Predictors of Steroid Resistance in Patients with Focal Segmental Glomerulosclerosis

Marwa Al Riyami[1], Maha Al Asmakh[2,3], Sara Al Ismaili[4], Faisal Al Ismaili[5], Amira Al Kharusi[6], Razan Zadjali[7], Zaina Al Harthi[7], Ali Al Lawati[8], Amal Kassab[9], Nafila Al Riyami[7] and Fahad Zadjali[10]*

[1]Department of Pathology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman

[2]Department of Biomedical Sciences, College of Health Sciences, QU-Health, Qatar University, Doha, Qatar

[3]Biomedical Research Center, Qatar University, Doha, Qatar

[4]Clinical Biochemistry Residency program, Oman Medical Specialty Board, Muscat, Oman

[5]Department of Medicine, The Royal Hospital, Muscat, Oman

[6]Department of Clinical Physiology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman

[7]Department of Clinical Biochemistry, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman

[8]Department of Medicine, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman

[9]Biomedical Technology and Cell Therapy Research Laboratory, Department of Biomedical Engineering, Faculty of Medicine, McGill University, Montreal, Canada

[10] Dean Office, Oman College of Health Sciences, Muscat, Oman

Received: 11 September 2025

Accepted: 8 March 2026

*Correspondence: fahad.alzadjali@ochs.edu.om

DOI 10.5001/omj.2026.54

Abstract

Objectives: Focal segmental glomerulosclerosis (FSGS) is highly heterogeneous and generally believed to be idiopathic due to circulating factors. Prognosis of FSGS relies on patient's response to corticosteroid treatment. By the time steroid resistance is recognized in a patient, the disease has often progressed to an advanced stage. Therefore, early biomarkers capable of predicting steroid resistance in patients with FSGS are essential for optimizing therapeutic management.

Objectives: To identify early prognostic biomarkers of steroid resistance in patients with FSGS based on routine clinical parameters before introduction of standard corticosteroid agents.

Methods: This was a retrospective cohort study where patients' data from 2006-2020 were collected at the point of diagnosis and follow-up. After the application of inclusion and exclusion criteria, 36 biopsy-proven FSGS cases were identified. Steroid resistance was defined by follow-up of proteinuria and serum creatinine levels

Results: 58.3% of patients were steroid resistant with no gender differences except for male being diagnosed at earlier age (P-value 0.008). Following parameters were showed significant higher levels in the steroid resistant group at the time of diagnosis: serum total cholesterol (P-value 0.01), LDL (P-value 0.04) , non-HDL (p-value 0.07) cholesterol and triglycerides with optimum cut-off of 6.7 (AUC 76%) , 4.0 (AUC 74%) and 4.8 mM (AUC 77%), respectively. These lipid markers showed sensitivity above 90% but specificity between 54-58%.

Conclusions: serum cholesterol levels at diagnosis serve as a potential predicting marker for patient responsiveness to steroid therapy. These findings support recent findings on lipid apheresis in enhancing management of steroid resistant-FSGS patients. They also hold valuable implications both prognostically and therapeutically, since it allows for alternative treatment courses using simple and routine lab parameters.

Keywords: Focal Segmental Glomerulosclerosis, Kidney, steroid resistance, LDL-cholesterol

Introduction

Focal segmental glomerulosclerosis (FSGS) is a progressive glomerular condition that leads to end stage kidney disease (ESKD). It is the most common cause of nephrotic syndrome ranging between 15-40% of total cases.[1-3] Clinical presentation of FSGS involves proteinuria, hypoalbuminemia, and hyperlipidemia. Specific diagnosis is defined by histopathological examination rather than specific disease manifestation, where gaps in the podocyte layer covering the glomerular basement membrane start to appear accompanied by podocyte foot process effacement.[4] Sclerosis in FSGS is focal identified by counting under histological slides with less than half of the glomeruli being sclerotic and segmental with less than 50% of the glomerular tuft affected.[5]

This histological podocytopathy is heterogenic in origin, with most sources categorizing them into three types: primary or idiopathic, caused by not yet fully identified circulating permeability factors; secondary, caused by other diseases or viral infections, such as type 2 diabetes, obesity, hypertension, toxins exposure, HIV infection and other environmental factors, in addition to genetic mutations.[6] In Primary FSGS, multiple studies investigate possible circulatory markers that include serum urine-type plasminogen activator receptor (suPAR), apA1b (ApoA1 isoform), cardiotrophin-like cytokine factor, and anti-CD40 antibody, plasminogen activator inhibitor type-1 and dystroglycan.[7-9,10] A recent review on FSGS categorized the disease into four groups adding to the three previously outlined ones an “unclassifiable” type that is of unknown causes [11]. The pathogenesis of idiopathic FSGS is yet to be fully understood despite extensive studies, however it clearly involves circulating factors that affect podocytes and endothelial cells in the glomerulus leading to sub-nephrotic phenotype [4, 12]. This is most clearly evidenced by the recurrence of FSGS in patients after kidney transplantation, with marked proteinuria occurring within hours of post-operation.[13-14]

Like other glomerular diseases, the diagnosis of focal segmental glomerulosclerosis is primarily based on the presence of proteinuria, typically detected through urine analysis, and the histological examination of renal biopsies.[11] Renal biopsy findings, including segmental glomerular sclerosis and podocyte injury, are critical for confirming the diagnosis. These features distinguish FSGS from other glomerular diseases and provide a foundation for further classification into subtypes. However, a comprehensive understanding of the underlying pathophysiology is necessary to tailor treatment approaches and improve patient outcomes.[11] The initial treatment for idiopathic FSGS typically involves corticosteroids, which aim to achieve a complete remission of proteinuria. This remission is crucial as it has been associated with a significantly reduced risk of progression to end-stage kidney disease (ESKD). In some cases, corticosteroid therapy is augmented with immunosuppressant treatments such as calcineurin inhibitors, plasmapheresis, or immunoadsorption, especially in steroid-resistant or refractory cases.[12,15,16] The primary goal of this combined therapeutic approach is not only to mitigate the inflammatory response but also to preserve renal function by minimizing glomerular injury. Despite these efforts, the effectiveness of treatment is highly dependent on the patient’s responsiveness to corticosteroids, making steroid responsiveness a more reliable prognostic indicator than renal histology alone in many cases.[17,18] However, steroid resistance remains a significant clinical challenge, with resistance rates varying widely but affecting up to 80% of patients with primary FSGS. This resistance is associated with persistent proteinuria, which contributes to progressive renal dysfunction, often culminating in critical complications such as nephrotic syndrome and an increased risk of ESKD.[19] These grim outcomes highlight the pressing need for early and reliable biomarkers that can predict steroid resistance in FSGS patients before the initiation of immunosuppressive therapies. Identifying such biomarkers would not only guide clinical decision-making but also reduce the exposure of patients to potentially ineffective and harmful treatments, thereby improving overall management and prognosis.

Prognostic biomarkers in FSGS generally include histopathological, blood, urine, and genetic ones.[20] Nevertheless, when it comes to biomarkers of steroid resistance (SR), studies are rare, and their predictive value is still a subject of validation and implementation in FSGS treatment guidelines. Of all possible biomarkers, urinary ones are non-invasive, thus presenting the most attractive solution. In 2017, Bennett et al. performed a urine proteomic analysis of children with nephrotic syndrome and identified 9 urinary proteins, among which VDBP, prealbumin, NGAL, fetuin-A, and AGP2, presented the most predictive value in identifying steroid resistance.[13] On the other hand, recent metabolomic analysis of 86 paediatric nephrotic syndrome plasma samples concluded that higher plasma levels of creatinine and glutamine and lower malonate can be predictors of SR.[16] Additionally, plasma proteomic analysis of paediatric nephrotic disease samples identified VDB and APOL1 as strong predictive biomarkers of steroid resistance.[21] From a practical standpoint, these biomarkers are not routinely used in clinical practice, while usually post-therapy FSGS is mainly monitored by urine analysis along with invasive renal biopsies. We herein aim to identify steroid resistance predicting markers in patients suffering from FSGS using routine clinical and histopathological data.

Methods

This is a retrospective cohort study where patients' data from 2006-2020 were collected at the point of diagnosis and subsequent follow-ups. Ethical approval was obtained from tertiary hospital centers (SQU-MREC#1941 and SRC#36/2019). Patients were not contacted during the study and all their data were obtained in the electronic system. Identifiers were anonymized and no personal information were shared with the researchers in this study, thus, the ethics committee waived the requirement for informed consent.

Inclusion criteria listed patients presenting with proteinuria as a part of nephrotic syndrome or isolated proteinuria, followed by a histopathological confirmation of FSGS. Exclusion criteria were secondary causes for FSGS such as HIV, sickle cell disease, severe hypertension, structural kidney defects, kidney transplant donor or recipient and autoimmune disorders. Patients undergoing steroid or immunosuppressant therapy, and androgen or herbal medication abuse were also excluded. The status of the disease was monitored through a maximum period of 6 years. Patients were identified as steroid resistance based on persistent proteinuria (not decreasing by 50%) or doubling of plasma creatinine 8 weeks post-therapy,[22]

Baseline parameters at the time of diagnosis included age, gender, BMI, presence of diabetes mellitus or hypertension, plasma and urine creatinine, urea, eGFR, uric acid, lipid profile, albumin, urine protein, urine protein/creatinine ratio, etc. These parameters were then compared between the two groups, steroid resistant (SR) and steroid sensitive (SS), using Man Whitney U or Fisher's exact tests for analysis. Multiple logistic regression was applied to adjust the association with age and gender. Receiver operation curve (ROC) were generated to identify optimum cut-off values at highest Youden-index. Area under the curve (AUC) and likelihood ratio (LR) were measured in ROC analysis. Power analysis was performed for non-parametric ROC curve using the Hanley & McNeil variance formula for power analysis,[23] P-value <0.05 was considered significant.

Results

We identified total of 137 patients with FSGS label in hospital files from year 2006 till 2020, Fig.1. Out of which 85 patients were confirmed for FSGS by histopathological analysis. Of which 60 patients were in-house patients with complete records prior confirmed diagnosis and with complete follow-up records. Following inclusion and exclusion criteria, we identified 37 cases of biopsy proven FSGS and available follow-up clinical data of which 19 (52.8%) were males, Table 1. Median (IQR) age at time of diagnosis was 22 (0.8-64) years. Male subjects were diagnosed at an earlier age with a median age of 19 (1.5-31) years compared to female subjects 34 (0.8-64) years, p-value <0.01. There was no significant gender difference in laboratory parameters or history of obesity, type 2 diabetes mellitus and hypertension. Also, there were no gender differences in renal function profile and extent of proteinuria measured by serum and urine creatinine, blood urea nitrogen (BUN), and urine protein levels, table 1. While, more than half of the patients suffering from FSGS (58.3%) showed SR post-therapy. Steroid resistance pattern differences were not significant between male and female patients.

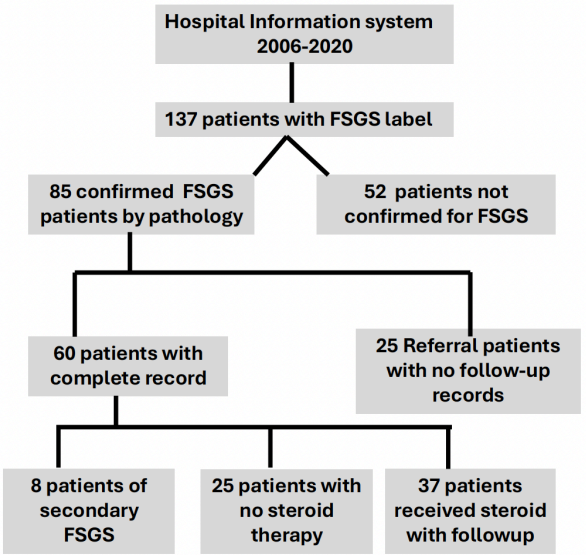

Figure 1: Chart flow of patient recruitment form hospital information system.

Table 1: Characteristics of patient suffering from FSGS at time of biopsy and steroid resistance.

Variables	Total	Male	Female	P-value
N (%)	37	20 (54.0%)	17 (45.9%)	
Age at diagnosis (years)	22 (0.8-64)	19 (1.5-31)	34 (0.8-64)	0.008
BMI (Kg/m^2)	27.6 (15.9-40)	25.3 (15.9-35.5)	30.3 (18-40)	0.62
Creatinine (mM)	83 (21-648)	64.5 (21-329)	113 (28-648)	0.08
Albumin (g/L)	19.5 (6-43)	12.5 (6-42)	21.5 (8-43)	0.07
Urine protein / creatinine (mg/mmole)	890.5 (113.9-6000)	1021.35 (113.9-6000)	661.1 (147.2-2812.28)	0.24
Blood urea nitrogen (mM)	6.25 (2.1-21.6)	6.45 (2.1-18.9)	5.65 (2.4-21.6)	0.99
Systolic BP (mmHg)	134.5 (96-175)	139 (96-172)	132.5 (100-175)	0.76
HbA1C (%)	5.95 (4.2-7.5)	5.65 (4.2-7.5)	6 (4.6-6.9)	0.68
LDL-cholesterol (mM)	5.4 (2.6-14.7)	4.2 (2.6-12.5)	7.15 (3.1-14.7)	0.39
Urine protein (g/dl)	4.35 (1.04-38.29)	4.2 (1.04-38.29)	4.78 (1.67-20.87)	0.23
Urine creatinine (mM)	7.03 (0.56-27.86)	4.8 (0.56-18.47)	10.7 (2.2-27.86)	0.06
Diabetes mellitus, N (%)	4 (11.1%)	1 (5.3%)	3 (20.0%)	0.06
Obesity, N (%)	10 (27.8%)	4 (21.1%)	6 (40.0%)	0.10
Steroid resistance, N (%)	21 (58.3%)	11 (57.9%)	8 (53.3%)	0.82

Data shown are median (interquartile range) or number (percentages). BP: blood pressure

Clinical and biochemical predictors of steroid resistance in patients suffering from FSGS

Several parameters were assessed as potential clinical predictors of steroid resistance at the time of diagnosis. These baseline characteristics included: age, body mass index (BMI), urine/serum creatinine, serum albumin, urine protein, systolic BP, uric acid and lipid profile, Fig 2. Except for the lipid profile, none these parameters were significantly different between SS and SR FSGS cases. More specifically, at the time of diagnosis, patients with SR had higher serum total cholesterol (P-value 0.01), LDL (P-value 0.04) , non-HDL (p-value 0.07) cholesterol and triglycerides. While serum HDL cholesterol was lower in the SR group; however, this difference did not reach statistical significance.

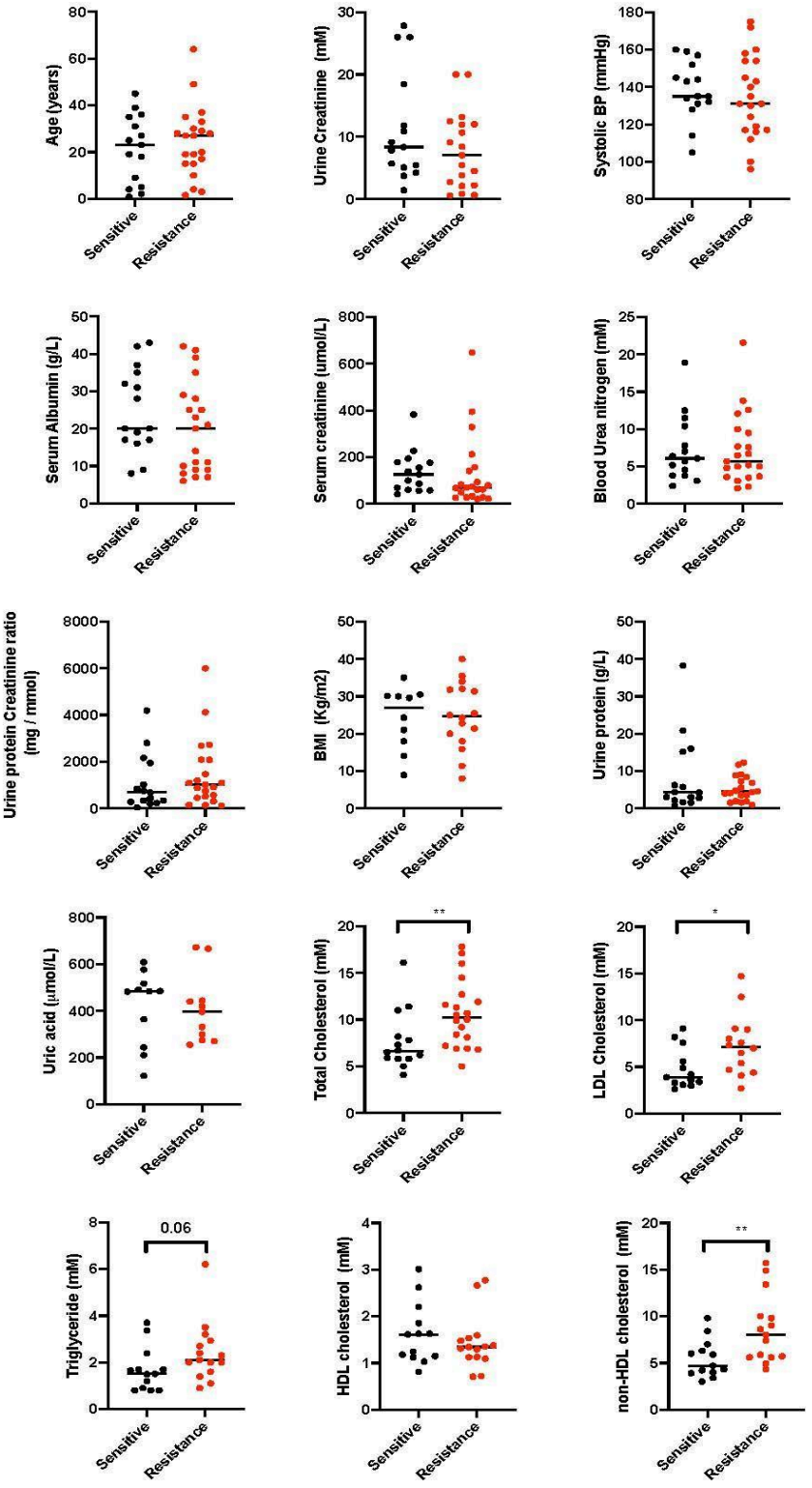

Figure 2: Clinical biochemical parameters associated with steroid resistance in patients with FSGS. Baseline parameters were collected in all patients prior to start of steroid therapy. Patients with steroid sensitive (SS, n=15) and steroid resistance (SR, n =21) were defined based on improvement of proteinuria or serum creatinine post-steroid therapy. * P-value < 0.05, ** P-value < 0.01 of Mann-Whitney U test.

More importantly, presence of comorbidities, such as type 2 diabetes and hypertension, were not associated with steroid resistance in the study cohort, Fig 3. As noted, type 2 diabetes was present in 15.8% of SS cases compared to 7.7% of SR cases with an odds ratio OR of 2.3 (95 C.I% 0.2-24.4) and p-value 0.46. While hypertension, which was a prevalent comorbidity in our cohort, was present in 61.5% of the SS group and 63.2% of the SR group, a difference that is not statistically significant, P-value 0.92. Multiple logistic regression was applied with adjustment to age , gender and presence of comorbidities. There was no significant association between the comorbidities with steroid resistance adjusted for age and gender.

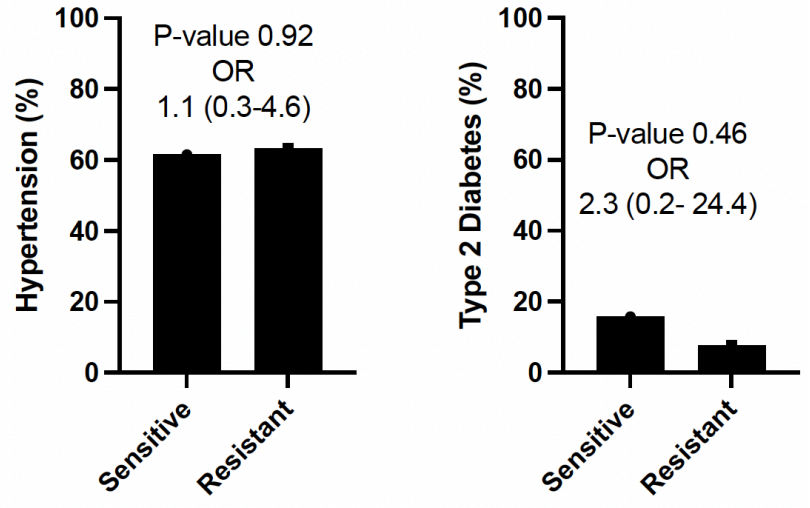

Figure 3: Association of comorbidities with steroid resistance in patients suffering from FSGS. Left: Percent of hypertension. Right: Percent of type 2 diabetes. OR: odds ratio and 95% confidence intervals. P-value: Chi-square test.

Optimum cut-off values of the lipid profile predicting SR in patients with FSGS:

Lipid parameters were used to identify a cut-off value to predict SR in patients at the time of diagnosis. With number of 21 steroid resistant and 16 non resistance, we calculated the ROC analysis power with significant level of 0.05 to detect AUC >0.75. The analysis power was 74%. The ROC curve analysis (Fig 4) showed that optimum cut-off values of 6.7mM (AUC 76%) for total cholesterol, 4.0mM (AUC 74%) for LDL cholesterol, and 4.8mM (AUC 77%) for non-HDL cholesterol could be used to predict SR at diagnosis. These cut-off values gave optimum sensitivity (>90%) to identify patients who might develop SR with a likelihood ratio of 2.0-2.3, Fig 4; However, specificity is weak with a range of 54-58%.

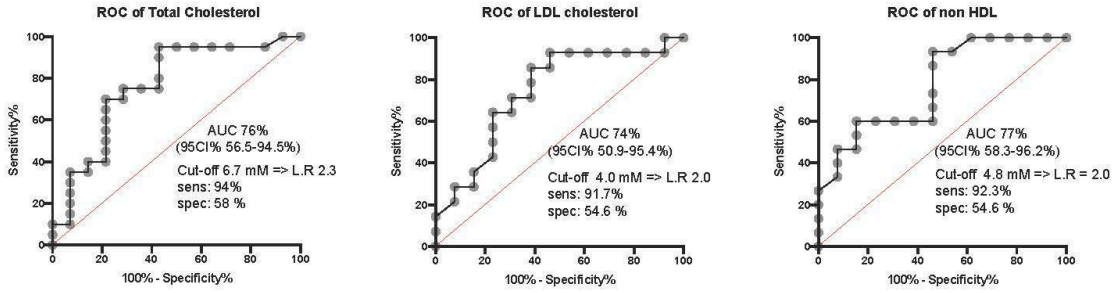

Figure 4: Optimum cut-off value of lipid parameters to predict SR in patients with FSGS. Lipid parameters were taken at the time of initial clinical presentation (A) Total Cholesterol (B) LDL Cholesterol (C) Non-HDL Cholesterol. AUC

Discussion

Steroid resistance in FSGS is common which exposes patients to unnecessarily high doses of corticosteroids, raising concerns of serious complications and side effects, while the disease is left untreated and mostly progresses to a more severe form.[12,24] Here we investigated early markers of SR in patients suffering from FSGS using common and easily available testing parameters. We identified lipid cholesterol parameters, with specific

total-cholesterol, LDL-cholesterol and non-HDL cholesterol, as potential biomarkers associated with SR in patients with FSGS.

In this regard, atherogenic LDL- lipoproteins are particularly significant due to their ability to penetrate the arterial tunica intima, primarily attributed to their small size. This penetration sets off a cascade of events that culminate in vascular damage and inflammatory responses, both of which are hallmarks of atherosclerosis.[25] Beyond their size and density, these LDL particles—carrying apolipoprotein B (apoB)—have recently been further characterized by their distinct charge. Emerging research highlights the role of electronegative LDL particles, which exhibit a unique molecular profile that predisposes them to deleterious effects. Specifically, these electronegative LDL particles have been strongly associated with cardiovascular disease and chronic inflammation. Moreover, they possess the capability to undergo self-aggregation under conditions of low LDL concentration, further exacerbating the pathological state in cardiovascular diseases.[26] Hypercholesterolemia introduces another layer of complexity to lipid metabolism by disrupting the normal lipolysis of various lipid classes, including high-density lipoproteins (HDL). While HDL is generally regarded as protective against atherosclerosis, the pathological processes triggered by hypercholesterolemia seem to override its beneficial effects in some cases. Notably, among the plethora of lipid variants, the apoB isoforms—specifically apoB48 and apoB100—have been prominently implicated in atherogenic processes. These apoB-carrying lipids are considered central players in the development of vascular lesions, contributing directly to the progression of atherosclerosis.[27] The intricate relationship between dyslipidemia and kidney disease is also well established in the scientific literature. Dyslipidemia, while commonly viewed as a secondary manifestation in most chronic diseases, occupies a unique position in the context of renal pathophysiology. In cases of kidney disease, lipid abnormalities may arise early, often preceding a significant reduction in the GFR.[28] For instance, albuminuria—a marker of kidney damage—can be accompanied by dyslipidemia even in its initial stages. This observation underscores the role of lipid metabolism in the pathogenesis of renal diseases, independent of the degree of renal impairment.[28] Further compounding the impact of lipids on kidney health is the role of dietary habits, particularly the intake of high-fat diets. Experimental studies in laboratory animals have provided evidence linking high-fat diet consumption to increased immune cell infiltration into renal tissues. This heightened immune activity is accompanied by structural and functional renal damage, manifesting as glomerulosclerosis.[29] The latter condition, characterized by the scarring of glomerular structures, highlights the influence of dietary lipids on kidney health and provides a mechanistic basis for the observed associations between lipid abnormalities and renal pathologies.[29] Additionally, in a 7-years follow up study, serum cholesterol was recognized as a prognostic marker of kidney injury in patients with type 1 diabetes.[30] Similarly, in patients with type 2 diabetes, both total and LDL-cholesterol serve as significant predicting markers of ESKD.[31] Moreover, lipid nephrosis is a condition where lipids accumulate within the glomerulus, and lipid-loaded “foam cells” are observed histologically in glomerulopathies.[32] Foam cells are more frequently observed in FSGS tissues than minimal change disease and play an important role in podocyte health.[33] In fact, patients with FSGS carrying mutations in APOL1 gene, involved in cholesterol efflux, present with a more progressive kidney disease.[34] Experimental studies in animal models of elevated cholesterol or LDL-cholesterol like apolipoprotein E null mice or LDL-receptor deletion,[35,36] show normal renal functions. However, with exogenous administration of fat or cholesterol, mice develop diffuse renal fibrosis and are more pronounced in LDL-receptor mice compared to wild type littermates.[36] Hyperlipidemia increases plasma viscousity and increases renal vascular resistance, a hallmark in pathogenesis of FSGS.[37] Altogether, our findings and these studies support the detrimental role of lipids in podocyte health and disease progression in glomerular disorders.

Steroid resistance is observed in management of inflammatory-associated diseases such as asthma, rheumatic diseases, inflammatory bowel disease and systemic lupus erythematosus (SLE).[38-40] Steroid and immunosuppressants are the most prevalent therapeutic interventions in FSGS and primary nephrotic syndrome. However, the associated side effects of these interventions like osteoporosis, infection, and metabolic alterations, are major challenges in the management of patients with FSGS.[41] Multiple factors can be associated with SR in FSGS cases such as age, genetic alteration in podocytes, mutations in genes related to glucocorticoid signalling pathway and abnormality in lipid metabolisms in the immune system.[22,41] Additionally, the role of plasma lipoproteins as biomarker of SR has been recently pointed out in a metabolomic study that involved 30 steroid sensitive and 15 steroid resistant nephrotic cases.[16] The study conducted a 4128261041282610paired analysis for post- and pre steroid resistance and identified plasma lipoproteins and plasma adipate as potential biomarker for regulating steroid resistance in clinical cases.[16] In autoimmune disease like SLE, steroid therapy is initiated with dose adjustment for proper management. A positive correlation is observed between cholesterol levels (total and LDL-cholesterol) and dose of steroid therapy.[42]

When it comes to the molecular mechanisms linking hypercholesterolemia with SR, no dedicated studies have thoroughly investigated this critical topic to the best of our knowledge. Despite extensive research on hypercholesterolemia and its systemic effects, including its role in cardiovascular and renal pathologies, the

specific connection between elevated cholesterol levels and SR remains largely unexplored.[43] This gap in the literature is surprising, given the well-established detrimental effects of hypercholesterolemia on the kidney, which include oxidative stress and an increase in oxidized LDL particles (ox-LDL). These ox-LDL particles are known to contribute to kidney damage by promoting immune cell infiltration and the deposition of foam cells, which are hallmark features of FSGS.[43] More specifically, the impact of high LDL levels on the kidney has been clearly delineated through mechanisms involving oxidative stress and inflammation. Oxidative stress induced by ox-LDL leads to a cascade of events that aggravates kidney damage, including the activation of inflammatory pathways and recruitment of immune cells to renal tissues.[44] This inflammatory response results in the accumulation of foam cells, which are lipid-laden macrophages, further exacerbating glomerular injury. Despite these well-documented effects of LDL on kidney function, no direct mechanistic link has been established between LDL and the pathology of SR in FSGS or other diseases characterized by steroid resistance.[44] In a recent study exploring the molecular mechanisms underlying SR, researchers outlined several key factors affecting the glucocorticoid receptor protein (GR) and its downstream signaling pathways.[45] These factors include genetic mutations, post-translational modifications, and conditions leading to GR downregulation. Among these, inflammatory signals have been identified as a significant contributor to impaired GR function. Notably, while genetic and epigenetic factors are often implicated in SR, inflammatory pathways provide a potential avenue to connect hypercholesterolemia-induced oxidative stress with GR dysfunction. This connection, however, remains to be conclusively demonstrated.[45] Inflammatory and oxidative stress-related pathways have been shown to negatively impact GR signaling in other chronic diseases, such as chronic obstructive pulmonary disease (COPD). In COPD, inflammation and oxidative stress interfere with the efficacy of corticosteroid therapy by altering GR structure, reducing its nuclear translocation, and impairing its transcriptional activity.[46] These findings suggest a plausible mechanism through which ox-LDL, known to trigger both oxidative and inflammatory processes, could similarly disrupt GR signaling in FSGS and other conditions relying on steroid-based therapies .[46] Thus, given our present findings, exploring possible direct links between LDL, and other non-HDL cholesterols with SR seem to be highly relevant with regards to various diseases that rely on steroids as therapeutic means, including FSGS.

It is Interesting to note that, reduction of plasma LDL via apheresis for patients suffering from kidney disease has been proposed as a solution to persistent high levels of proteinuria in SR cases for at least two decades.[47-51] This provides a support to our finding that elevated levels of serum cholesterol at an early stage of the disease may serve as predicting marker for steroid resistance. Interestingly, recent studies showed higher remission rates in patients with steroid resistance-FSGS following LDL-apheresis.[47] This could be due to direct reduction in ox-LDL particles or reduction in humoral factors implicated in proteinuria.[52] Nevertheless, more studies are necessary to clearly establish steroid resistance mechanism in FSGS and how to target it to improve the outcome of patients suffering from this chronic disease.

Prediction of steroid resistance at the time of diagnosis in patients with FSGS helps in determining the most suitable line of therapies for patients. We identified total, LDL- and non-HDL cholesterol as possible early predicting parameters for steroid resistance in patients suffering from FSGS. These parameters may not only present a simple tool for early diagnosis of this deadly disease, but it also brings about a novel insight into the possible mechanisms underlying steroid resistance in idiopathic FSGS cases and their aetiology. These findings shed a new light on the importance of LDL apheresis in FSGS cases that present with high LDL and total cholesterol, before initiating steroid treatment courses.

The main limitation in this work is the small number of our cohort, which requires confirmation of these findings using a larger number of participants. Although this is a major limitation, it is a challenge commonly faced by most research studies on FSGS,[53-55] as collecting a sufficient number of participants for such a rare condition remains a significant obstacle. Additionally, causality and pathway understanding of our results can only be established using suitable *in vivo* and *in vitro* models.

Conclusion

Steroid resistance presents a serious therapeutic obstacle in many diseases, particularly in FSGS, where it can be the harbinger of end stage renal disease and kidney failure. Nevertheless, prognostic methods that enables early detection of SR cases are lacking. Herein we show that total cholesterol, LDL cholesterol and non-HDL cholesterol levels can serve as an early predictive method for SR. Nevertheless, more studies are necessary to confirm our findings and to shed a light on the underlying mechanisms behind such an association.

Disclosure

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. Informed consent was obtained from all subjects involved in the study. The study is supported by a joint grant from Sultan Qaboos University and Qatar University: CR/SQU-QU/MED/21/01.

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