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Article

Sex-Dependent Physiological and Metabolic Alterations in Chronic Renal Failure: Insights from an Iraqi Cohort

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Abstract: Chronic renal failure (CRF), commonly known as chronic kidney disease (CKD), is a progressive, irreversible decrease of kidney function that eventually necessitates dialysis or a kidney transplant. Among male and female CRF patients, immune markers (IgG, IgA), liver function enzymes (AST, ALT and ALP) from major biochemical parameters such as Urea, Creatinine, UA Ca^{2+}, Na^{+} K^{+}, Cl^{-} were measured. Overall, 90 individuals were enrolled: 60 patients (≥25 years, both sexes) and 30 age-matched healthy volunteers (≥28 years). CRF patients had considerably higher immunoglobulins G and A with female preponderance (63.3%). The latter showed increased liver enzyme activities, together with several remarkable alterations in biochemical parameters when compared to controls. An interesting finding was the possible association of celiac disease with a propensity of CKD. The positive results from the present investigation suggest that consideration of these hepatic immune and metabolic markers tested for should be included within patient-based early diagnosis. Disease severity and complications can be predicted by means of these simple, rapid measurements. Such a timely diagnosis is of great significance for the health care providers and decision makers, with better prediction to have a better prognosis and slow down the progression of CKD.

Keywords: Biomarkers of Kidney Function, Celiac Disease Association, Electrolyte Imbalance, IgA, Liver Enzymes

Introduction

Kidney failure can occur as a sudden event, called acute renal failure (ARF), or a more insidious but gradual process, known as chronic kidney disease (CKD). ARF is, by definition, rapid and frequently results in some of the complications like uremia, oedema and hyperkalemia. In contrast, CKD progresses slowly and is often accompanied by hypertension, cardiovascular comorbidity, anemia (Norton et al., 2017). Kidney issues typically result in swelling of hands or feet, fatigue, loss of appetite, nausea and changes in thinking or abrupt mood swings.

The prevalence of new diagnoses of CKD has been rising, and it is now acknowledged as a significant health issue on a global scale (Bello et al., 2017). When the glomerular filtration rate (GFR) stays below 60 mL/min/1.73 m^2 or for more than three months after the beginning of kidney disease symptoms, chronic kidney disease (CKD) is diagnosed. Kidney failure (stage 5 CKD) is the last stage of disease (Webster, et al., 2017). Although ARF makes a major contribution to morbidity and mortality

– some reported case fatality rates include 11–63% among different populations of pediatric and critically ill patients (Schneider et al., 2010) CKD is the leading cause of long term renal dysfunction. Overall, 11–13% of the population is affected worldwide and almost 37 million adults in the United States have CKD, most commonly caused by diabetes or hypertension (Murray et al., 2021). CKD is associated with a high burden of cardiovascular disease, anemia, recurrent acute kidney injury, bone and mineral diseases and cognitive impairment which altogether adds significant morbidity as well as healthcare costs (Pendse et al., 2005; Hill et al., 2016; Lv et al., 2019).

Due to the therapeutic implications of correct staging of CKD with regard to GFR and biochemical surrogates, this information is important for care, particularly in low-resource settings where patients typically present late and require dialysis or transplantation (Breyer et al., 2016; Sin et al., 2020). Various factors cause or contribute to the development and progression of CKD, diabetes, hypertension, sedentary behavior, high salt intake smoking, family history of kidney disease ageing obesity, cardiovascular disease autoimmune diseases and also genetic causes such as polycystic kidney disease (Kelly et al., 2017). Lifestyles like meat consumption, less exercise and irregular sleep have also been associated with higher risk of CKD occurrence and progression (Bach et al., 2019).

A persistent autoimmune enteropathy brought on by gluten is called celiac disease (CD). It is mostly found in the small intestine and can result in weight loss, diarrhea, stomach discomfort, and malabsorption along with a lowered sense of life quality (Pinto-Sanchez et al., 2021; Catassi et al., 2022). It has been shown that the risk for kidney diseases is possibly increased in CD patients, particularly IgA nephropathy (Nurmi et al., 2022). Yet, the association between CD and renal dysfunction has been poorly characterised (Lai et al., 2023).

The objective of the present study is to better understand a potential association between CD and CKD in Iraqi patients by investigating kidney function and immunological markers (IgG, IgA), liver enzyme activities, as well as some biochemical markers in both males and females with CRF. The study also endeavors to facilitate an understanding of the progress process of CRF and establish alternative diagnostics and prognostic strategies.

Materials and Methods

Study design and setting

This cross-sectional investigation was conducted from January to June of 2024 at the Fallujah Teaching Hospital and Department of Pathological Analysis in Iraq. Two groups of a total of 90 subjects, comprising 60 CRF diagnosed patients and 30 controls, were enrolled. Clinical history and laboratory results, such as reduced GFR (< 60 mL/min/1.73 m^2) and/or elevated serum creatinine for more than three months, were used to diagnosis CRF.

Inclusion and Exclusion Criteria

Men and women aged 25 years or older were included in sample. Patients with acute kidney injury, active infections, chronic liver disease, autoimmune disease and malignancy were excluded to avoid potential confounding factors. Age- and sex-matched individuals, who were generally in good health with no evidence of renal or systemic disease, served as control subjects.

Sample Collection and Biochemical Analysis

Five ml of venous blood were drawn aseptically from each subject, and it is recommended blood sampling be done following an overnight fasting. Centrifugation at 1500 × g for 10 minutes was used to separate the serum after blood was drawn and allowed to clot. The serum was stored at -20^{o}C, and AST, ALT and ALP along with urea, creatinine, uric acid, calcium, sodium but also potassium and chloride were measured by analyser MS-380P (Zhejiang, China). ELISA test for IgG and IgA IgG and IgA ELISA tests were performed by Goat Immunoglobulin G from Dimension® EXL 200 Siemens (Germany). All tests were performed according to the manufacturers' instructions, with internal QC procedures in place to assure reliability.

Questionnaire and Demographic Data

Each patient was interviewed using a standardized questionnaire that included general demographic and clinical data (age, sex, marital conditions, place of residence, comorbidities in renal diseases). The survey was pilot tested for clarity and consistency before distribution.

Statistical Analysis

The data was analysed using SPSS software (version 18; IBM Corp.), and the findings are shown as the mean ± SD. The normality of the data was tested using the Shapiro-Wilk test. For normally distributed variables, differences between CRF patients and healthy controls were tested using independent samples t-tests or their nonparametric equivalents. Analysing statistics Pearson's correlation coefficient was used to evaluate the relationships between biochemical markers, and $p < 0.05$ was regarded as statistically significant.

Ethical Considerations

The University of Fallujah's Institutional Ethics Committee (UOF. CAS. 06-240520) examined and approved the study protocol. All procedures were carried out in compliance with the Declaration of Helsinki's principles, and each participant gave written informed permission.

Results and Discussion

Immunoglobulin profiles showed different changes in CKD patients from healthy controls, see Figure 1. Male patients showed lowered levels of IgG also compared to male controls, while in females the difference was not present. By contrast, IgA levels were increased in male and female CKD patients compared with the respective controls. These results reinforce the emerging role of immune dysregulation in CKD progression. High IgA is especially relevant since it occupies a central position in the pathology of IgA-nephropathy, the most frequent primary glomerulonephritis. Welander et al. (2013) found the prevalence ratio of IgA nephropathy in celiac disease to be threefold higher, and Nurmi et al. (2018) noted that kidney disease patients who were positive for tissue transglutaminase (tTG) antibodies had lower renal function; among these, tTG positivity was increased in IgA nephropathy compared to general kidney diseases. Additionally, 12–22% of patients with IgA nephropathy are seropositive for the anti-gliadin IgA antibody, supporting the link between gluten-related immune response and renal damage (Sategna-Guidetti et al., 1992; Moeller et al., 2014). This data in conjunction with the more recent work of Ge et al. (2024) and the meta-analysis of Wijarnpreecha et al. (2016), recommend considering IgA as a promising potential biomarker, for distinguishing CKD patients at high risk of immune-mediated renal damage, including those with underlying autoimmune conditions.

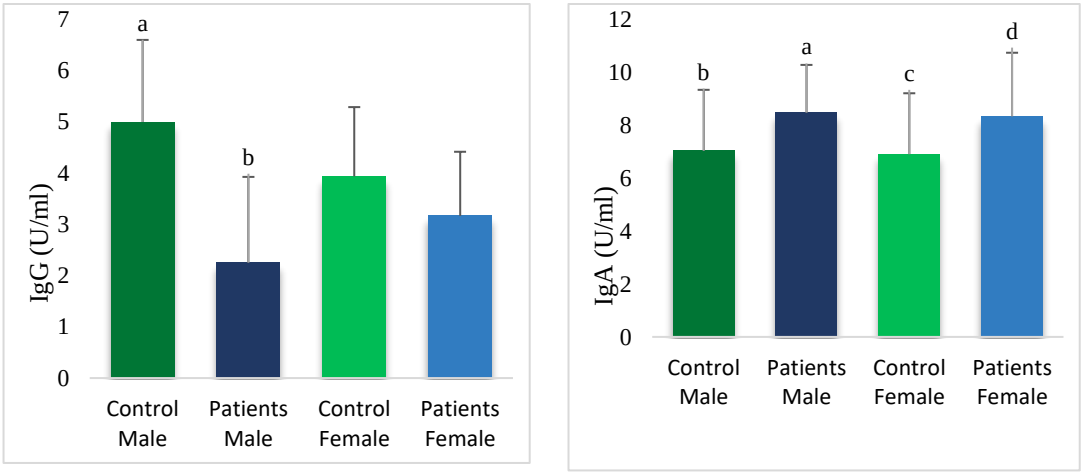

Figure 1. The concentration of Deamidated Gliadin Peptide (DGP) Antibodies (IgG) and (IgA), of patients with chronic kidney disease (CKD) and controls.

Mean values within a row not sharing a common superscript letters (a, b, c, d) were Significantly different, $p < 0.05$.

IgG = Immunoglobulin, IgA = Immunoglobulin A.

Serum AST, ALT, and ALP levels were considerably higher in CKD patients than in the control group, indicating a significant difference in liver enzyme activity, see Figure 2. These findings are indicative of liver and metabolic stress due to renal failure. Of particular importance, high ALP is linked with vascular calcification and higher cardiovascular mortality in CKD (Blayney et al., 2008; Shantouf et al., 2009). Ammar et al. (2025) also reported that CKD patients had elevated ALP and decreased albumin, aminotransferases: index of systemic inflammation and kidney related protein-energy wasting. The simultaneous rise in AST, ALT, and ALP activities in this study further highlights the necessary of evaluating liver status among CKD patients as a part of complete metabolic profile.

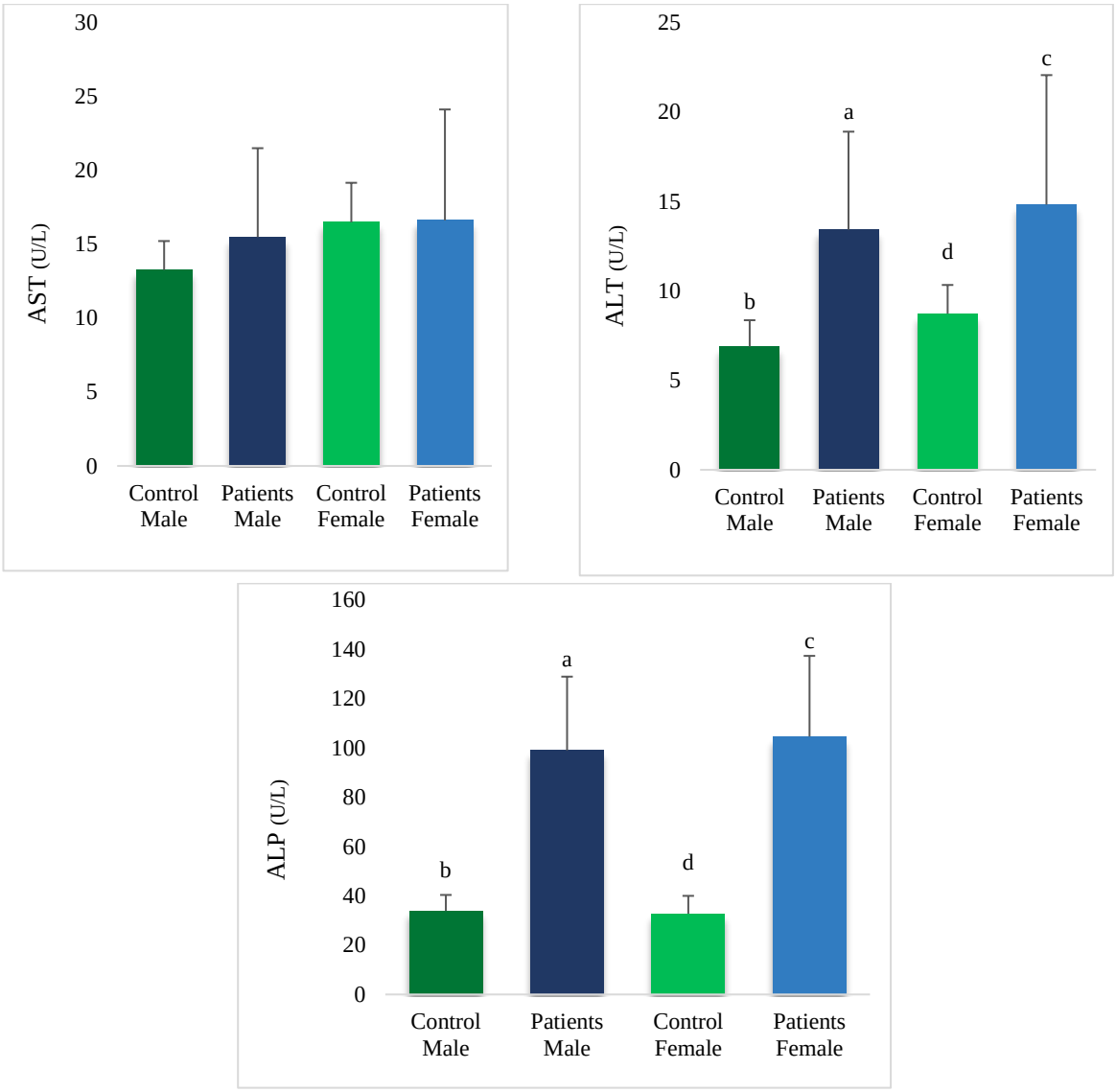

Figure 2. The concentration of AST, ALT, and ALP in patients with chronic kidney disease (CKD) and controls for males and females.

Mean values within a row not sharing a common superscript letter (a, b, c, d) were significantly different, $p < 0.05$

AST= Aspartate Aminotransferase, ALT= Alanine Aminotransferase, ALP =Alkaline Phosphatase

Biochemical parameters and renal function Male and female CKD patients had substantially higher levels of blood urea, serum creatinine, and uric acid than the controls, see Figure 3. Such alterations are evidence of a disturbed renal clearance and are consistent with previous studies where the retention of nitrogenous waste products has been recognised as key CKD pathology (Edward Arnold et al., 2008; Meri et al., 2022). Disturbances of electrolytes were also observed with higher levels

of potassium, calcium and chloride and lower level of sodium among cases compared to controls, see Figure 4. The clinical significance of hyperkalemia is particularly high because of the marked arrhythmogenic potential in advanced CKD and there were no association between chloride level and progression of eGFR, but it was directionally associated with declining renal function and prognosis (Hassab et al., 2023).

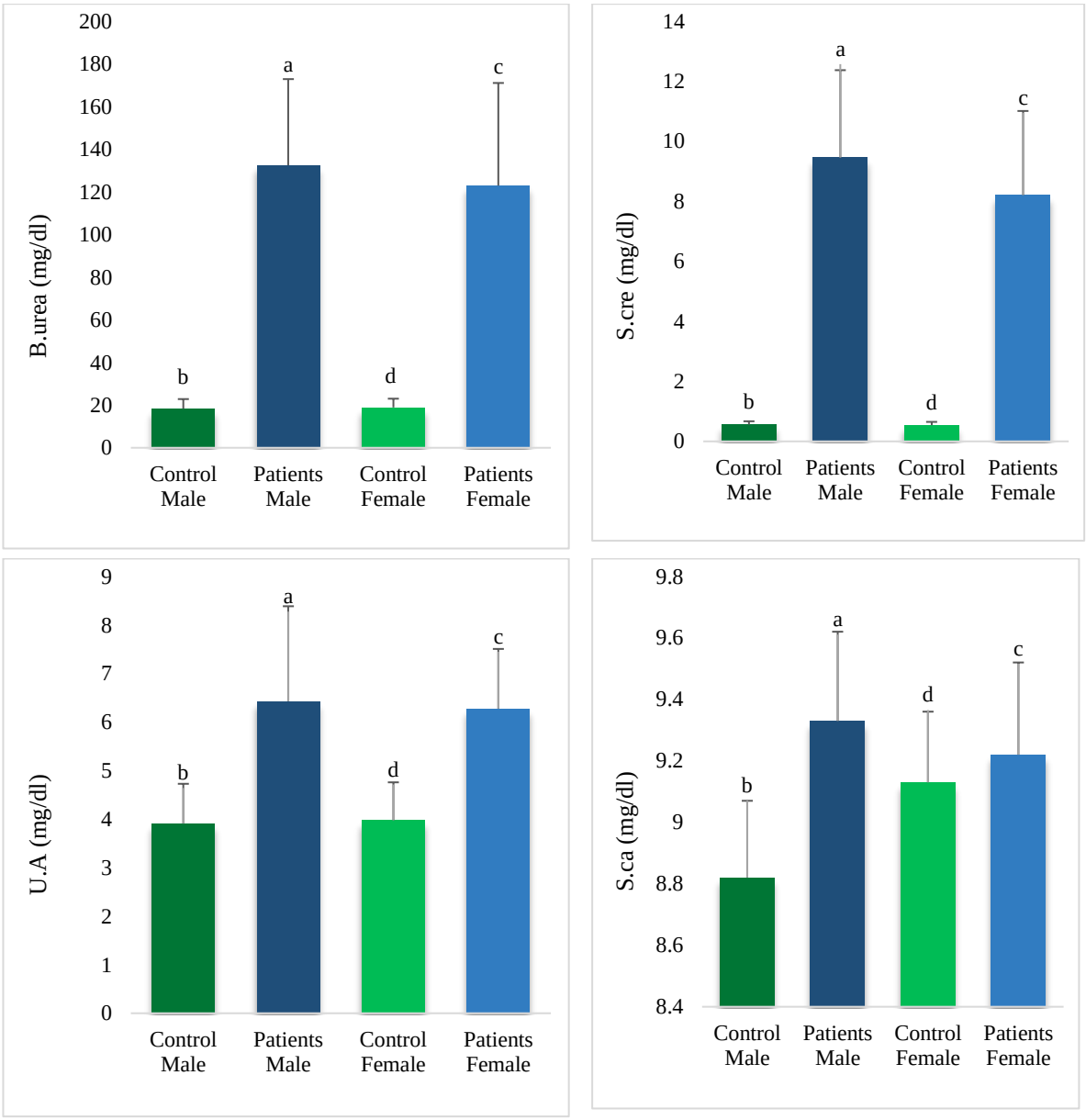

Figure 3. The concentration of B. Urea, S. Cre, U.A, and S. Ca of patients with CKD and controls for different males and females.

Mean values within a row not sharing a common superscript letter (a, b, c, d) were Significantly different, $p < 0.05$

B. Urea = Blood urea, S. Cre = Serum Creatinine, U.A = Uric Acid, S. Ca = Serum Calcium.

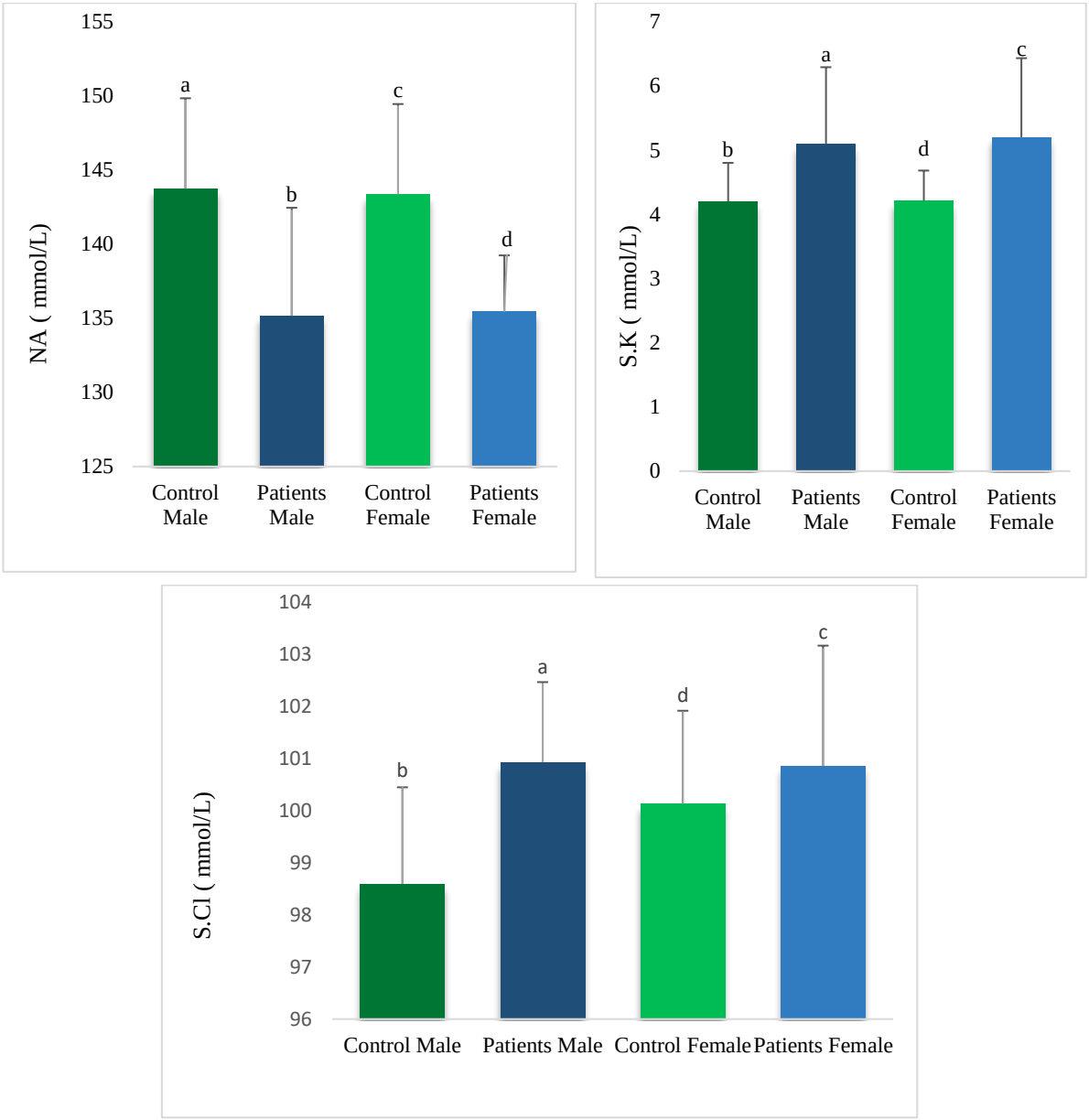

Figure 4. The concentration of NA, S.K, and S.cl of patients with CKD and controls for males and females.

Mean values within a row not sharing a common superscript letter (a, b, c, d) were Significantly different, $p < 0.05$

NA = Sodium, S.K= Serum Potassium, S.Cl= Serum Chloride.

Collectively, these data indicate that CKD is a multi-organ disease characterized by immune activation, hepatic stress and profound metabolic dysregulation which contribute extensively to the burden of disease. Our undirected approach towards a simultaneous assay of immunoglobulins, liver function test and electrolytes in this study provides an overall understanding about the complexity of CKD pathophysiology which may help to identify high-risk patients at an earlier stage. The early identification of these factors may allow for risk stratification, guide early treatment approaches and potentially reduce morbidity. Forthcoming studies could investigate whether specific immune or metabolic pathways can be modulated responsively to hamper disease progression and ameliorate outcomes.

Conclusion

Our results say that CRF is associated with alteration in the immune system, liver and metabolic balance, which makes it a systemic disease. High IgG and IgA levels indicate immune dysregulation and reinforce the relation between gut and kidney pathology, whereas raised AST, ALT, or ALP activities combined with striking changes in urea, creatinine, and electrolytes emphasize hepatic lesions and disrupted homeostasis. Of note, sex differences in these markers have potential for sex-specific risk assessment and management.

The main advantage of this report is to combine immunological, biochemical and enzymatic profiles that reveal a global view of CRF pathogenesis in one community of Iraq. These results, which include a relatively large independent validation cohort, lend support to the potential value of dual biomarker monitoring strategy for early detection, treatment planning and possibly disease progression.

Limitations and Future Directions

This study is subject to several limitations to be taken into account in interpreting the results. However, the small sample sizes and single-center study design are not sufficient to generate causal inference limiting generalizability of findings beyond that population. The study also took place in a regional setting and the findings may not have fully covered genetic, environmental, and lifestyle differences between populations. Furthermore, there was no histopathological verification of renal insult as the purpose here was to evaluate and compare early biochemical and immunological changes.

Further multi-center, longitudinal investigations with larger, more diverse cohorts are needed to confirm these observations and track changes in biomarker levels over time. Furthermore, the inclusion of genetic profiling, histological analysis and analysis of other immune and inflammatory markers would permit a more comprehensive understanding on mechanisms. Such studies may contribute to the definition of the predictive value of these biomarkers, for early diagnosis and targeted and personalized therapeutic strategies in CRF.

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