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# IMPACT OF CYTOKINES ON CHRONIC KIDNEY DISEASE PROGRESSION IN TYPE 2 DIABETIC PATIENTS FOLLOWING COVID-19

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**Abstract:** The ongoing COVID-19 pandemic, now entering its third year, is characterized by the widespread transmission of the SARS-CoV-2 virus, which exhibits a high contagiousness, diverse clinical presentations, and significant morbidity and mortality among individuals with underlying risk factors. Pathophysiologically, the disease is associated with a systemic inflammatory response, disturbances in cardiometabolic function, and varying degrees of glucose dysregulation, often manifesting as marked hyperglycemia leading to either new-onset or exacerbation of existing diabetes. Furthermore, beyond the acute phase, patients may experience persistent symptoms collectively termed "Long COVID" or "Post-COVID Syndrome," likely attributable to a prolonged state of low-grade inflammation and dysregulated immune response, lasting for weeks or even months. Despite advancements in understanding COVID-related hyperglycemia and diabetes, challenges remain in accurately predicting, managing, and comprehensively understanding the course of these conditions. Few studies have investigated the association of interleukin 17A, IL 11, TGFβ1, cystatin C, and apolipoprotein B (ApoB) with the progression of diabetic kidney disease (DKD) and the risk of CV.

**Keywords:** Diabetic kidney disease, chronic kidney disease, apolipoprotein B, IL17A, IL 11, TGFβ1, cystatin C

## Introduction

The COVID-19 pandemic has resulted in over 642 million confirmed cases and approximately 6.62 million deaths as of December 2022 (10). Despite the development of vaccines, global access remains unequal, and vaccinated individuals still face uncertainties regarding protection against new variants (9). Studies suggest a higher risk of severe COVID-19 outcomes in patients with pre-existing conditions such as diabetes and chronic kidney disease (CKD) (3). Diabetes mellitus (DM) affects over 425 million people globally and contributes to systemic inflammation, increasing susceptibility to infections like COVID-19 (4). Research has shown that CKD is prevalent in patients with severe COVID-19, with kidney dysfunction and acute kidney injury being common complications (5). The proposed solution of focusing on diabetic kidney disease (DKD) in relation to COVID-19 could provide critical insights into improving treatment strategies and patient outcomes, offering significant contributions to the medical field.

## Materials and Methods

The study employed a retrospective design, evaluating medical records of 120 adult patients from the Multidiscipline Clinic of Tashkent Medical Academy and Zangiata Infectious Diseases Clinical Hospital between December 2021 and December 2022. The study involved patients with diabetes mellitus (DM), chronic kidney disease (CKD), and COVID-19. Patients were categorized into four groups: Group 1 (65 patients with DM2T, CKD, and COVID-19), Group 2 (20 patients with DM2T and CKD without COVID-19), Group 3 (15 patients with DM2T and COVID-19), and a control group. The mean age of the participants was 59.27 years, with 56 males and 64 females. Blood samples were collected, processed, and analyzed for various biomarkers such as IL-17A, IL-11, TGF-β1, and COVID-19 IgG antibodies using ELISA kits. Hematological analyses were performed after venipuncture, and samples were stored at -80°C. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR). The study adhered to ethical guidelines, and the collected data were analyzed to identify the pathogenesis and factors contributing to the progression of CKD in the presence of DM and COVID-19.

**Results & Findings**

The results of this study focus on comparing various clinical and biochemical parameters between three groups of patients: those with type 2 diabetes (DM2T) and chronic kidney disease (CKD) with COVID-19, those with DM2T and CKD without COVID-19, and those with DM2T and COVID-19 but without CKD. Key variables such as age, gender, BMI, creatinine levels, inflammatory markers like IL-17A and IL-11, and kidney function markers like TGF-β1 were analyzed. Statistically significant differences were observed between groups, particularly in kidney function markers and cytokineMaterials and Methods levels, providing insights into how COVID-19 impacts diabetic patients with CKD. The results are presented in Table1 and and Tables 2.

**Table 1**.

The characteristics and clinical data of the post-COVID-19 patients.

| | Variables | 1st group (DM2T,CKD, COVID-19) n=65 | 2nd group (DM2T, CKD without COVID-19) n=20 | 3rd group (DM2T and COVID-19) n=20 | p Value |
|---|---|---|---|---|---|
| 1 | Gender<br>Male(%)<br>Female (%) | <br>29(44.61)<br>36(55.38) | <br>11(55.00)<br>9(45.00) | <br>8 (40.00)<br>7 (60.00) | <0.001 |
| 2 | Age (years), median (IQR) | 59 (61, 77) | 60 (65.25) | 60(65.25) | <0.001 |
| 3 | BMI/(kg/m2) median (IQR) | 24.79 (22.91, 26.83) | 23.76 (21.96, 26.98) | 22.67(20.89, 25.87) | 0.043 |
| 4 | Hypertension (%) | 47 (72.30) | 17 (85.00) | 12 (60.00) | 0.187 |
| 5 | cardiovascular disease (%) | 35 (53.84) | 8 (40.00) | 6 (30.00) | 0.881 |
| 6 | Diabetic retinopathy (%) | 49 (75.38) | 6 (30.00) | 5 (25.00) | 0.043 |
| 7 | HbA1C(%), median (IQR) | 7.75 (6.60, 9.10) | 7.10 (6.40, 8.05) | 7.15 (6.55, 8.10) | 0.042 |
| 9 | TG/(mmol/L), median (IQR) | 2.41 (1.73, 3.74) | 1.32 (1.02, 1.91) | 1.12 (0.92, 1.73) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| 10 | ApoB/(mmol/L), median (IQR) | 1.42 (1.23, 1.67) | 0.81 (0.70, 0.94) | 1,03 (0.97, 1.12) | <0.001 |
| 11 | Fasting blood glucose /(mmol/L), median (IQR) | 5.94 (4.78, 7.92) | 5.96 (4.64, 7.43) | 6.13(5.73, 7.24) | 0.492 |
| 12 | Creatinine/ (μmol/L), median (IQR) | 152.15 (128.25, 152.15) | 159.50 (122.00, 252.58) | 85.15 (59.5, 77.5) | 0.898 |
| 13 | CysC/(mg/L), median (IQR) | 1.98 (1.57, 2.60) | 1.95 (1.55, 2.86) | 0.79 (0.67, 0,1) | <0.001 |
| 14 | eGFR/[mL/(min·1.73m2)], median (IQR) | 40.24 (25.62, 51.38) | 42.04 (28.22, 50.46) | 87.69(90.5, 63.5) | <0.001 |
| 15 | D-dimer(μg/ml) median (IQR) | 1.77(0.3, 34.00) | 0.77(1.5, 46.5) | 1.15(2.00, 56.00) | 0.492 |
| 16 | IL 17A (pg/ml) median (IQR) | 45.79(41.5, 81.00) | 38.41(41.00, 81.00) | 1.80(2.00 78.00) | <0.001 |
| 17 | IL11 (pg/ml) median (IQR) | 809.83(19.00, 94.00) | 793.83(416.94, 178.00) | 7.25(8.00, 72.00) | <0.001 |
| 18 | TGFβ1 (ng/ml) median (IQR) | 5.27(12.5, 178.00) | 5.24(12.5, 175.00) | 2.94(10.00, 75.00) | <0.001 |
| 19 | COVID-19 IgG S-RBD (BAU/ml) median (IQR) | 927.50 (234.00, 449.00) | 6.08(6.00, 5.00) | 621.47(129.00, 1165.00) | <0.001 |
| 20 | SARS-COV-2 (COVID-19) IgG antibodies (U/mL) median (IQR) | 971.74 (129.00, 1165.00) | 4.73(5.00, 5.00) | 1971.74(92.00, 371.00) | <0.001 |

The key findings from Table 1 are as follows:

1. Gender Distribution: The 1st group (DM2T, CKD, COVID-19) had a higher proportion of females (55.38%) compared to males (44.61%), while the other groups showed similar male-female distributions.

2. Age: The median age across all groups was around 60 years, with no significant difference between them.

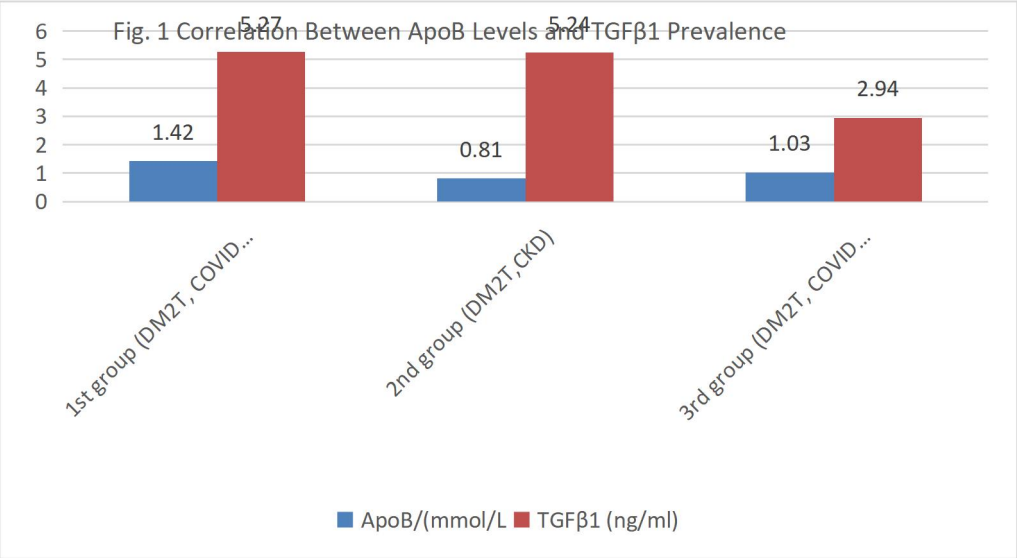
3. BMI: The 1st group had a slightly higher BMI (24.79 kg/m²) than the other groups.

4. Diabetic Retinopathy: The 1st group had the highest incidence of diabetic retinopathy (75.38%) compared to the other two groups.

5. Triglycerides and ApoB Levels: The 1st group had significantly higher triglyceride and ApoB levels compared to the other groups ($p < 0.001$).

6. Kidney Function (eGFR): The 1st and 2nd groups had notably lower eGFR values (40.24 and 42.04 mL/min·1.73m², respectively), indicating impaired kidney function, while the 3rd group had a much higher eGFR (87.69 mL/min·1.73m²).

7. Inflammatory Markers: IL-11, IL-17A, and TGF-β1 levels were significantly elevated in the 1st group compared to the 3rd group ($p < 0.001$), indicating higher inflammation and kidney damage in COVID-19 patients with CKD.




TGF-β1 (Transforming Growth Factor Beta 1) plays a significant role in the regulation of inflammation, fibrosis, and tissue repair, making it particularly relevant in the context of chronic kidney disease (CKD) and COVID-19. In these findings, TGF-β1 levels were significantly elevated in the 1st group (DM2T, CKD, COVID-19) compared to the 3rd group (DM2T, COVID-19 without CKD). This indicates that TGF-β1 may be a marker of worsened kidney function and disease progression, especially in COVID-19 patients with underlying CKD.

The higher levels of TGF-β1 in patients with both CKD and COVID-19 suggest that these individuals experience greater kidney damage and fibrosis, which could exacerbate the progression of CKD. Elevated TGF-β1 is also associated with inflammatory responses, contributing to the overall worsening of kidney function. This highlights TGF-β1 as a potential diagnostic and prognostic marker, helping to assess the severity of kidney injury in diabetic and CKD patients with COVID-19, guiding therapeutic strategies.

**Discussion & Analysis**

The findings of this study align with previous research indicating that patients with comorbidities, particularly diabetes mellitus (DM) and chronic kidney disease (CKD), experience more severe outcomes from COVID-19. DM has been shown to significantly increase the risk of ICU admission, mechanical ventilation, and mortality. Our study revealed that elevated levels of TGF-β1, IL-11, and IL-17A in patients with DM2T, CKD, and COVID-19 correlate with increased inflammation and kidney dysfunction, suggesting these biomarkers could serve as indicators of disease severity. CKD patients, especially those with diabetic nephropathy, are more susceptible to complications due to chronic systemic inflammation and immunosuppression, which exacerbates the progression of COVID-19.

The co-existence of DM and CKD further complicates the clinical management of COVID-19, as both conditions independently increase the likelihood of acute kidney injury and poor outcomes. Despite these findings, some limitations should be noted. The study's observational nature means causality cannot be definitively established. Additionally, the absence of detailed

clinical records, such as patient treatment history and renal therapy, limits the ability to assess the full impact of underlying conditions. Future research should explore the impact of multiple comorbidities on COVID-19 outcomes to provide more comprehensive clinical guidance.

**Conclusion**

To conclude the results it shows that, TGF-β1 and IL 11 might influence differentiation and/or function of almost all cells of the innate and acquired immunity. The role of TGF-β1 and IL11 in the pathogenesis of COVID-19 infection is insufficiently elucidated. It was proposed that SARS CoV-2 infection is associated with the release of cytokines from immune cells and injured cells.

Furthermore, increasing ApoB has until now not been correlated with the progression of CKD. In this study, increased and increasing ApoB were found to be independently associated with progression of CKD in diabetes patients. The increase of ApoB had an unfavorable prognosis. The study was limited by its small patient enrollment. Moreover, the increase of serum ApoB level might precede the occurrence of CKD, suggesting that monitoring and reducing serum ApoB levels may provide an alternative approach for the prevention and treatment of CKD.

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