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ORIGINAL ARTICLE

Differential Expression of Prophetic Variables of Diagnostic Importance Having Potential Role in the Development of Diabetic Nephropathy

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ABSTRACT

Introduction: Diabetes mellitus (DM), a metabolic syndrome with abnormality in metabolism of carbohydrates, protein and lipids, and characterized by absolute and relative deficiency of insulin secretion. DM leads to its most common and frequent complication- Diabetic kidney disease. Oxidative stress induced by decreased antioxidant defenses and/or increased free radical formation are involved in causative factor and disease in diabetics, is an evidence-based study.

Materials and Methods: Place of Study: This studied group consisted of 100 subjects with diabetic nephropathy recruited from Jinnah hospital Lahore.

Study Design: A comparative Clinical study.

Objectives: The present study was designed to investigate the key processes involved in the development of diabetic nephropathy.

Population size: total 100 patients were selected

Data collection procedure: Five ml of venous blood sample was taken from the antecubital vein of each participant. The sample bottles were centrifuged within one hour of collection, after which the serum was separated and stored at -70°C until assayed. The subjects with the history of taking drugs (Including alcohol and cigarette), pre-diagnosis medications (e.g. antiparkinsonian/antipsychotic), were excluded from this study.

Data Analysis Plan: Results were analyzed through T test by using SPSS version 16.

Results: Hematological profile of diabetic nephropathy patients were observed. Abnormal changes were found in platelet count and lymphocytes predicting coagulation and inflammation inside body. Antioxidants (SOD, CAT, GSH-GPx) and vitamins (A, E, C, D) were decreased. Oxidative markers and inflammatory markers such as MDA, MPO, and AOPPs were found to be increased.

Practical Implication: Present study will bring a positive change in the field of diabetology and will bring ease in the life of patients in the community .

Conclusion: Owing to present facts it is clear that hyperglycemia activates the various signaling pathways and reactive oxygen species (ROS) formation, which further activates signaling cascades which causes the structural and functional alterations in kidney that enhance the complications associated with diabetic nephropathy.

Keywords: Diabetic kidney disease, Oxidative stress, Reactive oxygen species, Antioxidants, AOPPs

INTRODUCTION

The most common cause of chronic kidney failure in both industrialized and developing nations is diabetes mellitus (DM). Albuminuria (>300 mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, a permanent and irreversible decline in glomerular filtration rate (GFR), and arterial hypertension are the hallmarks of diabetic nephropathy, also known as Kimmelstiel-Wilson syndrome, nodular diabetic glomerulosclerosis, or interpapillary glomerulonephritis[1]. Both type 1 diabetes (beta cell death and complete lack of insulin) and type 2 diabetes (insulin resistance and/or decreased insulin output) can result in diabetic nephropathy, a chronic consequence. The progression of diabetic nephropathy occurs in five stages. In the early 1980s, it was established that a trace level of albumin in urine can predict whether patients with type 1 or type 2 DM will suffer kidney impairment[2]. The microalbuminuria stage, also known as the early nephropathy stage, is the first stage of kidney injury. After 15 years of disease progression, 20-30% of patients experience microalbuminuria, and less than 50% experience true nephropathy[3].

Diabetic nephropathy has a complex etiology that is influenced by a number of variables, including the duration of diabetes mellitus, poor glucose control, oxidative stress, high blood pressure, and hypertriglyceridemia[4]. A disturbance surrounded by pro and antioxidant factors that result in tissue damage is referred to as oxidative stress. An increase in oxidative stress causes a number of clinical illnesses and acts as a significant pathogenic factor in many of these conditions. According to certain research, oxidative stress plays a crucial role in the onset and evolution of diabetes mellitus as well as the emergence of diabetic complications including diabetic nephropathy[5]. Recent research holds that the pathophysiology of diabetic nephropathy is directly related to inflammation and the activation of the innate immune system [6].

Oxi-flammation, also known as oxidative stress and inflammation, affects a variety of cellular responses in various organ systems and is linked to a chronic inflammatory mechanism. The positive feedback cycle involving ongoing inflammation, oxidative stress, and insulin resistance development contributes to a number of diabetes-related side effects, including cardiovascular diseases, renal ailments, and various cancers[7].Inflammatory molecules such chemokines, cytokines, and adhesion molecules have been shown in numerous studies to have an important role in the pathophysiology of diabetic nephropathy[8]. Despite advances in the understanding of the etiology of diabetic nephropathy, the exact mechanism is not fully understood that go from a long-term hyperglycemic situation to the onset of diabetic nephropathy. As oxidative stress and inflammatory pathways are both known to be activated by hyperglycemia, it is suggested that these two pathways interact to cause kidney damage caused by hyperglycemia[9]. These results have sparked research into an oxidative stress and inflammation biomarker that may be clinically helpful in individuals with diabetic nephropathy[10].

Rationale of Study: The main objective of the current study is to determine the levels of various stress biomarkers, inflammatory cytokines and their relationship in the development of diabetic nephropathy.
Significance of Study: Current study will determine the levels of various stress biomarkers, inflammatory cytokines and their relationship in the development of diabetic nephropathy, Present study will bring a versified positive change in the field of diabetology and will bring ease in the life of patients .
Research Gap: Due Lack of fund and modern technology, Further study is needed on current research topic for the betterment of life.

MATERIAL AND METHODS

Sample Collection: Study Design: A comparative Clinical study.
Objectives: The present study was designed to investigate the key processes involved in the development of diabetic nephropathy.
Place of Study: All the selected patients (100) were screened at the Jinnah hospital Lahore. Informed consent was obtained before been included in this study.
Population size: total 100 patients were selected
Sample size: n=100
Ethical Review Board: The experimental protocol was approved by the Research Ethical Committee of The Institute of molecular biology and biotechnology, The University of Lahore.
Development of Instrument: Oxidative stress biomarkers (SOD, GSH, Catalase, AOPPs, NO and MDA) were determined by using the methods of spectrophotometrically. Vitamins (C, E, A and D) and inflammatory markers (TNF-, and IL-6) were analyzed by using commercially available Elisa kits.
Data Collection Procedure: Hundred healthy individuals were included as controls and 100 diabetic nephropathy patients were taken in this study. Five ml of venous blood sample was taken from the antecubital vein of each participant. The sample bottles were centrifuged within one hour of collection, after which the serum was separated and stored at -70°C until assayed. The subjects with the history of taking drugs (Including alcohol and cigarette), pre-diagnosis medications (e.g. antiparkinsonian/antipsychotic), were excluded from this study. None of the controls were on any medication, history of chronic infections, malnutrition syndrome, metabolic dysfunction (Such as diabetes mellitus, liver diseases, renal disease cancer, previous history of PE and HTN, existence of vascular disease and CVA).
Data Analysis Plan: Results were analyzed through T test by using SPSS version 16.
Chemicals: All chemical reagents of analytical grades were purchased from Sigma/Invitrogen Chemical Co. (St. Louis, Mo, USA).
Biochemical Analysis: Complete blood count of the selected subjects was performed on the automated hematology blood analyzer by Sysmex (version. XP-2100). The levels of superoxide dismutase (SOD) were measured [20]. Catalase was measured by the method through spectrophotometer[21]. GSH concentrations were measured by the method.[19,21]The level of glutathione peroxidase (GPx) was measured by the method of Mills[22]. The levels of glutathione reductase were measured by the procedure[25]. The concentration of NO was determined by the protocol of the Griess assay.[18] The levels of AOPPs were determined by the protocol.[17] The method was used to determine the levels of MDA by spectrophotometrically[26]. Advanced glycation end-product pentosidine is considered to be a biomarker of non-enzymatic glycation of proteins which can be measured by the protocol.[22]Vitamin C level was measured by the method[17]. The level of Vitamin A was estimated via the protocol of in the serum sample[22]. Vitamin E was determined through the Emmerie-Engel reaction reported by Evans and Bishop[27]. The level of gamma glutamyl transferase was determined by the enzymatic colorimetric assay. The levels of different Vitamin D, MPO, IL-6, HsCRP and TNF-α were determined by the human available diagnostic ELISA kit (Invitrogen Elisa Kit) method.

Statistical Analysis: The statistical analysis and data processing were performed by using SPSS version 10. Independent sample t-test was used for the comparison of patients with diabetic nephropathy and healthy control. Pearson correlation coefficient (r) was also used in this study. All the results were expressed in Mean±SD, in which $p<0.05$ shows significant results.

RESULTS

Demographic Profile of Diabetic Nephropathy Patients Versus Healthy Control: Demographic distribution was examined in diabetic nephropathy patients as compared to healthy individuals as shown in table 1. Levels of weight (61.71±12.49 kg vs. 48.52±4.33 kg), age (43.74±19.89 Yrs vs. 37.93±4.16 Yrs), SBP (1.33±7.78 mmHg vs. 1.30±1.43 mmHg), DBP (84.76±3.20 mmHg vs. 80.74±2.13 mmHg) and body mass index (80.74±2.13 Kg/m^3 vs. 21.61±1.52 Kg/m^3) were recorded in diabetic nephropathy patients as compared to healthy control.

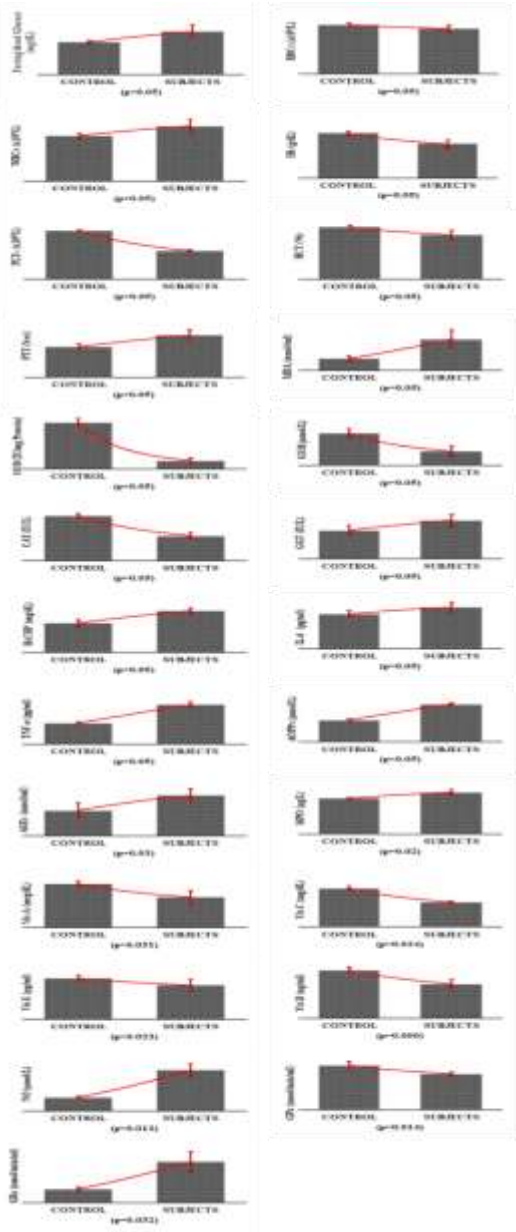

Figure 1: Levels of various prophetic variables and hematological profile of diabetic nephropathy patients versus healthy control

Table-1: Demographic Profile of Diabetic Nephropathy Patients Versus Healthy Control

Variables	Control (n=50)	Subject n=50)
Weight (kg)	48.52±4.33	61.71±12.49
Age (Yrs)	37.93±4.16	43.74±19.89
SBP (mmHg)	1.30±1.43	1.33±7.78
DBP (mmHg)	80.74±2.13	84.76±3.20
Body Mass Index (Kg/m^3)	21.61±1.52	34.79±6.72

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

Table-2: Pearson's Correlation Among the Parameters of Subjects with Diabetic Nephropathy

Parameters	Correlation coefficient
MDA vs TNF-α	.156*
MDA vs Vit D	-.553*
MDA vs NO	.653*
MPO vs MDA	.334*
MPO vs SOD	-.461*
MPO vs GSH	-.451**
MPO vs Catalase	-.239**
IL-6 vs Vit D	-.416*
TNF-α vs Vit D	-.191*
TNF-α vs IL-6	.379*

Hematological Profile of Diabetic Nephropathy Patients Versus Healthy Control: Hematological profile was measured in diabetic nephropathy patients as compared to healthy control as shown in figure 01. The mean value of fasting blood glucose was significantly increased in diabetic nephropathy patients (5.34±0.80 mg/dL) as compared to healthy control (4.01±0.71 mg/dL). Decreased trend of RBCs, Hb, platelets and HCT were recorded in patients group (4.30±0.31 x10^9/L, 10.41±1.25 g/dL, 179±8.77 x10^9/L and 34.97±3.43%) in comparison with healthy individuals (34.97±3.43 x10^9/L, 13.67±0.68 g/dL, 307±5.27 x10^9/L and 41.29±1.59%) respectively. On the other hand, the mean value of WBCs and PTT were significantly increased in diabetic nephropathy patients (9.24±1.69 x109/L and 13.31±1.75 Sec) as compared to healthy control (7.57±0.40 x109/L and 9.64±0.93 Sec) correspondingly.

Levels of Prophetic Variables in Diabetic Nephropathy Patients Versus Healthy Control: The data represented in figure 01 shown the levels of various stress variable and their significant role in the development of diabetic nephropathy in patients as compared to control individuals. The mean value of MDA (3.80±1.11 nmol/mL vs 1.43±0.36 nmol/mL), GGT (58.35±8.64 IU/L vs. 43.12±6.82 IU/L), HsCRP (1.47±0.10 mg/dL vs. 1.04±0.12 mg/dL), IL-6 (6.73±0.82 pg/mL vs. 5.64±0.51 pg/mL), TNF-α (55.78±4.03 pg/mL vs. 29.90±1.14 pg/mL), AOPPs (1.45±1.06 µmol/L vs. 0.84±0.04 µmol/L), AGEs (2.77±0.29 nmol/mL vs. 2.56±0.10 nmol/mL) and MPO (236±25.01 µg/L vs. 203±4.81 µg/L) were significantly increased in diabetic nephropathy patients as compared to control individuals respectively. Contrary to that, the levels of SOD, GSH, CAT, Vit-A, Vit-C, Vit-E, Vit-D, GPx and GRx were significantly decreased in diabetic nephropathy patients (0.09±0.03 IU/mg Protein, 4.23±1.64 µmol/L, 2.20±0.26 IU/L, 428±95.78 mcg/dL, 0.36±0.22 mg/dL, 0.24±0.09 µg/mL, 9.44±1.21 ng/mL, 6.61±0.37 nmol/min/mL and 1.47±0.22 nmol/min/mL) as compared to healthy individuals (0.49±0.04 IU/mg Protein, 9.79±1.22 µmol/L, 3.95±0.21 IU/L, 615±44.52 mcg/dL, 0.56±0.08 mg/dL, 0.29±0.05 µg/mL, 13.22±0.81 ng/mL, 8.22±0.69 nmol/min/mL, 4.36±1.59 nmol/min/mL) respectively. Increased trends of NO (57.67±8.87 µmol/L vs. 19.42±1.42 µmol/L) were recorded in diabetic nephropathy patients as compared to healthy individuals.

DISCUSSION

The most significant diabetes consequence is diabetic nephropathy. Only glomerulonephritis remains the first cause of end-stage renal disease. End-stage renal illness is frequently more challenging to treat than other kidney diseases due to its complicated metabolic abnormalities[11,12]. In order to delay diabetic nephropathy, prompt prophylaxis and treatment are therefore crucial[20,21]. The role of mitochondrial damage caused by oxidative stress in diabetic nephropathy was investigated in this study. The term "oxidative stress" describes the level of oxidation that occurs when the body is exposed to a range of damaging stimuli, causing an imbalance in the body's antioxidant system and tissue damage[15,17,19]. Reactive oxygen species (ROS) generation have been linked in recent years to a number of chronic metabolic disorders, including atherosclerosis and diabetes[14,1622,24].

According to earlier research, oxidative stress is a significant factor contributing to diabetic nephropathy[8,9,11,12]. One of the main byproducts of membrane lipid peroxidation is malondialdehyde (MDA), and its formation might worsen membrane damage. The presence of hyper oxidative stress in diabetic patients was confirmed in the current study by the discovery of ROS and MDA rise in the kidneys[1,24,25]. In the present study, a positive correlation was established between MDA and NO (MDA vs. NO, r=.653*) as shown in table 02. Thiol-containing antioxidant N-acetyl cysteine (NAC), a precursor of glutathione (GSH), protects tissue in vivo by turning it into glutathione (GSH)[13,15,16]. Early studies found that NAC reduced lung injury by preventing neutrophils and vascular endothelial cells from expressing adhesion molecules[7,10,14,15]. Additionally, it entered leukocytes and changed into physiological antioxidants to raise intracellular levels of reduction, causing ROS in cells and media to be inactivated[17,18,23].

A thiol-containing tripeptide, glutathione is found in large concentrations in live cells in its reduced form (GSH)[19]. It combines with ROS to make glutathione radical, which is then reduced back to its original form by glutathione reductase activity[20]. In this investigation, a considerable drop in GSH concentration was discovered in the patient group, which may be related to the excessive formation of reactive oxygen species that results in the conversion of reduced form to oxidized form (GSSH)[13]. Superoxide dismutase is catalyzed by sodium oxide dismutase (SOD) to hydrogen peroxide (H_2O_2), which is then further reduced by glutathione peroxidase and catalase activity[21,24,25]. According to the current study, patients' SOD activity has significantly decreased when compared to controls[15]. H_2O_2 is produced as a result of the auto-oxidation of glucose, and this inactivates SOD. Aging in DM patients may cause decreased SOD activity, which may lead to an increase in SOD glycation[19,20]. In the present study, a strong correlation was found between myeloperoxidase and SOD (MPO vs SOD, r=-.461*) as shown in table 02.

The other enzyme catalase (CAT) expresses and detoxifies the H_2O_2 using NADPH and GSH. In their investigations[25]. have demonstrated that when glutathione peroxidase activity declines, CAT activity rises in response. As H_2O_2 production increased with aging. It was also noted an increase in CAT activity. Because the number of antioxidant enzymes in extracellular fluids is typically very low, plasma proteins are more likely to be oxidized by ROS. As a result, higher levels of advanced oxidation protein products (AOPPs), also known as oxidized protein products, are frequently found in the plasma of dialysis patients[20,21,22]. The most prevalent plasma protein, albumin, was found to be the principal source of AOPPs in the plasma[25,26]. The albumin aggregates, which most likely resulted from disulfide bridges or dityrosine crosslinking, were primarily responsible for the formation of the high molecular weight AOPPs. The monomeric form of albumin was present due to the low molecular weight of AOPPs[23,24,25].

Proinflammatory cytokines are critical in the development of kidney damage and arteriolosclerosis. They result in diabetic microvascular problems, such as diabetic nephropathy. Additionally, it plays a role in controlling immunological responses and a number of inflammatory diseases[25,26]. Previous research has shown that diabetic nephropathy has characteristics in common with many chronic inflammatory diseases, and patients with diabetic nephropathy have also been found to have elevated levels

of classical inflammatory mediators like tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6).[27] Proinflammatory cytokines and overactive immune responses have also been linked to the emergence and development of this illness. It follows that if a polymorphism can affect the protein structure or gene expression of cytokines, it is likely that this variation will modify the status of inflammation[28]. In this study, a negative correlation was established between IL-6 and Vitamin D (IL-6 vs Vit D, r= 0-.416*) as shown in table 02.

CONCLUSION

In conclusion, the pathophysiology of diabetic nephropathy involves mitochondrial damage brought on by oxidative stress as a major factor. Clinical treatments for diabetic nephropathy may focus on reducing the production of ROS or inhibiting the processes that cause oxidative stress. From the onset of diabetes to the progression of renal failure, IL-6 exerts a significant variety of activities that are linked to diabetic nephropathy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Raw data will be available on demand.

Conflicts of Interest: The authors declare no conflict of interest.

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