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Morbidity and mortality after recognition of macroalbuminuria in Pasifika people with type 2 diabetes in a primary health-care practice

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ABSTRACT

INTRODUCTION: Macroalbuminuria in people with type 2 diabetes is common among Pasifika peoples and is associated with end-stage kidney disease and major cardiovascular disease.

AIM: In a primary care practice catering for Pasifika people, to determine the time after first recognition of macroalbuminuria to the occurrence of major cardiovascular and renal events, and to examine the relationship with retinopathy status.

METHODS: In a retrospective observational cohort study, we documented the occurrence of major cardiovascular events and amputations, end-stage kidney disease and death in 115 people with type 2 diabetes reviewed by a specialist diabetes physician at the Langimalie Tongan Health practice between 2005 and 2018. The follow up was 1–19 (median 9.5) years from the first recognition of macroalbuminuria (albumin:creatinine ratio of >30 g/mol). Survival was described by using Kaplan–Meier analysis.

RESULTS: Macroalbuminuria was detected a mean of 9 years after the diagnosis of diabetes, at a mean age of 52 (standard deviation 12) years. Within 6 years of macroalbuminuria detection, 4% of people had died, 15% had reached end-stage kidney disease, 15% had cardiovascular events or amputations and 30% had the composite outcome of any of these. Within 12 years, the respective proportions were: 24%, 29%, 20% and 48%. The composite outcome was less frequent ($P < 0.002$) in patients without retinopathy at the time macroalbuminuria was recognised. Compared to patients with retinopathy, this group were younger ($P = 0.025$), more obese ($P < 0.0001$), had better baseline renal function ($P = 0.018$) and a shorter interval between the diagnosis of diabetes and recognition of macroalbuminuria ($P < 0.0001$).

DISCUSSION: In this Pasifika population, macroalbuminuria was a marker for serious adverse cardiovascular and renal disease, and mortality, but in the 29% of patients without retinopathy at the time of recognition of macroalbuminuria, the natural history was more benign. The management of such comorbid patients is a substantial challenge for primary health-care services.

KEYWORDS: Cardiovascular disease; renal failure; macroalbuminuria; retinopathy; type 2 diabetes.

Introduction

Increased albumin excretion in people with diabetes is associated with increased rates of end-stage kidney disease, cardiovascular disease and death. These risks are related to the degree of albuminuria, being greatest when macroalbuminuria (commonly defined as a urine albumin:creatinine ratio (ACR) >30 g/mol) is present.[1–3] Research in New Zealand has found that the prevalence of macroalbuminuria is high in the Māori population and in migrants (and their descendants) from Pacific Island nations (Pasifika).[4,5] Macroalbuminuria is strongly linked to end-stage kidney disease in people with type 2 diabetes,[5–7] and the degree of albuminuria is now included in the New Zealand-developed tool for estimating cardiovascular risk in people with diabetes.[8,9] However, there are limited data to indicate the timecourse for major cardiovascular and renal events in people with type 2 diabetes and macroalbuminuria.

The complex burden of looking after people with diabetic kidney disease largely falls on primary health-care providers. Langimalie Tongan Healthcare is a primary health-care provider based in central Auckland with a largely, but not exclusively, Tongan clientele drawn from all around the greater Auckland region. The level of deprivation in the community is high. Assessed by the New Zealand Deprivation Index,[10] 81% of its clients live at addresses in the lowest four deciles and 56% at addresses in the lowest two deciles. In 2019, 21% of the adult patients registered with Langimalie Tongan Healthcare were known to have type 2 diabetes and of these, 16% had documented macroalbuminuria. It is notable that in Pasifika and Māori communities, macroalbuminuria may be present at the time diabetes is diagnosed, when there is minimal or no retinopathy.[11,12] In such cases, renal disease other than classical diabetic nephropathy – in particular, obesity-related focal segmental glomerulosclerosis – may be the initial driver of macroalbuminuria.[13]

In this study, we examine the time to the occurrence of major cardiovascular events, amputations, end-stage kidney disease, and death in adults with type 2 diabetes. We also compare the time to the occurrence of these major endpoints in patients with and without retinopathy at the time macroalbuminuria was first recognised, reasoning that in the latter, non-classical diabetic nephropathy is likely, and that the natural history may differ according to the nature of the underlying primary renal disease.

Methods

Study design

In a retrospective observational cohort study, we studied all patients attending the Langimalie Tongan Healthcare practice in Onehunga between 2005 and 2018 who were identified as having both macroalbuminuria and type 2 diabetes and had been reviewed by a visiting diabetes specialist. All people described in this report were of Tongan descent. Type 2 diabetes was defined as diabetes accompanied by other features of the metabolic syndrome that were not insulin-requiring within the first 2 years of diagnosis. The study was reviewed and approved by the Board of the Tongan Health Society.

Clinical evaluation

Macroalbuminuria was defined as two consecutive random urine ACRs >30 g/mol (normal is <3 g/mol). From the practice records, which included communication from local hospitals concerning attendances and admissions, we documented the occurrence of major cardiovascular events and amputations, end-stage kidney disease and death over a follow-up period of 1–19 (median 9.5) years from the first recognition of macroalbuminuria. Major cardiovascular events included: myocardial infarction, coronary artery bypass surgery, stroke, transient ischaemic attack, and percutaneous coronary artery intervention for coronary or peripheral vascular disease. Amputations included minor (eg single toe) and major amputations. End-stage kidney disease was defined as stage 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min on more than one measurement) or starting dialysis.

The composite outcome comprised any of: major cardiovascular events, amputations, end-stage kidney disease or death. Note was also taken of diabetic retinopathy status on screening close to the time that macroalbuminuria was first detected, as assessed independently by local retinal screening

providers. We also noted the use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, and insulin.

Statistical analysis

Survival time was defined as the time from baseline (first confirmed diagnosis of macroalbuminuria) to the first occurrence of the event in question or the first of any of the events for the composite outcome. Events were censored at time of loss to follow up or death.

Kaplan–Meier analysis was used to determine survival and the results are presented with 95% confidence intervals. Differences between groups in survival was compared by the Mantel–Cox log-rank test.

Data are expressed as the mean with standard deviation (s.d.) if the data were normally distributed or the median (with range) if not. Groups were compared using *t*-tests or Mann–Whitney *U*-tests, as appropriate. The GraphPad Prism programme was used for all the statistical tests.

Results

Patient characteristics

We identified 124 people with macroalbuminuria and type 2 diabetes for whom no follow-up information was available in nine. Of the remaining 115 people in the final analysis, the mean age at diagnosis of diabetes was 43 years (s.d. 10) and 57% were men. The mean body mass index was 35.1 (6.4) kg/m^2.

Macroalbuminuria was detected, on average, 9 years after the diagnosis of type 2 diabetes, but was already present at the time diabetes was diagnosed in 17% of people. At the time macroalbuminuria was first detected, the median ACR was 82 g/mol (range 31 to 875) and the mean eGFR was 66 mL/min (s.d. 30, range 7–144 mL/min). Chronic kidney disease categories 1 or 2 (eGFR ≥60 mL/min) was diagnosed in 58% of patients and 30% were in categories 3A or 3B (eGFR 30–59 mL/min). Retinal screening results from within 1 year of recognition of macroalbuminuria were available for 92 patients (80%): of these, 65 (71%) had retinopathy of varying degree and 27 (29%) had no retinopathy. Fourteen patients (12%) had either cardiovascular events or amputations before the recognition of macroalbuminuria. During the follow-up period, 99% were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 88% with insulin.

Major events over time

Within 6 years of macroalbuminuria detection, 4% of patients in the study had died, 15% had reached end-stage kidney disease, 15% had cardiovascular events or amputations and 30% had the composite outcome of any of these. Within 12 years of macroalbuminuria detection, 24% had died, 29% had reached end-stage kidney disease, 20% had cardiovascular events or amputations and 48% had the composite outcome (Figure 1).

Table 1 compares the demographic features of patients with and without retinopathy of any grade at the time of recognition of macroalbuminuria. Median ACR measurements were similar in the two groups, but patients without retinopathy were younger and significantly more obese, and had better baseline renal function than patients with retinopathy.

Figure 2 illustrates the Kaplan–Meier survival curves for the composite outcome (death, major cardiovascular events or amputation and end-stage kidney disease) in relation to retinopathy status. Patients without retinopathy at recognition of macroalbuminuria had significantly longer survival ($P < 0.002$).

Discussion

Our research confirms that macroalbuminuria is a marker for serious cardiovascular and renal disease and the subsequent risk of death, with 29% reaching end-stage kidney disease and 48% having the composite outcome within 12 years of the first recognition of macroalbuminuria.

Comparable research is limited, as most studies have reported results as relative risks and reported cardiovascular events or end-stage kidney disease as separate entities, although they clearly cluster together as cardiovascular disease is the commonest

Figure 1. Kaplan–Meier survival curves for the outcomes of death, end-stage kidney disease, major cardiovascular events or amputation, or the composite outcome in relation to time (in years) since first recognition of macroalbuminuria. Dotted lines indicate 95% confidence intervals. The numbers at risk are shown in light colour.

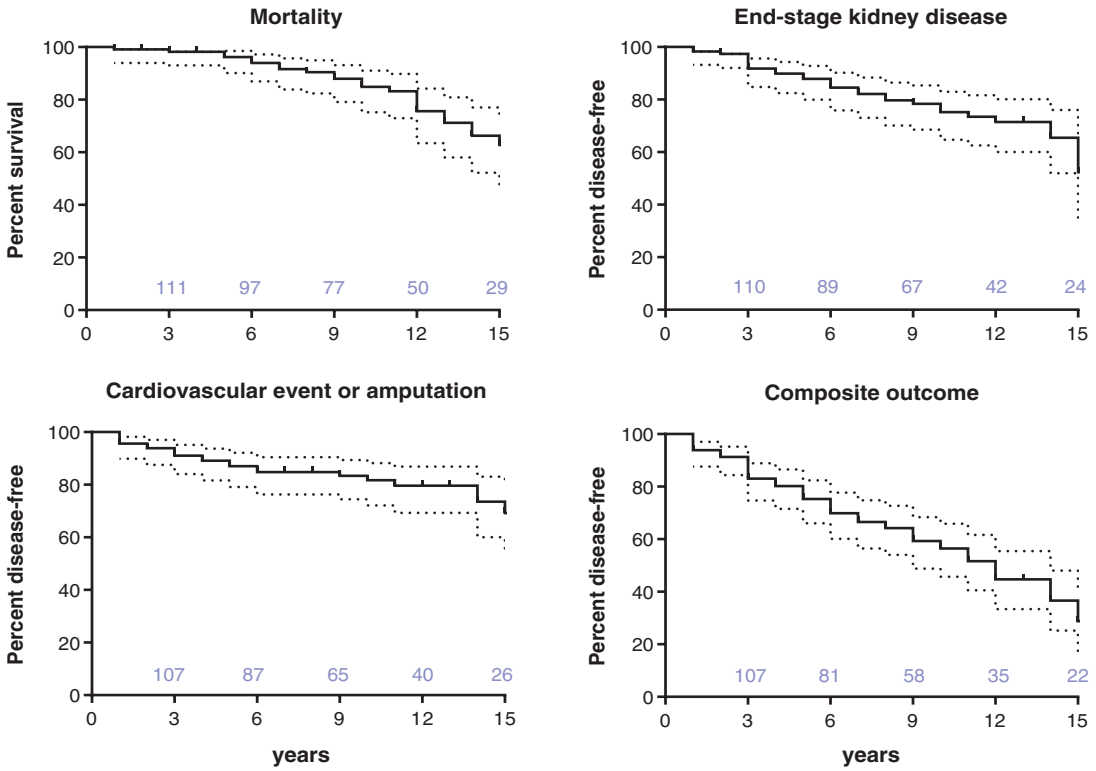


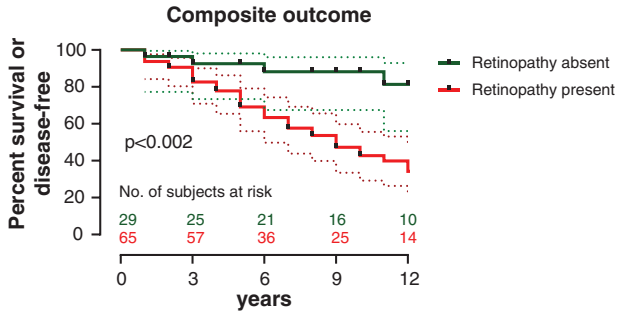
Table 1. Findings at the time of diagnosis of macroalbuminuria and in relation to retinopathy status

	All patients	Retinopathy status at first recognition of macroalbuminuria‡		*P*-value
		Present	Absent	
Number	115	65	27	
Age (years)	52 (10)	53 (11)	48(12)	0.025
Body mass index (kg/m^2)	35.1 (6.4)	32.8 (5.3)	39.4 (6.6)	<0.0001
Type 2 diabetes – macroalbuminuria interval (years)*,†	9 (–3 to 32)	10 (0 – 32)	0 (–3 to 15)	<0.0001
Estimated glomerular filtration rate (mL/min)*	66 (7–144)	61 (30 – 144)	80 (7 – 124)	0.018
Urine albumin/creatinine ratio (g/mol)*	82 (31–948)	81 (32 – 875)	67 (31 – 448)	0.360

* Results are given as median with range and compared by using the Mann–Whitney *U*-test. Other comparisons were made by using an unpaired *t*-test, with results given as mean and s.d.
† Interval between diagnosis of type 2 diabetes and detection of macroalbuminuria.
‡ Retinopathy status at time of recognition of macroalbuminuria unknown in 23 subjects.

cause of death in people with type 2 diabetes and end-stage kidney disease. In the study by Drury *et al.*[14] in a mainly European-origin type 2 diabetes New Zealand population, the 5-year risk of major cardiovascular events was 20–30% (depending on baseline eGFR). Although the 6-year risk of cardiovascular events in our cohort was less (15%), events occurred at a much younger average age

Figure 2. Kaplan–Meier survival curves with 95% confidence intervals (dotted lines) for the composite outcome (death, end-stage kidney disease, major cardiovascular events or amputation) in those with any degree of diabetic retinopathy at the time macroalbuminuria was detected (red lines) compared to that of those with no retinopathy (green lines). The numbers at risk are shown in a light colour.



(52 vs. 65 years) and this figure is likely to be an underestimate; some deaths could have been due to cardiovascular events and we did not have death certification data, and several cardiovascular events were documented before the first recognition of macroalbuminuria.

In New Zealand, more than half the people accepted into renal replacement treatment programmes (dialysis or renal transplantation) have diabetes, and the rate of admission of Pasifika people to renal replacement is six- to seven-fold greater than admission of New Zealand Europeans.[15] In part, this can be explained by the very high prevalence of type 2 diabetes in Pasifika communities; at age 55 years, its prevalence is five- to seven-fold greater than in Europeans and by 60–70 years of age, nearly half the population have type 2 diabetes.[16] Classical diabetic nephropathy is characterised by a progressive rise in albuminuria, reaching macroalbuminuric levels typically after 5–15 years of diabetes. Glomerular filtration rate then begins to decline and, without treatment, end-stage renal failure is reached in 5–7 years. Diabetic nephropathy develops in parallel with the other microvascular complications of retinopathy and neuropathy, so the development of macroalbuminuria in the absence of retinal disease suggests an alternative aetiology of the renal disease.[13,17]

Because of the complex aetiology of renal disease in conjunction with type 2 diabetes, the broader term 'diabetes kidney disease' is now preferred.[18] In the Pasifika population, obesity-related focal segmental glomerulosclerosis is the commonest non-diabetic renal disease and like classical diabetic nephropathy, with which it can co-exist, it is characterised by macroalbuminuria, a bland urine sediment and progressive loss of renal function. In the population, we describe 29% of people with type 2 diabetes and macroalbuminuria had no retinopathy at the time the latter was recognised – a similar proportion to our findings in an earlier study.[12] The people without retinopathy were substantially more overweight and had a shorter interval between the diagnosis of diabetes and the detection of macroalbuminuria than people with retinopathy (Table 1). In eight cases, macroalbuminuria was detected 1–3 years before the diagnosis of diabetes.
The prognosis was also better and although their higher eGFR and younger age would certainly have been important factors in this regard, there is evidence that the average rate of decline in eGFR may be lower in focal segmental glomerulosclerosis than in diabetic nephropathy.[13]

Remission of proteinuria can be associated with improved renal outcomes and survival,[12,19,20] but can be hard to achieve with the limited means available; maintaining good control of blood pressure and glycaemia. A high proportion of the cohort described in this paper were treated with insulin and antihypertensive agents that target the renin-angiotensin system, but the prognosis remained poor. None of the cohort were treated with sodium-glucose transport protein 2 inhibitors, a new class of antidiabetic drugs, which were not at the time funded in New Zealand. These agents can have significant effects on progression of renal disease and reducing the impact of cardiovascular disease.[21] A drug of this class (empagliflozin) has recently (February 2021) been funded for use in this high-risk population.

Limitations of our study are the relatively low numbers and lack of detailed information on causes of death. Some data on retinal status, body mass index and smoking at the time of recognition of macroalbuminuria were also incomplete. We did not collect data on aspirin or statin use, other co-morbidities, or changes in diabetes therapy across follow up.

In summary, we found that macroalbuminuria in people with type 2 diabetes in a Pasifika-based

general practice presaged high rates of mortality and serious morbidity (end-stage kidney disease, cardiovascular disease or amputation); nearly half had suffered at least one major event within 12 years of the recognition of macroalbuminuria. We also found that a substantial proportion (29%) had features suggesting that obesity-related focal segmental glomerulosclerosis, rather than classical diabetic nephropathy, was the major initial driver of kidney disease in diabetes. Intensive management of hypertension and cardiovascular risk can improve prognosis and the now available sodium-glucose transport protein 2 inhibitors should also help. However, the population affected is mainly drawn from the most economically deprived communities in New Zealand and this presents real challenges for primary health care, where most care is managed for these complex patients.

Competing interests

The authors have no competing interests to declare.

Author contributions

TCo, GD, FM and TCu all contributed to the conception and design of the study. TCo and TCu analysed the data. TCo, GD, FM and TCu drafted the article for publication and reviewed it for submission. All authors give their approval for publication.

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