal a notable elevation ($P \leq 0.05$) in the levels of kidney injury molecule KIM-1 in diabetics, as it reached (763.48 ±112.05) pg/ml compared to the control group amounted to (475.01 ±94.98), the results of the current study agreed with the study (14) where they found that patients with diabetes have an increase in the concentration of KIM-1 in blood serum compared to healthy people. According to age groups, the results in Table (2) demonstrate that there are no significant variances among the different age groups, as the concentration of the kidney injury molecule Kim-1 in the first age group (35-45) amounted to (727.81 ±115.54) pg/ml), compared to (774.73 ±107.47) pg/ml, in the third age group (56-65) amounted to (776.25 ±112.64) pg/ml, and in the fourth age group (66-75), which amounted to (775.14 ±115.16) pg/ml.

Elevated levels of the kidney injury molecule KIM-1 in individuals with diabetic nephropathy are attributed to a disorder in the renal tubules and also due to nephritis caused by high sugar levels; as its levels increase in diabetic patients, this rise results in damage to the function of tubular cells and an increase in the permeability of epithelial cells after a

disorder in the renal tubules even if albuminuria levels are within normal limits (15). The increase in KIM-1 levels occurs with the progression of kidney disease, even when all other indicators, including blood urea nitrogen (BUN) or creatinine, remain within the normal range. This observation implies that as kidney damage advances, greater amounts of KIM-1 protein are released. Consequently, KIM-1 levels can serve as an early detection marker for diabetic nephropathy in individuals with diabetes (16).

Endostatin concentration in patients with diabetes and control group

The data presented in Table (1) reveal a notable elevation ($P \leq 0.05$) in the levels of endostatin in patients with diabetes, which amounted to (665.00 ±162.88) pg/ml compared to the control group, which amounted to (350.00 ±65.69) pg/ml. The outcomes were in line with the results of a study (17), which showed that high endostatin was significantly associated with the risk of DN diabetic nephropathy in patients with diabetes mellitus and had good predictive effectiveness. According to age groups, the results in Table (2) indicate that there are no statistically significant variances among the different age groups among patients with diabetes, as the concentration of endostatin in the first age group (35-45) amounted to (710.62 ±136.89) pg/ml and in the second age group (46-55) amounted to (640.58 ±181.19) pg/ml and in the third age group (56-65) amounted to (627.50 ±148.92) pg/ml and in the fourth age group (66 - 75) amounted to (684.70 ±180.93) pg/ml.

The elevated levels of endostatin in the blood of individuals with diabetes can be attributed to heightened synthesis of extracellular matrix (ECM) proteins, increased cell proliferation, endothelial cell dysfunction, in conjunction with tubular atrophy, interstitial fibrosis, and thickening of the glomerular basement membrane, as endostatin levels increase as a result of inflammation, oxidative stress, expansion of glomerular mesenteric cells and excessive glomerular filtration, and glomerular foot cell injury also contributing to the onset and progression of diabetic nephropathy (18). Renal tubular cells secrete endostatin in response to both inflammatory and fibrous stimuli, overexpression of endostatin leads to cellular tubular fibrosis, and several clinical studies have also shown that serum levels of endostatin were higher and were associated with progression of nephropathy in people with diabetes and other chronic kidney disease (19).

Insulin concentration in diabetic patients and control group .

The findings in Table (1) reveal a notable elevation ($P \leq 0.05$) in the levels of insulin in patients with diabetes, as it reached (18.55 ± 4.70) mg unit / l compared to the control group (13.34 ±1.68) mm unit / l, and the outcomes were in line with the results of a study (20), as they found an increase in the rate of insulin values in diabetics compared to the healthy group. In accordance with the different age groups, the data presented in Table (2) reveal a notable rise in the levels of insulin in the first age group (35- 45), which amounted to (21.45 ±4.98) mU / L, compared to the second age group (46-55) amounted to (17.12 ± 4.14) mU / L, the third age group (56-65) amounted to (17.57 ±3.70) and the fourth age group (66 -75) amounted to (18.39 ±5.19) mU/L).

The results are consistent with the findings of (21) as there was a gradual decrease in the secretion of the natural hormone insulin with age. The most common cause of high insulin

concentration in people with diabetes is the sequence of events suggests that insulin resistance, which involves a reduced response of muscle and fat cells to insulin's glucose uptake signals, precedes and triggers hyperinsulinemia. Consequently, insulin resistance is recognized as the fundamental imbalance responsible for the eventual development of metabolic syndrome, hyperglycemia, and type 2 diabetes, which may occur years or even decades later. However, in genome-wide association studies (GWAS), insulin resistance is emphasized as a key factor in type 2 diabetes. Nonetheless, a significant proportion of sites identified by GWAS point to deficiencies in the beta cells of the pancreas (22).

Glucose concentration in patients with diabetes and control group

The data presented in Table (1) reveal a notable elevation ($P \leq 0.05$) in the levels of glucose in diabetics, as it reached (217.27 ± 67.43) mg / 100 ml, compared to the control group that amounted to (103.40 ±5.95) mg / 100 ml and this result was consistent with the findings of (23) which showed that the high level of glucose in diabetics may be a result of a decrease in the percentage of secretion of the hormone insulin from pancreatic beta cells or due to a defect in the insulin receptors in the cells of the body, According to age groups, the results presented in Table (2) indicate that there are no statistically significant variations among the various age groups among patients with diabetes, as the concentration of glucose in the first age group (35- 45) amounted to (207.37 ±86.39) mg / 100 ml, and in the second age group (46-55) amounted to (225.29 ±58.56) mg / 100 ml, in the third age group (56-65) amounted to (218.60 ±63.48) mg / 100 ml, and in the fourth age group (66-75) amounted to (217.00 ± 65.48) mg / 100 ml.

High fasting blood glucose occurs in almost all diabetics, and this may be due to hormonal imbalance, which leads to increased glucose transport in the liver and increased glucose transport means an imbalance in glucose such as decreased liver sensitivity to insulin or decreased insulin, this causes an elevation in hepatic glucose production and a decrease in the utilization of glucose by peripheral tissues (24-25). Elevated plasma glucose levels can directly harm renal tubular cells, resulting in various metabolic and cellular dysfunctions. The overproduction of reactive oxygen species (ROS) and the initiation of the apoptosis pathway are interconnected mechanisms that significantly contribute to the progression of Diabetic Kidney Disease (DKD). While renal tubular cells have the highest mitochondrial content, foot cells, mesenteric glomerular cells, and glomerular endothelial cells can all experience mitochondrial damage as a consequence of diabetes (26-27).

Insulin resistance concentration in diabetic patients and control group

The findings in Table (1) reveal a notable elevation ($P \leq 0.05$) in the levels of insulin resistance in patients with diabetes, as it reached (9.80 ±3.42) compared to the control group that amounted to (4.21 ±1.11), the results agreed with a study (28), they observed a rise in the mean insulin levels and insulin resistance, measured by HOMA-IR, in the diabetes patient group when compared to the control group. When examining different age groups, the data in Table (2) indicate that there are no substantial variations in the insulin resistance levels among various age groups. In patients with diabetes, in the first age group (35-45) it reached (11.00 ±4.80), in the second age group (46-55) it reached (9.34 ±2.67), in the third age group

(56-65) it reached (9.50 ±3.34) and in the fourth age group (66-75), which amounted to (9.49 ±2.59).

High insulin resistance is attributed to possible reasons behind the development of insulin resistance and these causes include genetic abnormalities of one or more proteins of the insulin action chain and an increase in obesity(29), insulin resistance is a component of a cluster of cardiovascular and metabolic disorders often known as "insulin resistance syndrome" or "metabolic syndrome(30)." This collection of irregularities can potentially give rise to type 2 diabetes, atherosclerosis, hypertension, or PCOS, contingent on the individual's genetic predisposition and the emergence of insulin resistance (31-33). Individuals with insulin-induced glucose-induced glucochasty absorption impairment in muscle tissue and adipocytes, as well as impaired hepatic glucose production, individuals experiencing insulin resistance are characterized by a multifaceted pathophysiological state marked by diminished sensitivity and compromised capacity to curtail glucose production and enhance peripheral glucose removal. This condition is frequently accompanied by hyperinsulinemia as a compensatory mechanism to uphold blood sugar equilibrium (34-35).

Table (1) Concentrations of kidney injury molecule KIM-1, endostatin, insulin, glucose, insulin resistance in diabetics and control.

Group / Variables	Patient	Control
KIM-1	**112.05 ±763.48 a**	**94.98 ± 475.01 b**
Endostatin	**162.88 ± 665 a**	**65.69 ±350 b**
Insulin	**4.70 ±18. 55 a**	**1.68 ± 13.34 b**
Glucose	**67.43 ± 217.27 a**	**5.95 ± 103.40 b**
Insulin resistance	**3.429 ± 9.80 a**	**1.11 ± 4.21 b**

***The values in the table indicate to (Mean ± S.D)**

*** Significant differences at (P ≤ 0.05) are denoted by dissimilar letters.**

Table (2) Levels of kidney injury molecule KIM-1, endostatin, insulin, glucose and insulin resistance by age groups in diabetics

Age group / Variables	Age (35 – 45)	Age (46 –55)	Age (56 – 65)	Age (66 –75)
KIM-1	**727.81 ± 115.54 a**	**774.73 ± 107.47 a**	**776.25 ± 112.64 A**	**775.14 ± 115.164 a**
Endostatin	**710.62 ± 136.89 a**	**640.58 ± 181.19 a**	**627.50 ± 148.92 A**	**684.70 ± 180.93 a**

Insulin	**21.45 ± 4.98 a**	**17.12 ± 4.142 b**	**17 .57 ± 3.70 B**	**18. 39 ± 5.193 b**
Glucose	**207. 35 ± 86.39 a**	**225.29 ± 58.56 a**	**218.60 ± 63.48 A**	**217 ± 65.02 a**
Insulin resistance	**11.00 ± 4.80 a**	**9.34 ± 2.67 a**	**9.50 ± 3.34 a**	**9.49 ± 2.59 a**

***The values in the table indicate to (Mean ± S.D)**

***Significant differences at (P ≤ 0.05) are denoted by dissimilar letters.**

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