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**Original Research Article**

# Impact of UTI in Both T2DM with and without Nephropathy on Renal Function Tests and Novel Biomarkers (Liver Fatty Acid Binding Protein (LFABP) and Secretory Leukocyte Protease Inhibitor (SLPI))

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**Abstract**: ***Background:*** Type 2 diabetic mellitus patients are more prone to suffering urinary tract infections (UTIs), a more common, severe and poor outcome problem. There has been a number of studies associating chronic renal disease and urinary tract infection (UTIs). ***objective:*** The patients with type 2 diabetes mellitus, diabetic nephropathy (DN) and urinary tract infections (UTIs) are to be studied in a combination, and new biomarkers such as blood concentrations of Secretory Leukocyte Protease Inhibitor (SLPI) and L-Fatty Acid Binding protein (L-FABP) are to be considered. ***Methods:*** The study we took was a case-control one. The 80 participants of the study were divided into two equal groups namely individuals with Type 2 diabetes and individual without DN. The size of every group was 40. Find out the concentrations of L-FABP and SLPI in the blood with the help of the ELIZA method. Urine samples of Karbala Governorate in Iraq were collected between October 2024 and January 2025 with an aim of testing the culture of the urine sample and measuring urinary parameters to access the standards of the urinary parameters of the sample in Karbala Governorate. ***Results:*** UTI was observed in 25 of diabetic and 37.5 of DN patients with no significant differences in renal functions tests in respect to UTI, with exception of Albuminuria and ACR. The level of LFABP was highly elevated in T2DM compared to DN with UTI. It was established that serum urea level showed a significant difference as per the type of the bacterial isolate with an E coli infection leading to a significant lower value of serum urea. ***Conclusion:*** The result of UTI can bring tremendous change between T2DM and DN in the level of Albumine in urine and ACR. Bacterial isolate may also influence Serum Urea level. UTI has an impact on the level of L-FABP in the serum.

**Keywords:** UTI, Diabetic nephropathy, T2DM, L-FABP, SLPI.

## INTRODUCTION

Diabetes mellitus (DM), sometimes called metabolic disease, can happen in case the insulin-producing pancreatic islet beta cells do not work correctly, or in case the body becomes resistant to insulin and cannot absorb the existing one effectively (Eizirik *et al.,* 2020). Diabetic nephropathy (DN) is a severe microvascular effect of diabetes, and it is estimated to affect almost 40% of patients with either type 1 or 2 DM. It is one of the major reasons of renal disease (Assmann *et al.,* 2018). Nitzan *et al.,* (2015a) confirmed that type 2 diabetes mellitus (T2DM) patients were more likely to experience these UTIs and more intense outcomes with debilitating UTIs. In addition, type 2 diabetic patients have more frequent emphysematous UTIs, intra- or perirenal abscesses, and severe urosepsis (Hirji *et al.,* 2012). UTI could occur in type 2 diabetic individuals due to glucosuria, poor immunological response, low white blood cell count, ineffective blood flow, nephropathy-related bladder dysfunction and several other reasons (Ellenberg, 1976; Truzzi *et al.,* 2008). Due to the of complex interplay of host factors and bacterial characteristics, UTIs express themselves clinically in many different ways. Typical manifestations entail dysuria, urine urgency and frequency, abdominal cramping of the lower abdomen, as well as systemic manifestations of fever, chills, and fatigue, but the kind and severity of these symptoms may vary widely and stretch anywhere between mild inconvenience and debilitating agony (Foxman, 2014). In the worst version of DN, chronic hyperglycemia leads to demyelination as a result of the damage to the Schwann cells. The axons are affected in many ways

upon the damage of Schwann cells as far as the two structures are linked and are dependent on one another (Dunnigan *et al.,* 2013). This injury to large nerve fibres results in many symptoms such as sensations of tingling, numbness, filling muscles (El-Mowafy *et al.,* 2022). Hyperglycemia further perturbs the balance of cytokines and reduces the adaptive immune system against an attack which renders diabetics even more susceptible toward microbial infections (Joshi *et al.,* 2024). Other emerging urine markers that are promising are liver fatty acid-binding protein (L-FABP) and secretory leukocyte protease inhibitor (SLPI). There is the rise of L-FABP which is released by the proximal tubular cells as an indication of early tubular damage in response to oxidative or ischaemic stress. The serine protease inhibitor SLPI has shown promise as a marker of inflammation and injury in the area of renal and urinary tract pathology. This study will measure the impact of UTI on the renal functioning of type 2 diabetic patients using the acknowledge nephropathy and traditional measures of renal functioning together with emerging biomarkers (L-FABP and SLPI).

## MATERIAL AND METHODS

Eighty T2DM (T2DM + and T2DM - DN) patients performed a case-control study.

**Samples Selection:**

The test was done by collecting blood and urine samples of patients with type 2 diabetes mellitus (DM) with or without a DN and UTI (DN and no UTI) or without a DN and UTI. Blood samples were taken in order to measure renal function test, SLPI, and L-FABP. In the cultures we applied the urine. There was coverage of all genders. All the patients were aged between 50-59. Patients who were not included due to the not fulfilling the study criteria include those who were on dialysis, had moderate or severe anaemia or had serious liver disease, those who were undergoing a transplant, and those who never signed a verbal statement to participate in the study.

**Ethical consideration:**

Ethical approval of this research was obtained by all three institutions in which a research was conducted at the University of Kerbala, College of Applied Medical Science, Imam Al-Hassan Centre of Endocrinology and Diabetes, along with Imam AL-Hussain medical city. All those that were to participate in this study were notified before and they also provided their verbal consent to be involved in the study.

**Data collection:**

Some of the data that were collected in the two individuals was the name, sex, type of diabetes, age and the onset of type 2 diabetes. Height and body mass index and diet.

**Statistical Analysis:**

The statistical analysis was done using the latest version of the IBM SPSS Statistics of trade (23). In order to summarize the data, descriptive statistics used. The means and standard deviations appeared in the case of continuous variables. Under statistical purposes, p value that is less than 0.05 was considered significant.

## RESULTS

This research study involved 80 patients with T2DM recruited and divided into two similar groups (with and without DN). Frequency was high among the male with DN as compared to female and the case was reverse among T2DM patients without DN. Mean age of the patients with and without DN were (52.329.66) and (54.738.7), respectively. The percentage of uncontrolled sugar level diabetes in T2DM patients was about 30%, but 42.5 percent of T2DM patients had diabetes of over 11 years, as indicated in Table 1.

**Table 1: Demographic data of patients**

| | | | T2DM with DN | T2DM | Total |
|---|---|---|---|---|---|
| **Sex** | **Male** | Count | 21 | 19 | 40 |
| | | % within Group | 52.5% | 47.5% | 50.0% |
| | **Female** | Count | 19 | 21 | 40 |
| | | % within Group | 47.5% | 52.5% | 50.0% |
| **Age mean ±SD** | | | **52.3 ±9.66** | **54.73±8.7** | ----- |
| **Disease Onset of T2DM** | | ≤11 years | 23 | 28 | 51 |
| | | % within Group | 57.5% | 70.0% | 63.8% |
| | | >11 years | 17 | 12 | 29 |
| | | % within Group | 42.5% | 30.0% | 36.3% |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy.

As shown in Table 2, (15/40, 37.5%) of patients with DN had UTI and about 66.6% of them had *E coli.* Whereas, (10/40, 0.25%) of T2DM patients had UTI and 50% of them had *E coli.*

**Table 2: Distribution of patients according to UTI presence and Type of bacterial isolates**

| Group | | | N (%) | Type of Bacteria N (%) | |
|---|---|---|---|---|---|
| | | | | E coli | Staph |
| **T2DM with DN** | **UTI** | Positive | 15(37.5) | 10 (66.7) | 5 (33.3) |
| | | Negative | 25(62.5) | 0 (0.0) | 0 (0.0) |
| **T2DM** | **UTI** | Positive | 10(25) | 5 (50) | 5 (50) |
| | | Negative | 30(75) | 0 (0.0) | 0 (0.0) |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy.

In what to determine whether there exist any variations in the renal functions tests between T2DM and DN, a comparison of the mean of the levels of the tests was carried out and Table 3 and 4 revealed that there is no significant variation in the renal functions tests in general and renal functions tests in relation to the existence of UTI respectively except in Albuminuria and ACR.

**Table 3: Differences in the mean of renal function tests between DN and T2DM patients**

| Renal Function test | Group of Patients | N | Mean | Std. Deviation | P-value |
|---|---|---|---|---|---|
| **eGFR** | T2DM with DN | 40 | 101.5 | 21.15 | 0.57 |
| | T2DM | 40 | 103.92 | 17.64 | |
| **Creatinine in urine(mg/dl)** | T2DM with DN | 40 | 98.77 | 40.88 | 0.36 |
| | T2DM | 40 | 90.23 | 40.71 | |
| **Albumin in urine (mg/dl)** | T2DM with DN | 40 | 14.50 | 23.40 | *0.001 |
| | T2DM | 40 | 1.20 | .86 | |
| **ACR** | T2DM with DN | 40 | 120.20 | 114.70 | *0.000 |
| | T2DM | 40 | 13.79 | 7.49 | |
| **S. Urea (mg/dl)** | T2DM with DN | 40 | 30.07 | 9.63 | 0.39 |
| | T2DM | 40 | 29.67 | 9.81 | |
| **S. Creatinine (mg/dl)** | T2DM with DN | 40 | .73 | .26 | 0.51 |
| | T2DM | 40 | .69 | .23 | |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy, eGFR: estimated Glomerular Filtration Rate, *Significant differences.

**Table 4: Differences in the mean of renal function tests between DN and T2DM patients according to UTI**

| Renal Function Test | Group | N | Mean | Std. Deviation | P-value |
|---|---|---|---|---|---|
| **eGFR** | DN | 15 | 103.33 | 21.32 | 0.76 |
| | T2DM | 10 | 100.70 | 20.33 | |
| **Creatinine in urine (mg/dl)** | DN | 15 | 90.25 | 37.39 | 0.98 |
| | T2DM | 10 | 89.99 | 36.48 | |
| **Albumin in urine (mg/dl)** | DN | 15 | 9.96 | 12.08 | *0.03 |
| | T2DM | 10 | 1.46 | .92 | |
| **ACR** | DN | 15 | 102.56 | 82.51 | *0.003 |
| | T2DM | 10 | 15.04 | 6.23 | |
| **S. Urea (mg/dl)** | DN | 15 | 31.14 | 10.98 | 0.59 |
| | T2DM | 10 | 33.48 | 9.81 | |
| **S. Creatinine (mg/dl)** | DN | 15 | .68 | .29 | 0.68 |
| | T2DM | 10 | .64 | .19 | |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy, eGFR: estimated Glomerular Filtration Rate

Serum urea level was found to be significantly differ according to the type of bacterial isolate, infection with *E coli* results in significant lower serum urea level, as shown in Table 5.

**Table 5: Differences in the mean of renal function test results according to the type of bacterial isolate**

| Renal Function Test | Type of Bacteria | N | Mean | Std. Deviation | P-value |
|---|---|---|---|---|---|
| eGFR | E coli | 15 | 104.73 | 17.33 | 0.47 |
| | Staphylococcus spp. | 10 | 98.60 | 25.15 | |
| Creatinine in urine (mg/dl) | E coli | 15 | 91.72 | 36.86 | 0.79 |

| | | | | | |
|---|---|---|---|---|---|
| | Staphylococcus spp. | 10 | 87.79 | 37.16 | |
| Albumin in urine (mg/dl) | E coli | 15 | 4.794 | 3.61 | 0.29 |
| | Staphylococcus spp. | 10 | 9.217 | 15.58 | |
| ACR | E coli | 15 | 58.24 | 47.81 | 0.46 |
| | Staphylococcus spp. | 10 | 81.53 | 108.70 | |
| S. Urea (mg/dl) | E coli | 15 | 28.71 | 10.07 | 0.04* |
| | Staphylococcus spp. | 10 | 37.14 | 9.07 | |
| S. Creatinine (mg/dl) | E coli | 15 | .65 | .21 | 0.68 |
| | Staphylococcus spp. | 10 | .69 | .30 | |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy, eGFR: estimated Glomerular Filtration Rate, *Significant differences.

This study found that LFABP serums were much higher in the T2DM as compared with DN than UTI in the table 6.

**Table 6: Differences in the mean level of SLPI and LFABP in Patients with and without UTI**

| Parameters | UTI status | T2DM with DN | | T2DM | | P. value |
|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Mean | Std. Deviation | |
| SLPI | Positive | 372.53 | 74.01 | 365.94 | 74.07 | 0.257 |
| | Negative | 381.93 | 63.00 | 373.92 | 53.42 | 0.64 |
| L-FABP | Positive | 149.12 | 28.83 | 177.50 | 31.08 | *0.028 |
| | Negative | 154.93 | 34.01 | 158.84 | 33.46 | 0.14 |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy, SLPI: Secretory Leukocyte Protease Inhibitor, L- Fatty Acid Binding Protein, *Significant differences.

In addition, Table 7 indicates that L-FABP level was significantly elevated in T2DM patients infected with E coli.

**Table 7: Differences in mean level of SLPI and LFABP between DN and T2DM according to bacterial isolate**

| | | Group | N | Mean | SD | P-value |
|---|---|---|---|---|---|---|
| *E coli* | SLPI | T2DM with DN | 10 | 368.73 | 74.03 | 0.59 |
| | | T2DM | 5 | 390.21 | 64.01 | |
| | L-FABP | T2DM with DN | 10 | 149.63 | 24.56 | 0.007* |
| | | T2DM | 5 | 190.29 | 20.09 | |
| *Staphylococcus spp.* | SLPI | T2DM with DN | 5 | 380.14 | 82.07 | 0.48 |
| | | T2DM | 5 | 341.66 | 82.3 | |
| | L-FABP | T2DM with DN | 5 | 148.08 | 39.36 | 0.51 |
| | | T2DM | 5 | 164.71 | 36.9 | |

T2DM: Type 2 Diabetic Mellites, DN: Diabetic Nephropathy, *Significant differences.

# DISCUSSION

DN is a principal reason of end-stage renal failure in industrialized and a number of the developing countries and also a leading microvascular complication in diabetic patients (Zhang *et al.,* 2016). In several research works, the linkage between the chronic kidney disease and the urinary tract infections has been noted. The aim of this study is to compare the urinary tract infection (UTI) in diabetic participants to participants who did not have this infection with renal function test and new renal biomarkers. Men and women occur innately on different rates, and have varying rates of progression. Microvascular problems are more probable in males when it comes to microvascular issues, whereas, when facing the consequences of diabetic macrovascular issues, women are more susceptible (Maric-Bilkan, 2017). A larger percentage of DN patients in our case had diabetes more than eleven years (Table 1). Microvascular complications such as retinopathy, neuropathy and nephropathy were associated with a 10-year incidence of type 2 diabetes mellitus, states Table (2) by Beckman and Creager (2016). 25-37.5% of diabetic patients and DN patients, respectively, had a urinary tract infection that was regarded as the main symptomatic indicator of type 2 diabetes mellitus, states Table (2) by Beckman and Creager (2016). Previous researches revealed that 43 percent of people with type 2 diabetes also had urinary tract infections (Sharma *et al.,* 2017). Conversely, in another meta-analysis and review study, 11.50 percent of T2DM patients experienced UTIs, and the cases increased with age (Salari *et al.,* 2022). Causative factors of symptomatic UTIs or bacteriuria may include hyperglycemia, resultant development of bladder autonomic neuropathy, and urinary tract malformations (Nitzan *et al.,* 2015b). In several research works, the linkage between the chronic kidney disease and the urinary tract infections has been noted. The cause may be the use of nephrotoxic drugs by the patients with UTIs, which may result in kidney damage (Dicu-Andreescu *et al.,* 2022). In addition, CKD patients are more prone to UTIs due to immunodeficiency (Shankar & Narasimhappa, 2021).

The frequency of E. coli as a UTI pathogen in this research has been tabulated; these scores follow the observation made by Nicolle *et al.,* (2019), who have documented that diabetes is associated with an elevated risk of infection with extended range beta-lactamase producing E. coli. Since it has been widely reported that E. coli is highly prevalent in the intestines and digestive system, it was hardly a surprise to anyone having urinary tract infections that E. coli can also colonise the urinary tract with its well-documented characteristics of causing virulence (Worku *et al.,* 2021). Individuals with glomerular hyperfiltration at early phases of DN or at both extremes of body-mass index have a compromise as far as the accuracy of creatinine-based GFR estimations is concerned. This makes albuminuria and eGFR worse early metrics of DN, i.e., new biomarkers have to be identified to enable the diagnosis of the disease at its initial stages (Zang *et al.,* 2019).

Individuals with type 2 diabetes and DN with a UTI and without UTI had a large difference in albuminuria (Table 3). Albuminuria is the most sensitive sign of a problem with kidney function (Warren *et al.,* 2019). The main cause of renal tubular proteinuria is the damage of the structures and the functions of the proximal tubules. The renal tubular epithelial cells exhibit the aberrant metabolism and haemodynamics when it is kept in hypoxia-ischemic or chronically high glucose conditions. Reactive oxygen species (ROS), advanced glycation end-product (AGE) and so on are also found in their metabolite expression. The final stage of events surrounding the deposition of extracellular matrix or the infiltration of macrophages leading to the generation of inflammation brings about the renal tubulointerstitial fibrosis and the damages to the tubular structures and therefore affecting the renal tubular reabsorption of the resulting effects of proteinuria in renal tubules (R. Zhang *et al.,* 2024). Conducting their own study, Li *et al.,* (2024) obtained similar results in ACR, where the parameter constituted 6.30 and 446.20 in T2DM and DN, respectively (P-value< 0.001). According to UTI, Table (4), no other significant differences were observed between T2DM and DN. This study included only five patients with diabetic nephropathy whose urea was above the normal range (15-45 mg\dl) as compared to two cases of patients with type 2 diabetes mellitus. One of the indicators of renal function is its blood urea levels and this implies that diabetic mellitus may not reflect that fall in individuals as compared to the healthy controls. Increased plasma urea may be associated with high-protein diet, extreme gastrointestinal haemorrhage, tissue breakdown, or administration of corticosterol, and decreased by low-protein diet or liver disease. It is possible that 40-50 percent of the filtered urea can be reabsorbed in the tubules, and in further stages of renal failure, the reabsorbed urea is reduced (Bispo *et al.,* 2013). As given in a research article published in the journal Ilmu dan Teknologi Kesehatan *et al.,* (2022), the patients who have DN and have high creatinine levels become more vulnerable to experiencing renal failure since they have less functional kidney. Reports indicate that the level of creatinine does not change until roughly half (50%) of the renal nephron tissue has been damaged (Benoit *et al.,* 2020).

The level of urea is significantly different according to the type of bacterium (Table 5 indicates that E. coli exhibited the least amount). Inferior kidney damage may be caused by either the microbe or the host response to an E. coli urinary tract infection as has been previously reported in vitro and in animal studies. It has been proved that rats have been proved to develop scar tissue in their renal parenchyma and due to above-mentioned type 1 fimbriae that are sticky organelles on the surface of the bacterial membrane to cause large foci of inflammation. One of the reasons behind this may be that the type 1 fimbriated strains stimulate the type of enzymes that destroy tissues, by activating the polymorphonuclear leukocytes. Although bacterial clearance process depends on the presence of neutrophils, the literature has revealed in mice that neutrophils can also produce damage to kidney (Mizunoe *et al.,* 1997; Raz *et al.,* 2003). Table 6 indicates that the new biomarkers indicated that the level of SLPI was higher in the type 2 diabetic patient group experiencing DN and positive urine culture than in the type 2 diabetic patient group experiencing UTI. Earlier studies on the connection between SLPI and renal function revealed that the former can be found at higher rates in the earlier to middle stages of DKD (Chen *et al.,* 2022). In the article by Sun *et al.,* (2024), a positive correlation between SLPI and renal impairment in DN patients was found. It can indicate the severity of inflammation in the process of DN and cause an increase in the level of SLPI due to the effects of stimuli of renal damage.

Adapala *et al.,* (2011) hold the view that SLPI has a part to play in the development and progression of DN by hindering the activation of NF-KB transcription which producerly inhibits the endotoxin response of monocytes and SLPI also blocks the recruitment of neutrophils and phagocytic activity. Being able to bind to mRNA and DNA of Escherichia coli bacteria, SLPI halts translation and arrests the development of the bacterium directly killing the bacteria and other kinds of microorganisms. Moreover, the cationic nature of SLPI potentially means that it can be attached and break the anionic bacterial cell membrane (Nugteren & Samsom, 2021). Table 6 reveals that the L-FABP levels were higher in patients with T2DM and positive cultures in comparison to those with DN and positive cultures. In a previous study, children with a feverish UTI that was identified as one of the toxins of polynephritis had L-FABP levels that were extremely elevated (Rafiei *et al.,* 2020), meaning that L-FABP may have played a critical role in the occurrence of diabetes type 2 in the case of urinary tract infection. The present work identified that the levels of SLPI and L-FABP were elevated in type 2 diabetic E. coli-infected people than in type 2 diabetic DN-infected people (Table 7) based on the type of bacteria infection. Potential explanation: The E. coli has more destruction on kidney cells and inflammatory effects than Staphylococcus spp. Rosen et al. (2024) trace an offer of defense against bacterial infection of the urogenital tract to an authored component of defense by the innate host called SLPI. It also demonstrates that SLPI is causative in the resolution of mucosal inflammation and it therefore could possibly be protective of other sites of mucosa against infection.

## CONCLUSION

The results indicate that DN patients had higher percentage of UTI compared to T2DM patients. UTI may also cause a lot of difference between T2DM and DN in Albumin in urine as well as ACR. The kind of bacterial isolate effect may influence the level of Serum Urea. UTI interacts with the L-FABP serum level.

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