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EVALUATION OF RFTS IN DIABETIC VS NON-DIABETIC PATIENTS

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Abstract

Diabetes mellitus is considered to be one of the most prevalent chronic metabolic diseases in the world and is identified by the persistent hyperglycemia caused by the defects of insulin secretion, insulin action or both. Uncontrolled long-term diabetes is linked with a series of microvascular and macrovascular complications which pose a high risk of morbidity and mortality. Of these complications, diabetic nephropathy is believed to be one of the most common causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Renal impairment in diabetic patients can progress slowly and can be asymptomatic in the initial stages, so it is crucial to make renal impairment diagnosis as early as possible. Thus, routine checks of renal functionalities with simple, reliable, cost-effective biochemical tests like serum urea and serum creatinine, also known as renal function tests (RFTs) are important to prevent irreversible renal impairment.

***Purpose of the Study**: The targeted study compared and contrasted the parameters of renal function tests in diabetic and non-diabetic people. It further attempted to establish the prevalence of renal failure in patients with diabetes, evaluated how length of diabetes affected renal functioning status, and found early biochemical predictors of diabetic nephropathy.*

***Methodology**: This comparative cross-sectional research was carried out on adult patients of age 18 years and above till 90 years. The patients were separated into two groups: diabetic and non-diabetic controls. The serum samples taken under normal aseptic condition were tested using a fully automated biochemistry analyzer. The estimation of parameters such as serum urea and serum creatinine were determined by the conventional laboratory procedures. Demographic and clinical information (age, gender, duration of diabetes, etc.) was also taken. The statistical comparison of the mean values of renal parameters in the two groups was conducted and the significant associations was established.*

***Results**: It was expected that the level of serum urea and serum creatinine would be very high among diabetic patients compared to non-diabetic individuals signifying a decreased renal function. Moreover, the patients that had a higher duration of diabetes were anticipated to exhibit more changes in the renal parameters, which indicated progressive nephropathy with the duration of chronic disease.*

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Conclusion: *The research results of the current study are likely to highlight the need of regular renal function check-ups in diabetic patients to help in early detection of nephropathy. Simple biochemical tests are also capable of early screening and various interventions can be initiated promptly and delay the onset of chronic kidney disease and patient outcomes. The research also gives baseline information on the renal dysfunction of the diabetic groups and reinforces the importance of proper laboratory practices in the effective management of healthcare.*

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease resulting from defects in insulin secretion, insulin action or both, leading to persistent hyperglycemia. It has more than millions of people all over the world and is a significant health issue in the world and prevalence continues to increase in both the developed and developing nations. Prolonged hyperglycemia brings about serious metabolic imbalances in carbohydrates, lipids and protein metabolism, which result in structural and functional damage of different organ systems. Microvascular and macrovascular complications are highly linked to diabetes and play a significant role in morbidity and mortality rates of the people affected [1].

Small blood vessel damage tissue integrity and functional impairment may result in retinopathy, neuropathy, nephropathy and other microvascular complications due to prolonged exposure to high blood glucose levels. These complications increase with the length of disease, inadequate glycemic control and comorbidities that accompany the disease like hypertension [2,3]. The diabetic kidney disease or diabetic nephropathy is one of the most common causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the world. Prolonged hyperglycemia causes metabolic and hemodynamic changes in the kidneys leading to thickening of the glomerular basement membrane, expansion of the mesangial, albuminuria and progressive loss of glomerular filtration rate [4].

Besides decreased renal function, diabetic nephropathy has also been shown to have a higher risk of cardiovascular disease, impairs quality of life, and raises healthcare costs. Patients with diabetes have been estimated to develop diabetic kidney disease at a rate of about one-third of the patients in their lifetime though the rate differs with demographic and clinical factors [4]. The pathophysiological processes that contribute to the renal injury in diabetes are oxidative stress, inflammation, and microvascular dysfunction that gradually deteriorate the renal structure and functioning [5]. The diabetic nephropathy can be asymptomatic at its initial stages when biochemical monitoring of the renal functions is necessary to identify and manage at the earliest time. Renal performance tests (RFTs) are serum creatinine, blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR) which are widely used to evaluate the performance of the kidney in diabetic and non-diabetic individuals. Early detection of parameters of RFTs enables the clinician to take prompt actions, slow the onset of the disease, and minimize complications. In addition, the possibility of comparing RFT parameters of diabetic and non-diabetic patients is of great importance as it can help to understand how hyperglycemia impacts the work of the kidneys. These comparisons can be used to recognize subclinical renal dysfunction in diabetes and enhance clinical decisions in management of the disease.

Altogether, an awareness of the systemic impacts of diabetes and how it affects the renal system, underscores why assessing RFTs in diabetic and non-diabetic patients is crucial to promote effective monitoring, treatment, and prevention of diabetes in clinical care.

1. Overview of Diabetes Mellitus

Diabetes mellitus (DM) is a set of chronic metabolic diseases that are manifested by sustained hyperglycemia due to insulin secretion defects, insulin action, or both. Longterm

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increases in blood glucose cause complicated biochemical and physiological imbalances, which impact several organ systems. Depending on the etiology and clinical presentation, diabetes mellitus is classified into a few major types [6].

- **Type 1 Diabetes Mellitus (T1DM):** Type 1 diabetes mellitus is an autoimmune disease that involves the destruction of pancreatic β-cells leading to absolute insulin deficiency. It is usually manifested in childhood or early adulthood and needs lifelong insulin therapy to survive [6].
- **Type 2 Diabetes Mellitus (T2DM):** The most prevalent type of diabetes is type 2 diabetes mellitus, which is caused by peripheral insulin resistance and progressive cell dysfunction in the β-cell. It is closely linked to obesity, lack of exercise, poor dietary practices and old age [6].
- **Gestational Diabetes Mellitus (GDM):** Gestational diabetes mellitus is a condition of glucose intolerance initially identified as pregnancy. It is linked to maternal and fetal risks and predisposes the women with it to have type 2 diabetes mellitus later in life [6].
- **Other Specific Types:** These consist of less widespread types which are monogenic diabetes syndromes (e.g. maturity-onset diabetes of the young [MODY]) and exocrine pancreatic diseases, endocrinopathies, and diabetes caused by drugs or chemicals [6].

These categories are indicative of the heterogeneity of etiology, pathogenesis and clinical management of diabetes mellitus. Proper classification is also necessary to identify the right diagnostic plans, treatment and are preventive to minimize complications associated with the disease.

2. Pathophysiology of Diabetes Mellitus

The pathophysiological processes of the major types of diabetes mellitus vary with their underlying causes [6].

- **Type 1 Diabetes Mellitus**: Type 1 diabetes mellitus is caused by the pancreatic 8-cells destruction caused by autoimmune responses, which causes an absolute insulin deficiency. The result of this immune-mediated process is decreased uptake of glucose by peripheral tissues and increased glucose production by the liver and pronounced hyperglycemia [6].
- **Type 2 Diabetes Mellitus**: The general characteristics of type 2 diabetes mellitus include insulin resistance in the peripheral tissues (particularly skeletal muscle and adipose tissue), and gradual dysfunction of the β-cells. Hyperglycemia initially triggers compensatory hyperinsulinemia but over time, as the β-cell fails, insulin secretion becomes ineffective. Obesity, over consumption of calories, and lack of exercise are the key environmental and lifestyle factors that lead to type 2 diabetes mellitus [6].

The overall impact of the impaired insulin action and decreased insulin secretion leads to metabolic dysregulation comprising of carbohydrate, lipid and protein metabolism. Chronic hyperglycemia increases oxidative stress, chronic inflammation, and microvascular damage, which are key to the emergence of long-term complications, including retinopathy, neuropathy, and nephropathy [6].

One of the most important and fastest growing global health issues of the 21st century is diabetes mellitus. In the past decades, diabetes has become an epidemic, mostly due to the aging of the population, the high urbanization rate, unhealthy eating habits, obesity, and the low level of physical activity [7].

Based on recent estimates worldwide, it is estimated that in 2022, there were about 800 million adults living with diabetes (a significant rise compared to the past decades). The burden of the disease has been increasing rapidly as diabetes is almost twice as prevalent globally now than it was in 1990. In adults, the most common type of diabetes mellitus is type 2 and is highly linked to obesity and lifestyle-related risks [7].

Diabetes is a significant cause of morbidity and mortality in the world. Directly linked to diabetes and diabetes-related kidney disease were a total of some 2 million deaths in 2019. Diabetes is becoming a significant burden on the healthcare system especially in the low- and middle-income countries where the accessibility of the diagnosis, treatment, and preventive care could be insufficient [8].

Diabetes is unevenly distributed throughout the world with higher growth rates being recorded in

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the developing countries that experience a rapid socioeconomic and lifestyle change. The prevalence of diabetes as well as related complications will perpetually increase over the next few decades unless effective population level interventions such as health education, early screening, lifestyle change and better disease management interventions are implemented.

Diabetes mellitus is a significant and swiftly escalating health menace among the population in Pakistan. It is estimated that the prevalence of type 2 diabetes mellitus (T2DM) in the country lies between 10 and 11 percent, but this depends on the region, gender, socioeconomic status, and urban-rural distribution [9]. The rate of prevalence is usually higher in urban populations because of sedentary lifestyle, change in diet, and rise in obesity rates.

According to recent estimates, in Pakistan, type 2 diabetes mellitus is affecting around 24 million people. Nevertheless, other national surveys and international reports indicate that the burden is even bigger, with almost 33 million adults having diabetes. This significant increase in the last 20 years is an indicator of what is occurring on a global scale and the dire necessity of preventive measures and management of the disease [10].

Further burden of diabetes in Pakistan is due to diagnosis at advanced stage, poor glycemic control, lack of awareness about disease prevention, access to healthcare and high rate of chronic complications like nephropathy, retinopathy, neuropathy and cardiovascular disease. These considerations lead to substantial healthcare cost, reduced quality of life and extra burden on the country's healthcare system [9, 10]. Without proper public health interventions in the form of awareness programs, early screening, lifestyle change, and availability of treatment services, the prevalence of diabetes and associated complications in Pakistan would only go on rising.

3. Physiological Function of the Renal System

3.1 Anatomy, Physiology of Kidney

Kidneys are two bean shaped organs which are retroperitoneal in blood and one found on each side of vertebral column. They are critical parts of the urinary system and contribute significantly towards homeostasis. The kidneys are made up of an outer area (cortex) and an inner area (medulla). These organs have millions of work units known as nephrons that play the role of filtering blood and making urine [11].

A nephron consists of a glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting duct. These elements work together to control the balance of fluids and electrolytes, eliminate metabolites, and ensure acid-base balance in the body [11].

The kidneys represent the essential organs that help to take care of internal environment in the body. Their contribution to homeostasis is critical to the normal functioning of the physiology. Renal performance is usually determined by renal function tests (RFTs), which indicate the efficiency of the different functions of the kidney. The kidney works have significant physiological roles [11,12]. These roles include, **Filtration of Blood**: Blood is filtered in the kidneys via the glomeruli and a protein free filtrate is produced and flows into the renal tubules. In this process, the blood is cleansed of toxins, metabolic waste products and excess electrolytes which are excreted through urine. Blood urea nitrogen (BUN) and serum creatinine are the metabolites that build up in the blood when the filtration process cannot take place and thus useful markers in RFT testing [12].

Electrolyte Balance: The kidneys ensure that there are normal levels of key electrolytes like sodium, potassium, calcium, and phosphate. Imbalances in these electrolytes can lead to cardiovascular arrhythmias, neuromuscular dysfunction and metabolic build-up. Electrolyte measurements can also be used to indirectly measure renal tubular functioning [11].

Acid-Base Balance: The kidneys aid in maintaining blood pH through the excretion of hydrogen ions and preservation of bicarbonate ions. Appropriate acid-base regulation is required to maintain cellular functions, enzyme activity and metabolic stability. Renal failure can cause either metabolic acidosis or alkalosis [11].

Blood Pressure: The kidneys help in the regulation of the blood pressure by the secretion of renin which stimulates the renin-angiotensin-aldosterone system (RAAS).

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This endocrine system regulates the tone of the vessels, sodium maintenance and fluid volume. The chronic dysfunction of kidneys can disrupt this process and result in either hypertension or hypotension [11].

Loss of Metabolic Waste Products: Nitrogenous waste products (e.g., urea, creatinine, uric acid, etc.) are excreted mainly by the kidneys. The presence of these substances in the blood signifies that glomerular filtration is impaired and is usually measured by tests of renal functions [12].

Endocrine Functions: The kidneys also carry out some significant endocrine functions in the production of erythropoietin which triggers the production of red blood cells and calcitriol (active vitamin D) which controls the metabolism of calcium and phosphate. The chronic kidney disease tends to interfere with these hormonal functions [11]. Because diabetes is a disease that profoundly influences the renal perfusion, filtration, and tubular activity, their measurement is a comprehensive measure of renal health and especially in diabetic and non-diabetic individuals [13].

4. Effects of Diabetes Mellitus on Renal Function

Diabetes mellitus (DM) is among the most common causes of chronic kidney disease (CKD in the world). Continuous hyperglycemia that comes with diabetes leads to a cascade of structural and functional changes in the kidneys that culminates to diabetic nephropathy. This complication leads to a high morbidity rate, rapid development of end-stage renal disease (ESRD), and adds a significant burden to the growing healthcare expenses across the globe [14,15].

Diabetic nephropathy (DN) is a microvascular complication of diabetes that is defined by a progressive deterioration of renal functioning. Clinically, it is characterized by a sustained albuminuria (≥30 mg/day), gradual decline of estimated glomerular filtration rate (eGFR), hypertension, and risk of cardiovascular disease. Diabetic nephropathy is a natural process that usually starts with glomerular hyperfiltration, then microalbuminuria, then overt proteinuria, and finally, leading to end-stage renal disease (ESRD) [16].

4.1 Mechanism of renal damage in Diabetes

The pathophysiology of diabetic nephropathy involves a complex interaction of metabolic and hemodynamic factors that progressively impair renal structure and function. Several mechanisms contribute to the development and progression of renal damage in diabetes [14,15].

Glomerular hyperfiltration caused by hyperglycemia is one of the initial pathophysiological processes in diabetic kidney disease. At an early age of diabetes, chronic hyperglycemia leads to dilation of the afferent arteriole and to augmentation of renal plasma flow, which leads to augmented glomerular filtration rate (GFR). Though at first compensatory, chronic hyperfiltration causes mechanical stress on glomerular capillaries, resulting in augmented albumin exudation, and glomerular harm [17]. At the same time, chronic hyperglycemia increases the rate of the development of advanced glycation end products (AGEs), which build up along the glomerular basement membrane (GBM) and mesangial tissues. AGEs enhance matrix protein cross-linking, oxidative stress, and inflammatory responses, and lead to glomerulosclerosis and tubulointerstitial fibrosis [18, 19]. Besides these metabolic disruptions, hyperglycemia triggers intrarenal renin-angiotensin system, which produces more angiotensin II. Angiotensin II is a potent vasoconstrictor, which elevates intraglomerular pressure by tightening the efferent arterioles, and further enhancing inflammation and fibrosis, thus aggravating renal injury [20]. High glucose levels at the cellular level raise the generation of reactive oxygen species (ROS), surpassing the ability of the antioxidant defenses and leading to oxidative stress. ROS damage podocytes and endothelial cells, trigger the production of pro-inflammatory cytokines and damage tubular and glomerular systems [21].

Lastly, the long-term effect of ongoing metabolic and haemodynamic disruptions promotes the proliferation of mesangial cells and overexpression of matrix protein. This enlargement of mesangium decreases the surface area of available filtration causing glomerulosclerosis and a progressive deterioration of kidney functions [22].

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4.2 Clinical and biochemical manifestation

Diabetic kidney impairment exhibits both clinical symptoms and biochemical indicators, and early detection of these findings is crucial for timely diagnosis and prevention of progression of renal damage.

Microalbuminuria is the first detectable manifestation of diabetic renal involvement and is a marker of increased glomerular permeability and early nephron damage. Progression to overt proteinuria signals worsening glomerular damage and is associated with an elevated cardiovascular risk [16].

High blood urea nitrogen (BUN) and serum creatinine levels are biochemical markers of decreased glomerular filtration and decreased elimination of metabolic waste products [12].

Routine monitoring of renal function tests (RFTs) in patients with diabetes to detect subtle declines in kidney function before irreversible damage takes place can facilitate early diagnosis and timely treatment to slow the progression of diabetic nephropathy. Early recognition of renal impairment allows early therapeutic intervention and improved long term outcomes. Effective strategies for preventing or delaying the progression of diabetic nephropathy include optimal glycemic control, blood pressure management (particularly with use of renin-angiotensin system (RAS)-blocking agents) and lifestyle modifications such as dietary control, physical activity and weight control.

5. Introduction of RFTs: An Overview

Renal Function Tests (RFTs) are a group of biochemical investigations used to assess the functional status of the kidneys. These tests evaluate the kidney's ability to filter blood, excrete metabolic waste products, regulate fluid and electrolyte balance, and maintain acid-base homeostasis.

Common RFT parameters that are performed include serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) and serum electrolytes such as sodium and potassium. In summary, these parameters give useful information on kidney glomerular filtration and tubular function [12].

The clinical importance of testing renal function rests on normal renal physiology. These studies evaluate the kidney's ability to filter the metabolic waste products from the blood and maintain the homeostasis of the body.

Creatinine is a by-product of muscle metabolism, produced at a relatively constant rate, and is eliminated primarily by glomerular filtration. Therefore, increased serum creatinine levels are usually indicative of reduced glomerular filtration and renal function.

A nitrogenous waste product produced in the liver during protein catabolism and excreted by the kidneys. This is often measured as blood urea nitrogen (BUN). High BUN levels can be a sign of poor kidney clearance, dehydration or an increased breakdown of protein.

Estimated glomerular filtration rate (eGFR) is considered one of the best markers of overall kidney function, as it reflects the kidney's ability to filter blood over time. Tubular reabsorption and secretion, which are often changed in renal failure, can also be evaluated using serum electrolyte tests, including sodium and potassium levels [12, 23].

5.2 RFTs' Clinical Use in Patients with and Without Diabetes

In clinical practice, renal function tests, or RFTs, are frequently used to evaluate kidney function in both diabetics and non-diabetics. These tests provide important information on tubular function, glomerular filtration, electrolyte balance, and the progression of renal disease.

In individuals with diabetes mellitus, RFTs are highly helpful in detecting early diabetic nephropathy and assessing the long-term effects of persistent hyperglycemia on renal function. Common indicators of renal involvement in diabetes include elevated serum creatinine, elevated blood urea nitrogen (BUN), decreased estimated glomerular filtration rate (eGFR), and altered urine albumin excretion. Frequent renal monitoring may delay the onset of chronic kidney disease (CKD) and end-stage renal disease (ESRD) and allows for timely therapeutic intervention [15,16].

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RFTs are useful in identifying renal impairment caused by glomerulonephritis, obstructive uropathy, hypertension, dehydration, urinary tract infections, and druginduced nephrotoxicity in individuals without diabetes. These tests also aid in the evaluation of acute kidney injury (AKI) and chronic kidney disease of non-diabetic cause [24, 25].

The specific role that diabetes plays in renal failure can be better understood by comparing the RFT features of groups with and without diabetes. These comparisons help distinguish diabetes-related kidney damage from other causes of renal impairment and supplement epidemiological knowledge of the incidence of kidney disease in different communities [15].

RFTs are crucial for diagnosis, monitoring a disease's progression, and determining how effectively a treatment is working. Serial measures of serum creatinine, serum urea, and eGFR are commonly used to assess rates of progression, stage chronic renal disease, and guide treatment decisions. Patients with deteriorating renal function should also have their electrolyte abnormalities monitored [23, 24].

Individualized treatment plans targeted at maintaining kidney function are supported by routine monitoring of renal parameters in diabetes patients. Ongoing renal evaluation can direct the use of renin-angiotensin system blockers, glycemic control optimization, blood pressure management, and more recent renoprotective medications like SGLT2 inhibitors [16, 26]. As a result, renal function testing is still a widely accessible, affordable, and trustworthy method that is essential to renal evaluation in both ordinary clinical practice and research contexts.

5.2 Common parameters of RFTs

The ability of the kidneys to filter blood and remove metabolic waste products is reflected in a variety of biochemical indicators seen in renal function tests. These tests are frequently used to evaluate renal status in both clinical practice and research. Among the most often utilized metrics are serum urea, serum creatinine, blood urea nitrogen (BUN), and the blood urea nitrogen to creatinine ratio (BUN/creatinine ratio). These markers provide crucial information about hydration, glomerular filtration, renal perfusion, and underlying renal illness. The assessment of these markers helps with kidney disease prognosis, tracking, and diagnosis [12, 24].

5.1 Serum Urea

Urea is the main nitrogenous waste product that the liver produces throughout the urea cycle, which breaks down proteins and amino acids. After synthesis, the circulation transports urea to the kidneys, where it is freely filtered by the glomeruli and partially reabsorbed by the renal tubules. Consequently, the rate of protein metabolism and renal excretory capability are both reflected in serum urea concentration.

Because of decreased glomerular filtration, elevated serum urea levels are frequently seen in renal failure. Dehydration, a high protein diet, gastrointestinal bleeding, fever, trauma, and increased tissue catabolism can all result in elevated levels. Azotemia is the outcome of urea being retained in the blood due to poor elimination in kidney disease.

However, when interpreted alone, serum urea is regarded as a relatively vague indicator of kidney function because it is impacted by a number of non-renal variables. For a more precise assessment of renal health, serum urea is therefore usually measured in conjunction with serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) [12,27,28].

5.2 Serum Creatinine

Skeletal muscle produces creatinine, a breakdown product of creatine phosphate, at a comparatively steady pace that is proportionate to a person's muscle mass. It is mostly removed by the kidneys through glomerular filtration, with very little tubular secretion and tubular reabsorption. Serum creatinine is thought to provide a more precise measure of renal function than serum urea due to these features. Serum creatinine levels are frequently used to gauge the degree of renal impairment since they typically indicate a decrease in glomerular filtration rate (GFR). Rising serum creatinine levels in individuals with diabetes mellitus may be a sign of poor kidney function and

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the advancement of diabetic nephropathy. However, in the early stages of renal impairment, serum creatinine may stay within the normal reference range, especially if there is still a significant nephron reserve. Age, sex, muscle mass, dietary status, and some drugs may also have an impact. Therefore, serial serum creatinine monitoring and interpretation combined with estimated glomerular filtration rate (eGFR) provides a more accurate assessment of renal status [23, 29, 30].

5.3 Blood Urea Nitrogen

Blood urea nitrogen (BUN), which is the amount of nitrogen in the blood in the form of urea, is a common alternative expression of serum urea level in clinical laboratories. Similar to serum urea, BUN is influenced by renal excretion, protein intake, liver function, hydration, and metabolic activity. Elevated BUN levels are often associated with renal failure, dehydration, congestive heart failure, gastrointestinal bleeding, and rapid protein catabolism. In people with diabetes, elevated BUN may indicate the onset of diabetic nephropathy, early renal involvement, or reduced renal perfusion. Although BUN is a useful screening measure, its concentration can be altered by several non-renal factors, hence it lacks specificity when used alone. BUN is therefore best assessed in combination with serum creatinine, estimated glomerular filtration rate
(eGFR), and other renal indices for an accurate assessment of kidney function [12,13,31].

5.4 BUN to Creatinine ratio

The BUN-to-creatinine ratio is a useful diagnostic measure for distinguishing between different forms of renal impairment. The normal physiological ratio of BUN to creatinine is between 10:1 and 20:1. A higher ratio of BUN to creatinine is anticipated in pre-renal circumstances where urea reabsorption is elevated, such as dehydration, decreased renal perfusion, or heart failure. Conversely, a normal or low ratio may indicate intrinsic renal disease, which is defined by decreased urea and creatinine clearance. Changes in the BUN-to-creatinine ratio in diabetic patients may assist identify the type and degree of renal involvement and differentiate diabetic nephropathy from other causes of renal or systemic failure (KDIGO, 2022).

Blood urea nitrogen (BUN), serum urea, serum creatinine, and the BUN-to-creatinine ratio provide a comprehensive assessment of renal function when taken collectively. When combined, these measurements demonstrate the state of renal perfusion, excretory capacity, hydration, glomerular filtration efficiency, and underlying metabolic diseases. Comparing these biochemical indicators between patients with and without diabetes supports the identification of renal alterations directly associated with diabetes mellitus and the early detection of diabetic nephropathy. These comparisons are particularly useful in clinical research to understand the long-term effects of chronic hyperglycemia on renal physiology, the progression of kidney disease, and patient risk assessment.

Combined interpretation of renal parameters significantly improves diagnostic accuracy when compared to using only one marker, which aids physicians in early intervention, illness monitoring, and treatment decision-making [15, 24, 32].

6. Importance of Early Detection of Renal Impairment in Diabetic Patients

Early identification of renal impairment is crucial for controlling diabetes because diabetic kidney disease is one of the most common microvascular complications and often has a silent onset. Many people have gradual renal impairment without exhibiting any clinical symptoms until their kidney function has significantly declined.

If not detected and treated promptly, persistent hyperglycemia causes glomerular hyperfiltration, mesangial enlargement, and thickening of the glomerular basement membrane, which ultimately results in a progressive deterioration in renal function [15]. Early detection of kidney involvement before irreparable damage occurs is made possible by routine evaluation of renal parameters, such as serum urea, serum creatinine, blood urea nitrogen (BUN), urine albumin excretion, and estimation of glomerular filtration rate (eGFR) [24,33]. Prompt treatment

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approaches, including rigorous blood pressure control, enhanced glycemic control, renin-angiotensin system blockage, and lifestyle adjustment, are made possible by early identification. These actions have been demonstrated to lower the risk of end-stage renal disease (ESRD) and decrease the progression of the disease [16,34].

Kidney surveillance is a crucial part of all-encompassing diabetes management because it dramatically reduces cardiovascular morbidity and death in individuals with diabetic nephropathy [35].

6.1 Comparison between diabetic and non-diabetic individual

Determining the impact of diabetes mellitus on renal physiology and biochemical markers requires a comparative analysis of renal function tests (RFTs) comparing individuals with and without the disease. Compared to people without diabetes who have adequate glucose metabolism, diabetic patients are far more likely to experience renal impairment due to the increasing microvascular damage caused by chronic hyperglycemia [15]. Serum urea, serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) are examples of RFT markers that can be compared between these groups to detect minor renal changes linked to diabetes at an early stage. However, in this study we will only focus on the roles of serum creatinine and serum urea is the detection of renal imparement.

These findings can be used to detect subclinical renal dysfunction before overt nephropathy manifests [35]. A comparative approach also improves the study's clinical value, lowers confounding variables, and strengthens causal interpretation. When diabetes-related renal impairment is distinguished from kidney dysfunction caused by other conditions, research results are more trustworthy [24]. Furthermore, information from comparison studies improves diagnostic accuracy, encourages regular renal screening in diabetes patients, and supports prophylactic actions intended to delay the development of chronic kidney disease and end-stage renal illness [16].

Rationale

One of the primary causes of chronic kidney disease, diabetes mellitus is a rapidly expanding global health concern, particularly in developing countries with possibly insufficient systems for routine follow-up and early diagnosis. Early-stage renal impairment in diabetics is frequently asymptomatic, which raises the possibility of irreparable kidney damage and postpones identification. Despite the fact that renal function tests are frequently carried out in clinical settings, there is a dearth of comparative information about renal function parameters in individuals with and without diabetes in local populations. The necessity for additional research and population-specific analysis is highlighted by this paucity of regional data [35]. In order to detect early biochemical alterations linked to diabetes mellitus, the current investigation is required to assess and compare renal function test parameters in patients with and without diabetes. Blood urea nitrogen (BUN), serum urea, serum creatinine, and related indicators can be compared to identify subclinical renal disease early on. The results of this study could support the role of medical laboratory scientists in preventive healthcare, enhance laboratory-based diagnosis, and strengthen early screening programs. In the end, these actions might improve clinical results and lessen the impact of diabetic kidney disease [16,24].

Scope of the study

The research is restricted to assessment of the renal function tests in diabetic and nondiabetic patients who visit a healthcare facility of choice. The population of the study will consist of both male and female adults and the parameters of measurement will be serum urea, serum creatinine, blood urea nitrogen, and BUN to creatinine ratio. The study area includes the laboratory-based comparison of renal function parameters of both groups without the evaluation of the advanced renal markers or imaging research. The limitations are a small sample size, single-centre design, and the removal of patients with identified chronic kidney disease or other systemic disorder which may have its independent

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effect on renal functioning. These shortcomings notwithstanding, the study offers very useful baseline data in early renal evaluation and comparative analysis in diabetic and non-diabetic population.

METHODOLOGY

Study Design

This is a comparative cross-sectional study which evaluated the parameters of renal functions between diabetic and non-diabetic people.

Study Settings

This research was carried out in Biochemistry Section of Doctors Laboratory in AlHaram Hospital, Sargodha, Pakistan.

Sample Size and Selection

The convenient sampling technique was used to recruit 300 participants, comprising of 150 diabetic patients and 150 non-diabetic controls.

Level of Confidence	95%
Margin of error	5%
Population Proportion	31.4
Population size	2500000

Specimen Collection

The participants will be sampled (3-5 mL of blood) through venipuncture by standard aseptic sampling.

The samples were taken in plain serum tubes, and clotted at room temperature (30 minutes).

The serum was centrifuged at 3000 rpm at 10 minutes and kept at 2-8deg C awaiting analysis.

5.2 Biochemical Analysis

We have used the following biochemical procedure to run the test on samples and obtain the accurate results

3.1.1 Creatinine

Principle

Creatinine forms a yellow-orange compound in alkaline solution with picric acid. At the low picric acid concentration used in this method a prescription of protein does not take place. The concentration of the dyestuff formed over a certain reaction times is a measure of the creatinine concentration. As a result of the rapid reaction between creatinine and picric acid, later secondary reaction do not cause a interference

Sample Material

Serum, Heparin plasma, Urine

Stable for 24 hours at +2 to +8 °C or several months at -18 to -20°C.

Reaction without pre-mixture

Since the reaction is highly temperature sensitive, care must be taken to ensure that the solutions are preheated to an exact temperature and the reaction must proceed at a constant temperature. The temperature of the standard and that of the sample must be identical. Provided these conditions are fulfilled, the determination can be performed at any chosen temperature between +20 and +37°C.

Wavelength: 492, 500nm or 509. Light path1cm. Temperature 37°C. Prepare one or two standards for each test series

	Sample	Standard
Reagent 1	500µl	500µl
Reagent 2	500µl	500µl
Serum	100µl	-

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Standard	-	100µl

Mix, Measure the absorbance of the sample (A_{s1}) and standard (A_{s2}) after 1 minute.
Exactly 2 minutes after the first measurement, redetermine the absorbance of the sample (A_{s1}) and standard (A_{s2}). If the reaction is performed at a temperature above +30°C read the absorbance after 30 seconds.

Dilution Limit
If the creatinine value is higher than 15mg/dL in serum or 1+99 diluted urine, repeat the determination with the sample diluted 1+5 with isotonic saline and multiply the results by 6.

Procedure with pre-mixture
Mix Reagent1 and Reagent 2 in a ratio of 1+1. The solution mixture is stable for three days when stored at +15 to +25°C.
Since the reaction is highly temperature-sensitive, care must be taken to ensure that the solutions are preheated to an exact temperature and the reaction must proceed at a constant temperature. The reaction temperature of the standard and that of the sample must be identical. Provided these conditions are fulfilled, the determination can be performed at any chosen temperature between +20 and +37°C.
Wavelength: 492, 500nm or 509. Light path1cm. Temperature 37°C. Prepare one or two standards for each test series

	Sample	**Standard**
Serum	50µL	-
Standard	-	50µL
Working reagent	500µL	500µL

Mix, Measure the absorbance of the sample (A_{s1}) and standard (A_{s2}) after 1 minute. Exactly 2 minutes after the first measurement, redetermine the absorbance of the sample (A_{s1}) and standard (A_{s2}). If the reaction is performed at a temperature above +37°C read the absorbance after 30 seconds.

Dilution Limit
If the creatinine value is higher than 15mg/dL in serum, repeat the determination with the sample diluted 1+5 with isotonic saline and multiply the results by 6.

Quality Control
For precise and accurate control:
Use quality control (HS Norm/HS Path)
Control serum is analyzed in the same way as the sample material.

Reference Range

Serum	
Women	0.6-0.9mg/dL
Men	0.7-1.1mg/dL

3.1.2 Urea
Principle
Urea is reacted enzymatically according to the following equations:
$UREASE$
$Urea+2H2O\rightarrow 2NH4+2HCO3$
$GLDH$
$2OXOGLUTARATE+NH4+NADH\rightarrow L GLUTAMATE+NAD+H2O$

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The decrease in NADH absorbance per unit time is proportional to the urea concentration.

Specimen

Serum, Plasma

Do not use any lipemic, icteric or hemolytic serum or plasma.

Stable at +4°C for 7 days, +20 to + 25 °C for 2 days

Preparation

The reagents are ready to use and stable up to the end of the indicated month of the expiry, if contamination is avoided.

Procedure

Mix 4 parts of Reagent1 with 1 part of Reagent2 =mono-reagent. Leave the monoreagent for atleast 15 minutes at 15 t 25°C before use.

Stability after mixing:	• 4 weeks at 2-8°C • 5 days at 15- 25°C

Protect the mono-reagent from direct light

- Wavelenght 340nm, Hg 334nm, Hg 35nm
- Optical Path: 1cm
- Temperature: 25°C, 30°C, 37°C

Substrate Start

	Blank	**Sample/Standard**
Sample/Standard	-	10µL
Reagent 1	1000µL	1000µL
Mix. Incubate 0-5 Minutes and then add		
Reagent 2	250µL	250µL

Sample Start

	Blank	**Sample/Standard**
Sample/Standard	-	10µL
Mono-reagent	1000µL	1000µL

Mix. Incubate for approx. 60 sec. at 25°C/ 30µLC or approx. 30-40 sec. at 37µLC, then read absorbance A1. After exactly 60 sec. read absorbance A2

ΔA = [(A1-A2) Sample or Standard]- [(A1-A2)Blank]

Dilution Limit

If the concentration exceeds 300mg/dL urea in serum/plasma or 30 g/dL in urine, dilute 1 pat of sample with 2 parts of 0.9% NaCl solution. Multiply the result by 3.

Quality Control

For precision and accuracy use quality controls HS Norm and HS Path

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Reference range

Serum/Plasma	10-50mg/dl
Urine	20-35 g/24h

Blood Urea Nitrogen (BUN)

In case the analyzer provides urea, BUN will be computed in terms of:

BUN = Urea (mg/dL) x 0.467

BUN/Creatinine Ratio

BUN/Creatinine Ratio = BUN (mg/dL)/ Creatinine (mg/dL)

Selection Criteria

Inclusion Criteria

- Aged patients (18 years to 90 years) who submitted serum samples for Renal Function Tests (RFTs).
- Diagnosed diabetic patients (Type 1 or Type 2) whose diagnosis was verified by help of medical records.
- The patients who did not have diabetes mellitus, and who were not diabetic patients with no history of diabetes mellitus established by clinical records or recent blood sugar levels.
- Patients who had their samples of sufficient pre-analytical quality (proper labeling, sufficient volume, no hemolysis, adequate storage/transport).
- Patients who submitted all the demographic and clinical details required in the study (age, gender, disease status).

Exclusion Criteria

- Patients below 18 years of age.
- Those who had known renal diseases (acute or chronic kidney disease) at the time of sample taking.
- The patients who had other systemic conditions which can impact renal BK (e.g., severe liver disease, heart failure, sepsis).
- The samples that were hemolyzed, insufficient in volume, clotted, contaminated or improperly labelled.
- Patients undergoing nephrotoxic medication (e.g., aminoglycosides, NSAIDs, some antivirals) that could change the result of renal functions tests.
- Gestating women (since physiological changes could affect the renal parameters).
- Patients who were not willing to share or provide all the clinical information pertinent to the study.

Data Analysis

The SPSS version 25.0 was be used to analyze the data.

Continuous variables were represented in descriptive statistics (mean +- SD). A comparison of diabetic and non-diabetic groups was done by the use of MannWhitney U Test or Independent t-test depending on the normality of data.

The relationship between length of diabetes and parameters of renal functions was assessed by the rank-order correlation provided by Spearman.

Any p-value of m= 0.05 will be deemed as significant.

Ethical Considerations

All the participants were asked to give informed consent in writing prior to the collection of samples.

Anonymity was carefully ensured during the study.

None of the samples were taken without the consent of patients.

Confidentiality was ensured during the process.

RESULTS

This chapter discusses the results of the study to assess renal function tests (RFTs) in diabetic and non-diabetic subjects. The aim was to assess various biochemical markers of renal function in the two groups and to explore the relationship between diabetes mellitus and renal function. The parameters of both diabetic and non-diabetic subjects were compared using statistical tests, and the findings are presented in tables and figures. The results of this research offer a glimpse into the effects of diabetes on kidney function, and may help in the early detection and treatment of diabetic nephropathy and other complications

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Table 4.1: Age and gender distribution of study population

		Frequency	Percent
Age	20-40	127	42.3
	41-60	99	33
	More than 60	74	24.7
Gender	Male	158	52.7
	Female	142	47.3
	Total	300	100

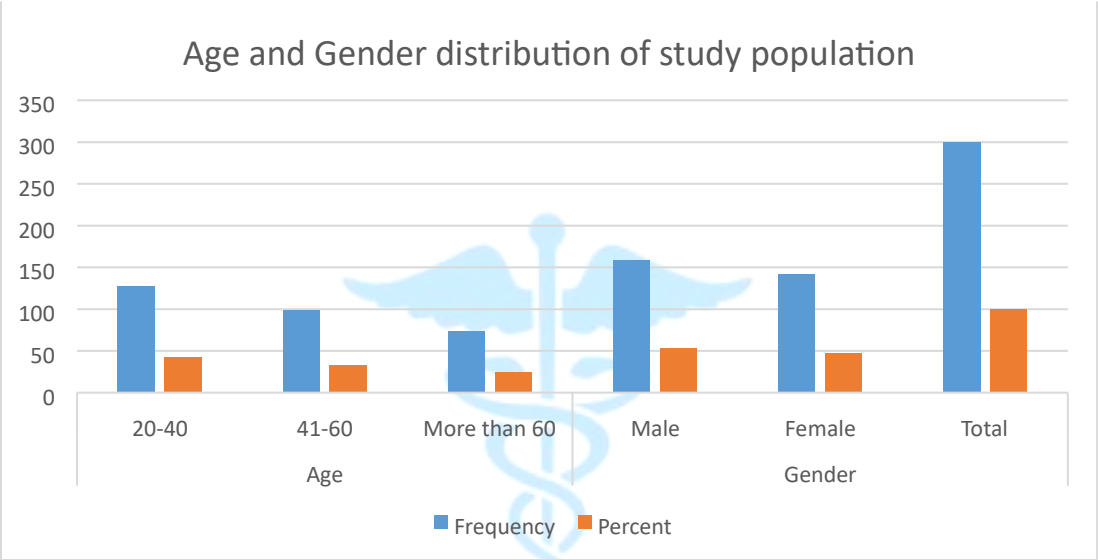


Figure 1.1: Distribution of study population

In terms of age and gender, the sample is fairly balanced. The share of younger individuals (20–40 years old) is higher, while the gender distribution is equal. This ensures the sample's representativeness for comparative research across age and gender groups.

Table 4.2: Mean RFTs values in diabetic vs non-diabetic groups

Parameter	Diabetic	Non-Diabetic
Creatinine	3.691	0.973
Urea	128.05	32.61
BUN	59.142	15.253

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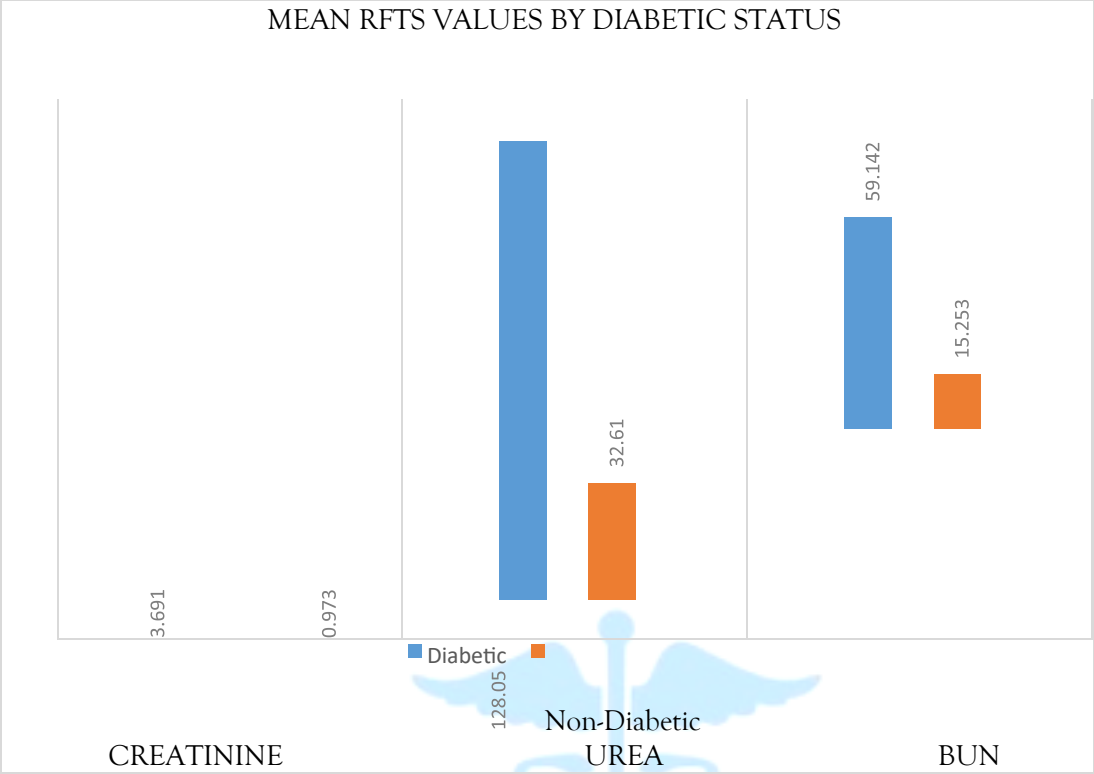


Figure 4.2: Mean RFTs values by diabetic status

The mean RFTs were significantly higher in diabetics than their controls, showing renal dysfunction in diabetics and a potential link between diabetes and renal injury.

Table 4.3: Correlation between Diabetic status, Gender, and Renal Function Parameters among study population

Variables	Diabetes Status	Gender	Creatinine	Urea	BUN
Diabetes Status	1	0.127	0.331	0.735	0.728
Gender	0.127	1	0.148	0.087	0.084
Creatinine	0.331	0.148	1	0.364	0.341
Urea	0.735	0.087	0.364	1	0.996
BUN	0.728	0.084	0.341	0.996	1

A Pearson correlation analysis was conducted between diabetes status, gender and renal biochemical markers. The correlation coefficient for diabetes status and gender was weak but statistically significant ($r = 0.127$, $p < 0.05$), suggesting a weak link between gender and diabetes status.

Diabetes status also showed a moderate significant positive correlation with creatinine ($r = 0.331$, $p < 0.01$), indicating that the presence of diabetes was associated with increased creatinine levels. Moreover, diabetes status showed a strong significant positive correlation with urea ($r = 0.735$, $p < 0.01$) and BUN ($r = 0.728$, $p < 0.01$),

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suggesting a strong association between diabetes and renal dysfunction markers.

A weak significant positive correlation was found between gender and creatinine ($r = 0.148$, $p < 0.05$) but weak and insignificant correlations were observed with urea and BUN.

Of the renal parameters, creatinine showed a moderate significant positive correlation with urea ($r = 0.364$, $p < 0.01$) and BUN ($r = 0.341$, $p < 0.01$). The highest correlation was found between urea and BUN ($r = 0.996$, $p < 0.01$), as these two parameters are biochemically related.

Table 4.4: Gender rank using mann-whitney test

Variable	Male Mean Rank	Female Mean Rank	U value	p-value
Creatinine	129.47	169.15	8244	<0.001
Urea	135.06	164.19	9033	0.004
BUN	134.61	164.59	8968.5	0.003

A Mann-Whitney U test revealed statistically significant sex differences in renal biomarkers, with females having higher mean ranks than males for blood urea nitrogen (BUN) (164.59 vs. 134.61; $U = 8968.5$, $p = 0.003$), urea (164.19 vs. 135.06; $U = 9033$, $p = 0.004$), and creatinine (169.15 vs.47; $U = 8244$, $p < 0.001$). These results show that the study population's creatinine, urea, and BUN readings were generally higher in females than in males, and the observed differences were statistically significant.

Table 4.5: Comparison of RFTS according to T-Test

Parameter	t-value	df	p-value	Mean Difference	95% CI of Difference
Creatinine	-6.053	150.605	<0.001	-2.7187	-3.6062 to -1.8312
Urea	-18.733	159.227	<0.001	-95.447	-105.509 to -85.384
BUN	-18.307	161.255	<0.001	-43.8887	-48.6230 to -39.1543

The two study groups' mean levels of creatinine, urea, and blood urea nitrogen (BUN) were compared using an independent samples t-test. All renal function measures had statistically significant changes, according to the data. The groups' creatinine levels varied considerably, with a mean difference of -2.7187 and a 95% confidence interval (CI) of -3.6062 to -1.8312, *t*(150.605) = -6.053, *p* < 0.001. Additionally, there was a significant difference in urea levels, with a mean difference of -95.447 and a 95% CI of -105.509 to -85.384, *t*(159.227) = -18.733, *p* < 0.001. BUN levels again demonstrated a significant difference between groups, with a mean difference of -43.8887 and a 95% confidence interval of -48.6230 to -39.1543, *t*(161.255) = 18.307, *p* < 0.001.The first group's mean values of BUN, urea, and creatinine were generally lower than those of the second group, as indicated by the negative mean differences.

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DISCUSSION

Our study showed a significant variation of renal parameters in diabetic and nondiabetic subjects. Serum creatinine and blood urea concentrations were significantly elevated, and estimated glomerular filtration rate (eGFR) significantly decreased in diabetics when compared with the non-diabetic group. This suggests reduced renal function and diabetes mellitus is strongly linked to the development of renal disease.

These findings could be due to chronic hyperglycemia having a damaging effect on the structure and function of the kidneys, compromising its filtration and retention of waste products. The results suggest the need for routine measurement of renal biomarkers in diabetes patients for early identification and management of progressive renal dysfunction. This observation should be validated in larger population studies, along with an investigation of other potential factors.

These results can possibly be understood by considering the physiological consequences of long-term hyperglycemia on the kidney. Chronic elevated blood glucose concentrations can cause glomerulosclerosis and vascular changes in the kidney, resulting in diabetic nephropathy and a decline in renal function. Furthermore, chronic poorly controlled diabetes places an increased workload on the kidneys, which have to excrete excess glucose. These microvascular complications, with time, lead to damage, poor renal perfusion and decreased glomerular filtration rate, leading to increased levels of serum creatinine and urea.The results of the current study are in agreement with previously published studies, which have reported renal dysfunction in diabetic patients. Some studies have demonstrated elevated levels of serum creatinine and blood urea in diabetes patients, in comparison to the healthy control group, and reduced glomerular filtration rate (GFR) has also been commonly reported, especially in patients with type 2 diabetes. These observations confirm the link between diabetes and the development of renal disease. These discrepancies may be due to differences in sample size, duration of diabetes, age of subjects, level of glucose control, compliance to medication and presence of other co-morbids (e.g. hypertension).

It's well known that serum creatinine is a significant indicator of renal function and is used to measure the capacity of the kidneys to clear waste products. A lower glomerular filtration rate, which may be an early or advanced indicator of diabetic kidney disease, may be indicated by elevated serum creatinine levels in diabetic patients. Chronically elevated blood glucose levels can impair nephron function, causing creatinine retention. Blood urea, which is frequently increased in situations of reduced renal clearance, is another indicator of renal function. According to this study, lower renal excretory capacity may be the cause of elevated blood urea levels in diabetic patients. This may be brought on by diabetic nephropathy, reduced renal blood flow, or nephron loss as a result of long-term metabolic problems in diabetes mellitus.The significance of monitoring renal function tests (RFT) in diabetes patients to identify early indicators of kidney impairment is highlighted by these clinically significant findings. Early identification of anomalies in serum creatinine, blood urea, and eGFR can lead to rapid management, which may halt or stop the progression of chronic renal disease. . Furthermore, it is impossible to overestimate the significance of maintaining renal function and enhancing the quality of life for those with diabetes by managing additional risk factors like hypertension and maintaining appropriate glucose management.

It is crucial to consider the study's limitations when assessing the findings. Because of the small sample size and data collection from a single center, the results might not be as widely relevant as they could be. Furthermore, the interpretation of causation is limited by the cross-sectional study design. Furthermore, the link between HbA1c and renal function tests, lifestyle-related factors, and the length of diabetes were not extensively evaluated. Further research using multicenter methods and larger sample sizes is advised. Further studies with larger sample sizes and multicenter participation are recommended to improve the generalizability of the results. Longitudinal studies should also be conducted to evaluate the

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progression of renal impairment in diabetics. To precisely evaluate diabetic management and early renal damage, future studies may include other markers such as HbA1c and microalbuminuria. For people with diabetes mellitus, frequent renal function screening is strongly recommended for the early detection and management of issues. The current investigation supports the connection between diabetes mellitus and deteriorating renal function by highlighting the need for regular biochemical monitoring and early preventive actions.

CONCLUSION

The current study found a strong correlation between changes in renal function measures and diabetes mellitus. Serum creatinine, urea, and blood urea nitrogen (BUN) levels showed statistically significant differences between the study groups; diabetic patients had greater values than the control group, suggesting a decline in renal function. These results suggest that chronic hyperglycemia may raise the risk of diabetic nephropathy and contribute to progressive kidney damage. The study's findings confirm the necessity of routinely assessing renal biomarkers in diabetics in order to detect renal damage early.

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