ORIGINAL ARTICLE

# Association of Janus kinase 1 and 2 expression with clinical indices in diabetic kidney disease

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**Background:** Diabetic Kidney Disease (DKD) is a prevalent complication of uncontrolled hyperglycemia that imposes a considerable burden on the health system due to the need for renal replacement therapy in the long term. Therefore, early diagnosis and prevention of renal damage in diabetic patients is critical. In the present study, we investigated the expression level of Janus kinase (Jak) 1, 2, and 3 genes, which play a role in the signal transduction of inflammatory cytokines and growth factors, for therapeutic or diagnostic purposes. **Materials and Methods:** Sixty patients with DKD, 60 diabetic patients without nephropathy, and 60 healthy individuals were recruited, and the expression level of the Jak1, Jak2, and Jak3 genes was evaluated using real-time polymerase chain reaction in peripheral blood mononuclear cells. **Results:** The results showed that Jak1 and Jak2 gene expression was significantly upregulated in DKD patients compared to healthy controls (*P* values: 0.02 and 0.002, respectively). A significant negative correlation was observed between the expression of Jak1 and 2 genes and glomerular filtration rate in patients (*P* values: 0.047 and 0.03, respectively). There was also a positive correlation between the urine albumin-creatinine ratio of the DKD group with Jak1 and 2 gene expression levels (*P* values: 0.008 and 0.015, respectively). Moreover, receiver operating characteristic curve analysis showed a fair diagnostic value for Jak2 expression in DN (0.71, 95% confidence interval: 0.59–0.834 [*P* = 0.002]). **Conclusion:** Gene expression evaluation showed an increased expression of Jak1 and Jak2 in DKD, suggesting Jak1/2 inhibition for the treatment of patients. In addition, Jak2 expression might have diagnostic or predictive value in diabetes.

**Key words:** Diabetes mellitus, diabetic kidney disease, Janus kinase 1, Janus kinase 2, Janus kinase 3

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## INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease, the prevalence of which is increasing due to the increasing number of diabetic patients worldwide. The problem is exacerbating as the number of people with type 2 diabetes is estimated to increase to 643 million by 2030 and to 783 million by 2045.[1] Therefore, strict control of hyperglycemia and regular surveillance of microalbuminuria are critical for the prevention and early diagnosis of renal damage in diabetic patients. The standard treatment of DKD includes blood glucose and blood pressure control, targeting A1c below 7%, and blood pressure lower than 130/80 mmHg.[2] However, current treatments such as metformin, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers seem not to be efficient in the prevention or treatment of DKD suggesting a significant role for inflammatory responses and oxidative stress damages in disease progression.[3] In recent years, anti-inflammatory approaches, such as cytokines and chemokines inhibition, nuclear factor κB inhibition, mesenchymal stem cells therapy, and Janus kinase inhibitors have been considered to treat

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dysregulated immune responses in diabetic patients.[4] The Janus kinase family, including Janus kinase (Jak) 1, Jak2, Jak3, and Tyrosine kinase 2 (Tyk2) enzymes, is involved in cytokine signaling through the activation of signal transducer and activator of transcription (STAT) molecules that enter the nucleus after phosphorylation and affect inflammatory gene transcription.[5] These molecules also play a role in signal transduction of certain growth factors, including granulocyte colony-stimulating factor (CSF), growth hormone (GH), granulocyte-macrophage CSF, insulin-like growth factor I, and prolactin.[5] These functions suggest the implication of Jak molecules in inflammatory and antiapoptotic damage in DKD. Accordingly, a study reported upregulated expression of Jak1, 2, and 3 genes in glomeruli and tubulointerstitial samples of patients with DKD compared to healthy controls. In addition, the expression of these genes was negatively correlated with the estimated glomerular filtration rate (eGFR) in the DKD group. Nonetheless, there was little or no expression of Jak genes in the experimental model of DKD.[6] Furthermore, one *in vitro* study showed impaired autophagy, enhanced apoptosis, and activated Jak/STAT pathway in podocytes under high glucose conditions, which was reverted with ruxolitinib, a Jak1/2 inhibitor, in both *in vitro* and *in vivo* experiments.[7,8] Noteworthy, inhibition of Jak activity has shown some encouraging results in diabetic patients since treating type 2 diabetic patients with baricitinib, a Jak 1/2 inhibitor, ameliorated the albuminuria and reduced the inflammatory markers levels.[9] Regarding these and other findings, it is necessary to elucidate the implications of Jak enzymes in the pathogenesis of DKD and its association with disease progression and clinical findings. If sufficient evidence is provided for the implication of Jak molecules in the pathogenesis of DKD, Jak inhibitors may be considered as an alternative to prevent or treat kidney damage in diabetic patients. Besides, if a significant association is established between Jak expression and clinical indices, it might be suggested as a part of a noninvasive test for patients' follow-up. Therefore, in the present study, we aimed to evaluate the expression level of Jak1, 2, and 3 genes in the DKD patients compared to the diabetic patients without nephropathy and healthy individuals in correlation with clinical findings.

## PATIENTS AND METHODS

### Patients

The present research was conducted as a case–control study. The peripheral blood samples were taken from 60 type 2 diabetic patients diagnosed with nephropathy according to the clinical (albuminuria >30 mg/g and/or decline in GFR ranging from 2 to 20, with a median of 12 mL/min/year),[10,11] and/or pathological (interstitial fibrosis and tubular, arteriolar hyalinosis, arteriosclerosis, thickening of the glomerular basement membrane, mesangial expansion, nodular sclerosis, and glomerulosclerosis) criteria.[12] Sixty type 2 diabetic patients without albuminuria and normal GFR were also recruited to the study, along with 60 age- and sex-matched healthy individuals with A1C <6.5% and fasting blood glucose <125 mg/dl.[13] The control group was selected from the volunteer hospital staff, faculty staff, friends, and relatives who were not using medications and did not have any signs or symptoms of chronic or acute disease. Participants with a medical history of other autoimmune disorders, allergies, malignancies, active infections, pregnancy, and eGFR <15 mL/min were excluded from the study. The patients were treated with either metformin or empagliflozin for hyperglycemia. Amlodipine, diltiazem, losartan, or valsartan were used for control of hypertension, none of which are known to affect Jak gene expression. No patient was receiving insulin treatment. Patient selection and sampling were performed in Shohada-ye-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, between February 2023 and April 2024. All subjects gave informed consent before participating in the study. The study was conducted under the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.200).

### Gene expression assay

Isolation of ribonucleic acid (RNA) from peripheral blood mononuclear cells was performed with the High Pure RNA Isolation Kit (ROJE Technologies, Tehran, Iran) regarding manufacturer's instructions. The quality of RNA was evaluated with a spectrophotometer (NanoDrop ND1000; Thermo Scientific, USA). RNA samples with an A260/A280 absorbance ratio of 1.8–2.2 and an A260/A230 ratio of 2–2.2 were considered acceptable. Reverse transcription from peripheral blood RNA to complementary deoxy RNA (cDNA) was performed using Transcriptor First Strand cDNA Synthesis Kit according to the company instructions (ROJE Technologies, Tehran, Iran). cDNA samples with A260/A280 ratios 1.8–2 were stored in a –70°C freezer for real-time polymerase chain reaction (RT-PCR) test.

The relative gene expression was performed using SYBR-Green RT-PCR. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal control. The target gene primer sequences included: Jak1: Forward: GAGACAGGTCTCCCACAAACAC, Reverse: GTGGTAAGGACATCGCTTTTCC; Jak2: Forward: CCAGATGGAAACTGTTCGCTCAG, Reverse: GAGGTTGGTACATCAGAAACACC; Jak3: Forward: AGTGACCCTCACTTCCTGCTGT, Reverse: GGCTGAACCAAGGATGATGTGG, GAPDH: Forward: GTCTCCTCTGACTTCAACAGCG, Reverse: ACCACCCTGTTGCTGTAGCCAA).[14] To perform the

procedure, 10 µL of master mix (RealQ Plus Green, Ampliqon, Denmark), 7 µL distilled water, 1 µL assay mix (forward and reverse primers), and 2 µL diluted sample cDNA (5 ng/µL) were mixed in the wells. The reaction cycles included 50°C (2 min), 95°C (10 min), 45 cycles of 95°C (15 s), and 60°C (1 min) provided by StepOnePlus RT-PCR System (Applied Biosystems, USA). Nontemplate controls were used in each run. All tests were performed in duplicate form and were quantified relative to the internal control (GAPDH) expression. To calculate the relative expression of samples, a threshold cycle number was applied. The relative expression was calculated with the Livak formula: relative mRNA expression = ($2^{-\Delta\Delta Ct}$).[15]

### Statistical analysis

The data were presented as mean ± standard deviation (SD) or mean ± standard error of means. The normality of the distribution was evaluated with the Kolmogorov–Smirnov test. The One-Way analysis of variance (ANOVA) test was used to compare quantitative variables with a normal distribution, and the Kruskal–Wallis test was applied for nonparametric variables. The comparison between the two groups was performed using *post hoc* test. The correlation between quantitative variables was assessed using Pearson's correlation presented with R and Correlation Coefficient ($R^2$). $P < 0.05$ was considered significant. Statistical analysis was performed using IBM SPSS 26.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Basic characteristics of the studied population

180 participants were recruited to the study, including type 2 diabetes patients with nephropathy ($n$ = 60), diabetic patients without nephropathy ($n$ = 60), and healthy individuals. One-way ANOVA analysis showed that, in addition to the kidney function tests, the smoking rate, fasting blood sugar, C-reactive protein, erythrocyte sedimentation rate, hemoglobin, white blood cell, neutrophil count, and neutrophil-to-lymphocyte ratio were significantly different in the studied groups. The clinical and paraclinical findings have been presented in Table 1.

### Upregulated expression of the Janus kinase 1 and Janus kinase 2 genes in patients with DN

Jak1 gene relative expression in patients with DKD (1.21 ± 0.64 [mean ± SD]) was higher than in diabetic patients without nephropathy (1.11 ± 0.51 [mean ± SD]) and healthy individuals (0.82 ± 0.41 [mean ± SD]); however, only the difference between two groups of nephropathy and healthy controls was statistically significant ($P$ = 0.02). Similarly, Jak2 expression was significantly higher in DKD than in healthy individuals (0.93 ± 0.48 vs. 0.55 ± 0.32 [mean ± SD] [$P$ value: 0.002]). Still, it showed no significant difference between other groups. Regarding Jak3 gene, neither the difference between patient groups (0.92 ± 0.38 vs. 0.8 ± 0.43 [mean ± SD]) nor the difference between patients and healthy subjects (0.79 ± 0.30 [mean ± SD]) was significant [Figure 1].

## CORRELATION BETWEEN JANUS KINASE GENES EXPRESSION AND CREATININE LEVELS IN PATIENTS

There was a positive correlation between serum creatinine levels and Jak2 expression in the patient group (diabetic with and without nephropathy) ([Pearson Correlation: 0.28, Correlation Coefficient: 0.077[ [$P$ = 0.05]). In addition, a weak correlation was observed between serum creatinine levels and Jak1 ([Pearson Correlation: 0.17, Correlation Coefficient: 0.029] [$P$ = NS]), and Jak3 expression ([Pearson Correlation: 0.19, Correlation Coefficient: 0.038] [$P$ = NS]) [Figure 2].

### Correlation between Janus kinase genes expression and estimated glomerular filtration rate in patients

Regression analysis showed a significant negative correlation between Jak1 expression and eGFR in patients including diabetic with or without nephropathy ([Pearson Correlation: −0.26, Correlation Coefficient: 0.066] [$P$ = 0.047]). Jak2 gene expression also showed a significant correlation with eGFR values ([Pearson Correlation: −0.29, Correlation Coefficient: 0.089] [$P$ = 0.03]). However, the correlation between Jak3 expression and eGFR was not statistically significant ([Pearson Correlation: −0.23, Correlation Coefficient: 0.056) [$P$ = NS]) [Figure 3].

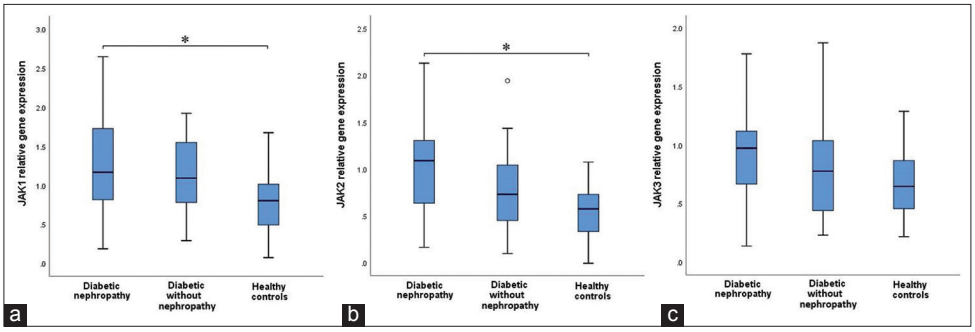


**Figure 1:** Box plot graphs (mean ± standard deviation) presenting increased expression of Janus kinase (Jak)1 ($P$ = 0.02) and Jak2 ($P$ = 0.002) in diabetic kidney disease compared to the healthy controls. (a) JAK1, (b) JAK2, (c) JAK3

**Table 1: Demographic and clinical data of the studied groups**

| | Diabetic kidney disease | Diabetic patients without nephropathy | Healthy controls | *P* (between 3 groups) |
|---|---|---|---|---|
| Number | 60 | 60 | 60 | - |
| Age (year) (mean±SD) | 56.7±8.03 | 58.8±4.4 | 53±8.3 | 0.1 |
| Gender ratio (Male: female) | 28/32 | 28/32 | 28/32 | - |
| Smoking (yes/no) | 18/42 | 14/46 | 11/49 | 0.02* |
| Disease (month) (mean±SD) | 120.2±10.8 | 96±8.3 | - | 0.08 |
| Duration of the disease (month) (mean±SD) | 53±41 | - | - | - |
| DN (stage) | Stage 1: 20<br>Stage 2: 16<br>Stage 3: 22<br>Stage 4: 2 | - | - | - |
| Systolic pressure (mmHg) (mean±SD) | 130±14 | 125±12.6 | 122±10.5 | 0.05 |
| Diastolic pressure (mmHg) (mean±SD) | 77±8 | 76.4±7 | 71±6.7 | 0.08 |
| Weight (kg) (mean±SD) | 75±10 | 72±15 | 70±15 | 0.4 |
| BMI (mean±SD) | 27.4±3.3 | 25.3±5.1 | 23.3±5.1 | 0.09 |
| BUN (mg/dL) (mean±SD) | 58.6±27.6 | 24±12.7 | 25.3±3.8 | 0.001* |
| Creatinine (mg/dL) (mean±SD) | 1.6±0.7 | 1±0.2 | 0.9±0.1 | 0.001* |
| Calcium (mg/dL) (mean±SD) | 8.5±0.7 | 8.5±0.4 | 8.9±0.5 | 0.63 |
| Serum Albumin (g/dL) (mean±SD) | 3.3±0.5 | 3.4±0.3 | 3.5±0.5 | 0.42 |
| Urine Albumin (g/L) (mean±SEM) | 115±32 | 5±2 | - | <0.0001* |
| FBS (mg/dL) (mean±SD) | 154±36 | 113±21 | 105±14 | 0.03* |
| HBA1C (mean±SD) | 8.3±1.9 | 6.2±1.7 | - | 0.3 |
| CRP (mg/L) (mean±SEM) | 30±6.5 | 23±6.3 | 1.5±1.1 | 0.002* |
| ESR (mm/h) (mean±SD) | 32±15 | 23.3±19 | 20.3±4 | 0.008* |
| HB (g/dL) (mean±SD) | 10.8±2 | 11.5±2.2 | 11.8±2.5 | 0.03* |
| WBC count (mean±SD) | 8370±2036 | 8442±2010 | 6713±1973 | 0.004* |
| Lymph count (mean±SD) | 1754±651 | 2162±828 | 1871±678 | 0.14 |
| Neut count (mean±SD) | 5609±1503 | 5612±1399 | 4483±1409 | 0.009* |
| PLT count (mean±SD) | 238,400±9615 | 222,550±9033 | 243,000±8160 | 0.6 |
| LDL (mg/dL) (mean±SD) | 83.1±23.2 | 83.6±19.5 | 80±18.5 | 0.6 |
| HDL (mg/dL) (mean±SD) | 37±10 | 38±7 | 37.7±6 | 0.4 |
| TG (mg/dL) (mean±SD) | 128±52 | 131±41 | 111±39 | 0.8 |
| NLR (mean±SD) | 3.46±1.19 | 2.9±1.08 | 2.51±0.7 | 0.004* |
| Urine Creatinine (mg/dL) (mean±SEM) | 66±10.8 | - | - | |
| Proteinuria (mg/24 h) (mean±SEM) | 1591±195 | - | - | |
| UACR (mean±SEM) | 218±45 | - | - | |
| eGFR (mean±SD) | 52.6±20.6 | 90.8±18.3 | 92.3±15.3 | <0.0001* |
| Other diseases | HTN (33)<br>CVD (14) | HTN (24)<br>CVD (10) | -<br>- | 0.07<br>0.2 |

*Statistical significance (*P*<0.05). DN=Diabetic kidney disease; BMI=Body mass index; BUN=Blood urea nitrogen; FBS=Fasting blood sugar; ESR=Erythrocyte sedimentation rate CRP=C-reactive protein; HB=Hemoglobin; WBC=White blood cell; PLT=Platelet; LDL=Low-density lipoproteins; HDL=High-density lipoproteins; TG=Triglyceride; NLR=Neutrophil to lymphocyte ratio; UACR=Urine albumin-creatinine ratio; eGFR=Estimated glomerular filtration rate; SD=Standard deviation; SEM=Standard error of means; HTN=Hypertension; CVD=Cardiovascular diseases

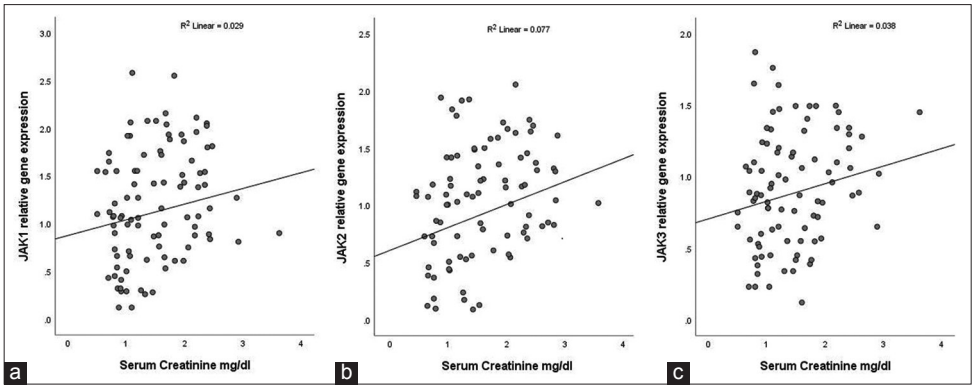


**Figure 2:** Correlation between Janus kinase gene expression and serum creatinine level of patients (diabetic and diabetic kidney disease). (a) JAK1, (b) JAK2, (c) JAK3

### Correlation between Janus kinase genes expression and urine albumin-creatinine ratio in DN patients

The correlation analysis demonstrated a significant correlation between Jak1 gene expression and Urine albumin-creatinine ratio (UACR) of the patients with DKD ([Pearson Correlation: 0.48, Correlation Coefficient: 0.23] [$P = 0.008$]). Jak2 also showed a direct correlation with UACR ([Pearson Correlation: 0.44, Correlation Coefficient: 0.19] [$P = 0.015$]). However, Jak3 expression was not correlated with UACR values ([Pearson Correlation: 0.31, Correlation Coefficient: 0.099] [$P$ = NS]) [Figure 4].

### Diagnostic value of Janus kinase genes expression levels

The receiver operating characteristic curve analysis of Jak genes expression in the peripheral blood of patients showed area under the curves (AUCs) 0.6 (95% confidence interval [CI]: 0.47–0.74 [$P$ = NS]), 0.71 (95% CI: 0.59–0.834 [$P$ value: 0.002]) and 0.62 (95% CI: 0.5–0.75 [$P$ = NS]) for Jak1, Jak2, and Jak3 in the diagnosis of DKD, suggesting an acceptable sensitivity and specificity for Jak2 gene [Figure 5].

## DISCUSSION

In recent years, the increasing prevalence of type 2 diabetes and its complications such as cardiovascular diseases,

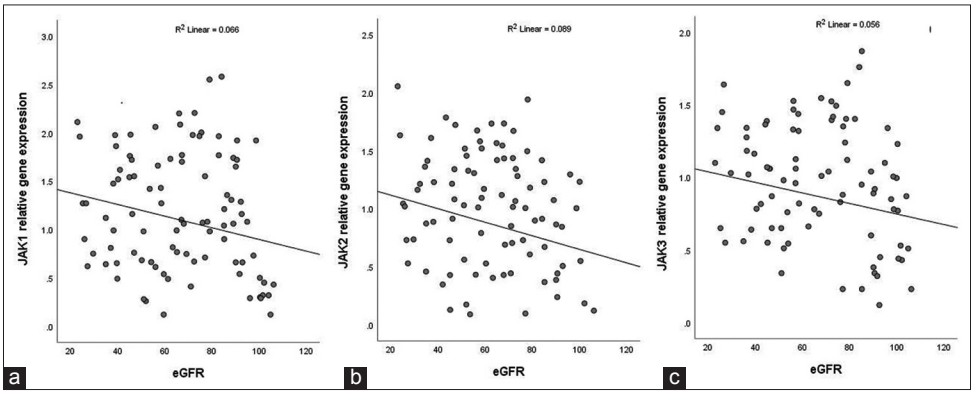


**Figure 3:** Correlation between Janus kinase genes expression and estimated glomerular filtration rate in patients (diabetic and diabetic kidney disease). (a) JAK1, (b) JAK2, (c) JAK3

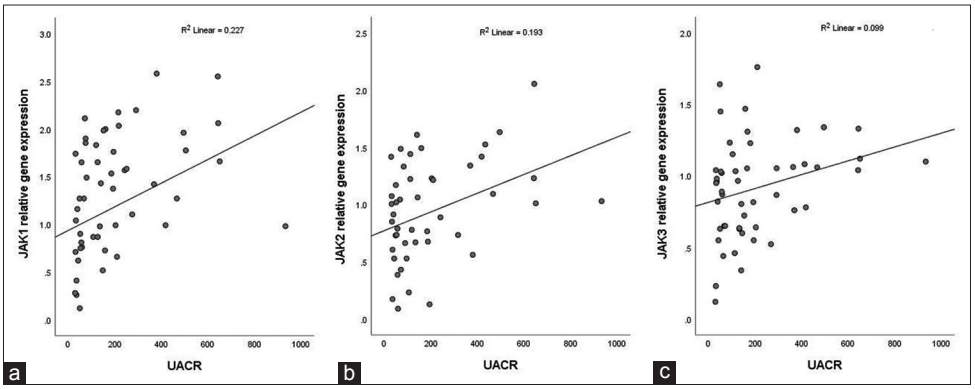


**Figure 4:** Correlation between Janus kinase genes expression and urine albumin-creatinine ratio in diabetic kidney disease patients. (a) JAK1, (b) JAK2, (c) JAK3

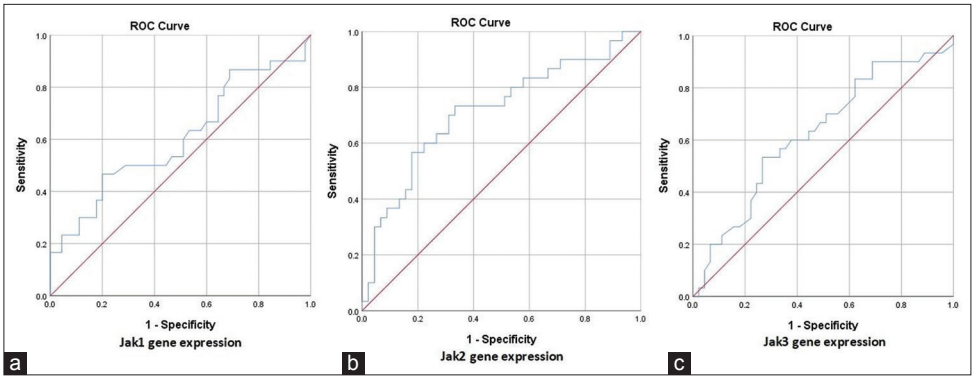


**Figure 5:** Diagnostic value of Janus kinase 2 gene expression with area under the curve 0.71 (95% confidence interval: 0.59–0.834 [$P = 0.002$]) in diabetic kidney disease. (a) JAK1, (b) JAK2, (c) JAK3

peripheral neuropathy, retinopathy, and DKD have created significant problems for the health care system in all countries.[1] DKD presented with proteinuria and/or reduced GFR is considered the most prevalent complication of diabetes mellitus, affecting approximately 40% of diabetic patients.[16] Therefore, there have been efforts to prevent or delay irreversible renal damage in patients. The current treatments mainly focus on the regulation of glucose levels and blood pressure; however, accumulating evidence suggests a considerable role for inflammatory responses in the initiation and progression of DKD.[3]

The Jak/STAT pathway, with its implication in signal transduction of many inflammatory cytokines and growth factors, has also been considered in the pathogenesis of DN.[17,18] The Janus kinase family consists of four members, including Jak1, Jak2, Jak3, and Tyk2 enzymes that approach the intracytoplasmic domain of the receptors upon cytokine engagement. This leads to Jak phosphorylation and consequent STAT phosphorylation, resulting in STAT molecules dimerization and transfer to the nucleus that triggers the inflammatory genes' transcription.[19] Noteworthy, some growth factors such as angiotensin II (ANG-II) exert their function through the Jak/STAT pathway. It has been reported that the Jak/STAT pathway is involved in ANG-II-induced growth in glomerular mesangial cells, contributing to glomerular filtration dysfunction.[20] Moreover, an experimental study demonstrated that high glucose levels promote ANG II-induced activation of the Jak/STAT pathway in kidney glomeruli.[21] It was also found that Jak2 inhibition with AG-490 resulted in a significant improvement of nephropathy in diabetic rat models.[21] The Jak/STAT pathway also appears to contribute to transforming growth factor beta signaling, secondary collagen production, and fibronectin synthesis in mesangial cells.[22] Furthermore, an *in vitro* study demonstrated the implication of ANG-II-induced Jak2/STAT3 signaling in mitochondrial dysfunction and oxidative stress of mice podocytes.[23]

The upregulated expression of Jak1, 2, and 3 as well as STAT1/3 genes, has already been reported in kidney biopsy samples of patients with DKD, which was negatively correlated with eGFR.[6] Our study also showed an enhanced expression of Jak1 and 2 in peripheral blood of DKD patients compared to healthy subjects. Similarly, one study reported upregulated expression of Jak1, 2, and 3 genes in glomeruli and tubulointerstitial samples of patients with DKD compared to healthy controls. In addition, the expression of these genes was negatively correlated with the eGFR in the DKD group. Nonetheless, there was little or no expression of Jak genes in the experimental model of DKD.[6] Furthermore, one *in vitro* study showed impaired autophagy, enhanced apoptosis, and activated Jak/STAT pathway in podocytes under high glucose conditions, which was reverted with ruxolitinib, a Jak1/2 inhibitor, in both *in vitro* and *in vivo* experiments.[7,8] Noteworthy, inhibition of Jak activity has shown some encouraging results in diabetic patients since treating type 2 diabetic patients with baricitinib, a Jak1/2 inhibitor, ameliorated the albuminuria and reduced the inflammatory markers levels.[9]

To evaluate the clinical relevance of this finding, correlation analysis was performed, which demonstrated a significant association between Jak1 and 2 expression and eGFR of the patients. Similarly, a recent study has reported an improved GFR in mice model of lupus nephritis following Jak inhibition with miRNA-155.[24]

In addition, the UACR of the DN group was directly correlated with Jak1 and 2 gene expression levels. Previous studies have also shown that Jak/STATs phosphorylation in peripheral blood cells of patients with focal segmental glomerulosclerosis was associated with increased proteinuria levels and decreased renal function levels.[25]

According to these and other findings, Jak gene expression levels might have diagnostic or prognostic value in diabetic patients. The significant AUC of Jak2 expression in our study was suggestive of an acceptable specificity and sensitivity for this gene, besides other factors, in the diagnosis of DKD. However, the Jak expression difference between diabetic and DKD patients was not statistically significant; a probable explanation of this finding might be subclinical kidney injuries in diabetic patients without nephropathy that could only be diagnosed by tissue biopsy. Therefore, this result requires further evaluation in large prospective cohort studies, including pathological evaluation of tissue samples in both groups.

The recent developments in understanding the immunopathogenesis of DKD s suggest novel therapeutic targets for the efficient treatment of patients. Accordingly, Jak inhibitors have been evaluated in a few clinical trials showing encouraging results but some side effects, particularly hematological complications.[26] For instance, the efficacy of baricitinib, a Jak1/2 inhibitor, was demonstrated in a phase 2 placebo-controlled clinical trial as it reduced patients' UACR and decreased urinary levels of proinflammatory cytokines and chemokines. However, almost two-thirds of the participants developed anemia.[9] Moreover, a recent study has shown that miR-203 improved renal cell damage in diabetic nephropathy by targeting SOCS6/SOCS7 and inhibiting the activation of the JAK/STAT pathway.[27] A recent study also showed advantages of CD3D silencing in reducing inflammatory responses and renal injuries in a mouse model of diabetic nephropathy via blocking the JAK/STAT pathway.[28] The results of the

present study, indicating upregulated expression of Jak1 and Jak2 in DN patients, corroborate previous findings and suggest the probable advantages of Jak1/2 inhibition in diabetic patients, especially for those with rapid progression of nephropathy. With the development of new generations of Jak inhibitors with less cytotoxicity to hematopoietic progenitors, it is anticipated that more clinical trials will be conducted to evaluate the preventive or therapeutic potential of Jak inhibition in diabetic patients.

The expression of Tyk2 was not evaluated in this study because there was no evidence of its implication in the pathogenesis of DKD in previous investigations. Tissue expression of Jak/STAT genes was not evaluated in this study due to the risk of tissue biopsy, as none of the participants were subjected to biopsy for other reasons. Moreover, the tissue expression of inflammatory genes, despite having considerable pathologic value, could not be proposed as a convenient test for long-term monitoring of diabetic patients. It is also suggested to evaluate STAT gene expression in correlation with paraclinical findings and clinical manifestations of DKD patients in future studies. The other limitation was the small number of participants who were recruited in a short time and cross-sectional form; nonetheless, the results provided baseline data for a follow-up study to evaluate the changes in Jak gene expression in the peripheral blood of diabetic patients and to define its association with clinical and paraclinical alterations.

## CONCLUSION

In summary, Jak1 and Jak2 gene expression levels were increased in the peripheral blood mononuclear cells of patients with DKD compared to healthy individuals. The Jak1/2 genes also showed significant correlations with eGFR and UACR of the patients. In addition, Jak2 expression showed an acceptable specificity and sensitivity for the diagnosis of DKD.

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### Conflicts of interest

There are no conflicts of interest.

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