KI REPORTS
KIReports.org
RESEARCH LETTER

Epidemiology of End-Stage Kidney Disease in French Polynesia: A Plea for Standardized Diagnosis Workflow in Young Adults of First Nations People

Lorraine Gueguen[1], Belinda Boyle[2], Valérie Chune[3], Marine Dancer[4], Sylvie Leou[1], Pascale Testevuide[1], Ronan Delaval[1] and Stanislas Faguer[5,6,7]

[1]Service de Néphrologie, Hôpital du Taaone, Papeete, Tahiti, Polynésie Française; [2]Service d'Obstétrique, Hôpital du Taaone, Papeete, Tahiti, Polynésie Française; [3]Laboratoire de Biologie, Hôpital du Taaone, Papeete, Tahiti, Polynésie Française; [4]Laboratoire Biomnis, Eurofins, Lyon, France; [5]Département de Néphrologie et Transplantation d'organes, Centre de référence des maladies rénales rares, Toulouse, France; [6]Université Toulouse 3, Faculté de Médecine, Toulouse, France; and [7]Institut National de la Santé et de la Recherche médicale, UMR 1297, Institut de Maladies Métaboliques et Cardiovasculaires, Toulouse, France

Correspondence: Stanislas Faguer, Department of Nephrology and Organ Transplantation, University Hospital of Toulouse, 1, avenue du Pr. Jean Poulhes, 31059 Toulouse Cedex, France. E-mail: stanislas.faguer@inserm.fr

Received 11 September 2023; revised 22 December 2023; accepted 29 January 2024; published online 4 February 2024

Kidney Int Rep (2024) **9,** 1111–1114; https://doi.org/10.1016/j.ekir.2024.01.056
KEYWORDS: autoimmune diseases; end-stage kidney disease; genetic; Indigenous People; Polynesians

INTRODUCTION

First Nations people, defined by the World Health Organization as those who first lived in a region and have distinct cultural traditions, knowledge, and language,[1] are at high risk of chronic diseases, including hypertension, diabetes mellitus, and chronic kidney disease (CKD). Beyond a higher incidence of CKD risk factors in these populations, CKD may also occur at an earlier stage of life in indigenous people and progress more quickly to kidney failure owing to specific environmental or genetic factors.[2] Concomitantly, inequitable access to Western health information and services may preclude up-to-date nephrology care,[1,3] which may lead to impaired detection of a specific kidney disease.

In studies performed among indigenous people from Australia, New Zealand, and Canada, diabetic kidney disease was reported as the main cause of end-stage kidney disease (ESKD).[4,5] This statement might be false about younger people, due to the fact that CKD risk factors, other than diabetes mellitus, occur more frequently in these populations due to their low socioeconomic status (tobacco and alcohol use, very limited access to health care systems) and may only reflect the poorer general health of these individuals, challenging the diagnosis of other causes of CKD (e.g., genetic kidney diseases or immune nephropathies) and precluding personalized and accurate prevention of ESKD.

We therefore aimed to clearly define ESKD etiology in the indigenous population of French Polynesia, a group of 5 archipelagos in the South Pacific (number of inhabitants in 2022: 278,786). Public health policies mainly aim to reduce the burden of metabolic or cardiovascular risk factors of CKD. However, we and others have reported the high incidence of rare genetic kidney diseases or autoimmune diseases in this area.[6,7] For example, because of founder effect, recurrent variations in *COL4A5* and *FAN1* respectively explain the high incidence of X-linked Alport syndrome and recessively inherited karyomegaly in French Polynesia.[6,8] In addition, we also reported the high incidence of systemic lupus erythematosus in this geographic area.[7] The epidemiology of CKD may be more complex, especially in young adult patients, and therefore requires refinement using the most recent clinical workflow to improve nephrology-focused public health policies.

RESULTS

In this retrospective study, we reviewed the clinical charts of all patients who had reached ESKD (kidney transplantation or dialysis) before 45 years of age and who were followed in one of the 3 Nephrology

Table 1. Causes of end-stage kidney disease in a cohort of 151 Polynesian individuals (age at ESKD below 45 years)

Overall cohort ($N = 149$; May 2022)		Cause of ESKD
Metabolic syndrome	42 (28%)	Diabetic nephropathy ($n = 33$)
		Obesity ($n = 4$)
		Hypertension ($n = 5$)
Undetermined nephropathy	30 (20%)	Chronic glomerulopathy ($n = 15$)
		Chronic interstitial nephropathy ($n = 9$)
		Unknown ($n = 7$)
Genetic kidney disease	47 (32%)	Alport syndrome ($n = 20$)
		CAKUT ($n = 14$)
		ADPKD ($n = 5$)
		Karyomegaly ($n = 2$)
		NPHP1-nephronophtisis ($n = 2$)
		INF2-related FSGS ($n = 1$)
		AD FSGS ($n = 1$)[a]
		Additional diagnosis with WES:
		INF2-malignant hypertension ($n = 1$) *mtDNA* A3243G mutation ($n = 1$)
Immune nephropathy	21 (14%)	SLE ($n = 7$)
		IgA nephropathy ($n = 7$)
		ANCA-associated vasculitis ($n = 2$)
		Steroids-responsive FSGS ($n = 2$)
		Antiphospholipids syndrome ($n = 1$)
		Ig-MPGN ($n = 1$)
		C3 glomerulopathy ($n = 1$)
Lithiasis	4 (3%)	
Infection	2 (1%)	
Other	3 (2%)	

AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; ANCA, antineutrophilic cytoplasmic antibody; CAKUT, congenital abnormalities of kidneys and urinary tract; ESKD, end-stage kidney disease; FSGS, focal and segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus.
[a]Inherited FSGS was considered in this patient, whose brother was also followed-up with for FSGS with early onset and a molecular diagnosis of autosomal dominant FSGS (causative gene not available).

Care Units in French Polynesia (Supplementary Methods).

At the time of the review of epidemiological data (May 2022), 563 patients were receiving chronic hemodialysis and 188 were kidney transplant recipients with a functional graft (ESKD patients $N = 751$). The prevalence of ESKD was therefore estimated at 2680 per million inhabitants of French Polynesia (1321 per million inhabitants in mainland France during the same period, according to data from the French national R.E.I.N registry (https://www.agence-biomedecine.fr/IMG/pdf/rapport_rein_2021_2023-06-26.pdf). Among these 751 patients, 178 (23.7%) had reached ESKD before the age of 45 and clinical charts could be adequately reviewed for 149 of them.

Among these 149 patients (mean age at ESKD 33 ± 10 years), ESKD was related to diabetes mellitus, obesity, or hypertension in only 41 patients (27%) (Table 1). Among the others, an immune nephropathy (mainly systemic lupus erythematosus-related glomerulonephritis or IgA nephropathy) was identified in 21 patients (14%), and a genetic kidney disease in 47 patients (32%). In lattermost patients, X-linked Alport syndrome was the main cause of ESKD (44%), followed by congenital abnormalities of the kidneys or the urinary tract (31%). The cause of ESKD remained undetermined in 30 patients (20%).

In 2022, a standardized clinical and biological workflow, including whole-exome sequencing (WES) and reverse-phenotyping in patients with undetermined nephropathy, was implemented in French Polynesia to improve the characterization of kidney diseases. WES was proposed to all patients with undetermined nephropathy who gave written informed consent after dedicated genetic counseling. Since 2022, among the 24 patients who had WES (15 in the former cohort), a genetic kidney disease was confirmed in 7 (33%) as follows: Alport syndrome (partial deletion of chromosome X involving *COL4A5* [del ChroXq2.1-2.8; $n = 1$], or partial deletion of *COL4A3* [$n = 2$]), malignant hypertension with thrombotic microangiopathy ($n = 2$) (pathogenic mutation in *INF2* [p.Arg214His; ACMG 4] or *CFH* [p.Ser1196Pro, which is localized in SCR20 of factor H; ACMG 3]), mitochondrial cytopathy (pathogenic A3243G mutation of the mitochondrial DNA, $n = 1$), and nephronophthisis (homozygous whole-gene deletion of *NPHP1*). One additional patient had a pathogenic variation in SCNN1G at the heterozygous state (p.Gln119Ter; ACMG 5), suggestive of Liddle' syndrome, but a clear genotype-phenotype correlation could not be drawn.

Beyond the cause of ESKD, WES identified a likely pathogenic mutation of *ABCC8* (p.Leu511Val, ACMG 4), a gene whose mutations are associated with

hyperinsulinism and obesity, in a 30-year-old female with prematurity, severe obesity (body mass index >50 kg/m^2), and ESKD at the age of 25 years. Analyzing a subset of genes associated with genetic kidney diseases, we could also confirm the very high allelic frequency of the c.2120G>A pathogenic variation of *FAN1* (p.Trp707*) in French Polynesia,[6] which was identified at the heterozygous state in 3 of 24 individuals (12.5%). Therefore, genetic screening with WES may help to characterize the prevalence of rare genetic kidney diseases in populations where there is little information on their genetic background.

DISCUSSION

Overall, in this cohort of Polynesian patients who have reached ESKD before the age of 45 years, ~75% of patients had a kidney disease not directly related to diabetes mellitus, hypertension, or obesity. Although metabolic disorders are recognized risk factors of CKD development or progression, our study sheds new light on the epidemiology of ESKD in indigenous people. Notwithstanding the major public health issue represented by metabolic disorders in the Pacific islands, the specific genetic background (related to insularity and the increase rate of endogamy) and environment (including high sun exposure) expose Polynesian people to autoimmune or genetic diseases. Such high incidence of CKD in indigenous populations or other neglected segments of societies was also identified in other parts of the world, such as in Samoans living in New Zealand.[9] From a policy-making perspective these findings should prompt us to improve access to general health care systems, and thus implement a systematic and simple kidney screening in adolescents or young adults (e.g., ambulatory measure of blood pressure, urinary dipstick, measure of the serum creatinine). This was performed with success in rural indigenous communities in Canada.[S1,S2] From the perspectives of both patients and populations, identifying a cause of CKD other than metabolic disorders may also help to reduce the guilt young adults may feel when CKD is considered only secondary to their lifestyle, and improve adherence to programs of CKD prevention. Our results also highlight how a standardized clinical workflow, including kidney biopsy WES, kidney biopsy, and immunological tests, if necessary, can optimize the diagnosis of kidney diseases in a population of young adults also characterized by a high prevalence of usual CKD risk factors. This approach has already been validated in high-income countries[S3] and should be tested in other geographic areas where diabetes mellitus and obesity are high in frequency.

In summary, we have shown that, in French Polynesia, nonmetabolic kidney diseases are highly prevalent in patients who have reached ESKD before 45 years of age, thereby highlighting the need to consider other diagnoses, including genetic kidney disease, before retaining metabolic kidney disease. It also points to the need to implement an early, simple program of screening for CKD in adolescents or young adults in populations at high risk of kidney diseases, and a standardized diagnosis workflow to allow precision medicine in a population at very high risk of ESKD and with high prevalence of confounding CKD risk factors.

DISCLOSURE

MD is an employee of Biomnis laboratory, whose activity is dedicated to genetic tests. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We acknowledge all the nephrologists of the Taaone Hospital who took care of patients who are included in this study.

AUTHOR CONTRIBUTIONS

SF, LG, RD, and PT designed the study. LG, BB, MD, and VC performed genetic counseling or analysis. SF and LG reviewed clinical charts. SF wrote the first draft of the manuscript. All authors read and approved the last version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

REFERENCES

1. Kerr M, Evangelidis N, Abbott P, et al. Indigenous Peoples' perspectives of living with chronic kidney disease: systematic review of qualitative studies. *Kidney Int*. 2022;102:720–727. https://doi.org/10.1016/J.KINT.2022.05.030
2. Zhao Y, Dempsey K. Causes of inequality in life expectancy between Indigenous and non-indigenous people in the Northern Territory, 1981–2000: a decomposition analysis. *Med J Aust*. 2006;184:490–494. https://doi.org/10.5694/J.1326-5377.2006.TB00340.X
3. Hughes JT, Dembski L, Kerrigan V, Majoni SW, Lawton PD, Cass A. Gathering perspectives - finding solutions for chronic and end stage kidney disease. *Nephrol (Carlton)*. 2018;23(suppl 1):5–13. https://doi.org/10.1111/NEP.13233
4. McDonald SP, Russ GR. Burden of end-stage renal disease among indigenous peoples in Australia and New Zealand. *Kidney Int Suppl*. 2003;63:S123–S127. https://doi.org/10.1046/J.1523-1755.63.S83.26.X
5. Yeates K, Tonelli M. Indigenous health: update on the impact of diabetes and chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2006;15:588–592. https://doi.org/10.1097/01.MNH.0000247495.54882.E4

6. Gueguen L, Delaval R, Blanluet M, et al. Recurrent FAN1 p.W707X Pathogenic Variant Originating Before ad 1800 Underlies High Frequency of Karyomegalic Interstitial Nephritis in South Pacific Islands. *Kidney Int Rep*. 2021;6:2207–2211. https://doi.org/10.1016/J.EKIR.2021.05.010
7. Delarche A, Lumbroso C, Fournier A, et al. Incidence and outcome of lupus nephritis in French Polynesia. *Clin Nephrol*. 2018;89:41–49. https://doi.org/10.5414/CN109194
8. Arrondel C, Deschênes G, Le Meur Y, et al. A large tandem duplication within the COL4A5 gene is responsible for the high prevalence of Alport syndrome in French Polynesia. *Kidney Int*. 2004;65:2030–2040. https://doi.org/10.1111/J.1523-1755.2004.00622.X
9. Tafuna'i M, Turner RM, Richards R, Sopoaga F, Walker R. The prevalence of chronic kidney disease in Samoans living in Auckland, New Zealand. *Nephrol (Carlton)*. 2022;27:248–259. https://doi.org/10.1111/NEP.13990