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High HbA1C Levels Associated with Microalbuminuria in Melanesian Adults with Diabetes of Atleast 1-Year Duration

Billy I[1] and Aglua I[2]*

1Specialist Physician, Nonga General Hospital, Papua New Guinea

2Internal Medicine Registrar & Clinical Research Fellow, Simbu Provincial Health Authority-Clinical Research Center, Papua New Guinea

***Corresponding author:** Izzard Aglua, Internal Medicine Registrar & Clinical Research Fellow (MPH, GCSRT, MBBS), Simbu Provincial Health Authority-Clinical Research Center, P. O. Box 346, Kundiawa, Simbu Province, Papua New Guinea, Tel: +67572162214; Email: izzard.agua@gmail.com

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Abstract

Background: Evidence suggests a potential relationship between high or variable HbA1C levels and presence or rate of change of microalbuminuria. Disruption of the vascular endothelial glycocalyx has been linked to chronic hyperglycemia and microalbuminuria, suggesting a possible shared pathophysiological mechanism.

Aim:

- To Explore potential association between microalbuminuria and high HbA1C levels in Melanesian adults with diabetes mellitus, and
- Assess predictive value of a high HbA1C level as an indicator for the presence or progression of microalbuminuria.

Method: A cross-sectional study on 190 patients with either type 1 or 2 diabetes of at least 1-year duration was conducted at a provincial hospital in Papua New Guinea in 2017.

Result: A significant correlation between UACR and HbA1C (p-value = 0.056, 95% CI 0.02 - 1.98), and UACR and duration of diabetes (p-value = 0.010, 95% CI 0.19 - 1.40) was observed in a multivariate regression model.

Conclusion: A significant correlation between UACR and HbA1C level was observed, which supports usefulness of HbA1C as a clinical indicator for onset or progression of microalbuminuria and subclinical diabetic kidney disease. In settings without microalbuminuria testing, high HbA1C levels can serve as a proxy to presence or progression of microalbuminuria, prompting timely interventions to prevent progression of diabetic nephropathy.

Keywords: HbA1C; Microalbuminuria; Diabetes Mellitus; UACR

Abbreviations: HbA1C or A1C: Hemoglobin A1C; UACR: Urine Albumin-Creatinine Ratio; PNG: Papua New Guinea; R2: Regression Coefficient.

Introduction

An estimated 40% of patients with type 1 or type 2 diabetes develop diabetic nephropathy within 5 to 15 years of diagnosis [1]. Microalbuminuria, defined as urine albumin of 30-300mg/day, is a clinical test for assessment of renal functional status or progressive deterioration in diabetes of many years [2-5]. Microalbuminuria testing is widely used in clinical practice for early detection and monitoring of subclinical diabetic nephropathy to overt diabetic kidney disease [5, 6]. Hemoglobin A1C (HbA1C) is a form of glycosylated hemoglobin resulting from non-enzymatic

glycosylation of hemoglobin following longstanding hyperglycemia in diabetes mellitus [7]. It serves as a reliable measure of glycemic control over a 90-120-day period, coinciding with erythrocyte life span [7, 8]. Recent evidence suggest a potential relationship between high or variable HbA1C levels and presence or rate of change of microalbuminuria [9, 10].

Disruption of the vascular endothelial glycocalyx has been identified as a contributing mechanism to the development of microalbuminuria in diabetic kidney disease [11-14]. Chronic hyperglycemia has also been shown to independently contribute to systemic endothelial dysfunction, including endothelial glycocalyx dysregulation [14-16]. This suggests a potential biochemical association between chronic hyperglycemia and microalbuminuria. Most primary health care facilities in developing countries do not have point of care tests or even laboratories for measuring microalbuminuria to inform treatment decisions for diabetic patients [16]. Dipstick, a bedside test commonly available in most resource-poor settings, can only detect overt albuminuria (≥ 300mg/day), and not microalbuminuria (30-300mg/day) [3, 4]. This study was therefore done to assist clinicians in suspecting and/or detecting microalbuminuria earlier using high or variable HbA1C levels in diabetic patients, which will allow for timely and appropriate interventions to minimize progression of microalbuminuria to macro albuminuria (proteinuria) and established diabetic nephropathy [17,18].

Aim

- Explore for a potential association between high HbA1C readings (HbA1C ≥ 6%) and microalbuminuria (urine albumin creatinine ratio > 30 mg/day) in adult diabetics with at least one-year duration, and
- Assess the predictive value of a high HbA1C level (HbA1C ≥ 6%), initial or progressive, as a reliable indicator for presence of microalbuminuria in adult diabetics of at least one-year duration.

Methods

A cross-sectional observational study was conducted on 190 Melanesian adults (age >13) with either type 1 or 2 diabetes of at least one-year duration at the Angau Memorial Hospital in Papua New Guinea in 2017. Single point-of-care HbA1C and Urine Albumin-Creatinine Ratio (UACR) levels were measured in patients during one of their visits to the diabetic clinic. Venous blood was sampled from patients at the diabetic clinic by the treating doctor and sent in standard serum bottles for analysis at the hospital laboratory. HbA1C was measured using the SD- HbA1C analyzer, while microalbuminuria was tested using the urine-albumin-creatinine ratio from standard biochemical analyzers. Measurements were recorded onto a Microsoft Excel spreadsheet and analyzed using Stata statistical software. Microalbuminuria was defined as urine-albumin-creatinine ratio > 30 mg/day and a HbA1C level ≥ 6% was defined as high [19]. Linear regression models (univariate, multivariate) were performed on the data set for associations between UACR and HbA1C, age, gender, weight, systolic blood pressure, systolic hypertension, and duration of diabetes. Patients with previous or existing other-cause-kidney-disease were not included in the study.

Data and Resource Availability Statements

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Percentiles (cumulative %)	HbA1 (%)	UACR (mg/day)	Diabetes Duration (Years)
1%	2.4	0.4	1
5%	4.5	0.5	2
10%	5.8	0.6	2
25%	6.8	1.2	3
50%	8.3	3.25	4
75%	10.1	14.4	7
90%	12.4	33.2	10.5
95%	13.9	45.5	10.5
99%	14	73.2	10.5
Subjects (n)	190	190	190
Mean	8.59	10.9	5.1
SD	2.57	15.76	2.98
Variance	6.63	248.5	8.91

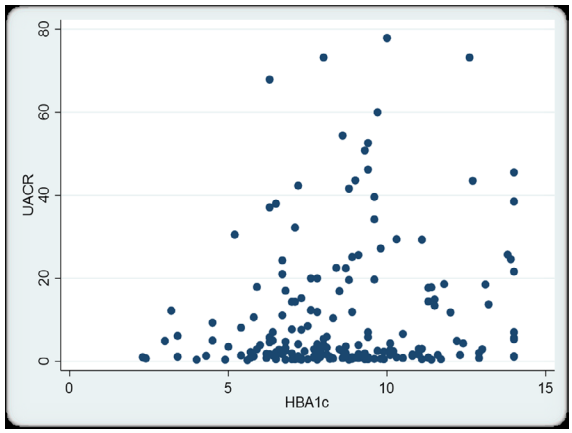
Table 1: Summary Statistics.

- 10% of subjects had HbA1C < 5.8%. 90% had HbA1C ≥ 5.8 % at time of testing. Mean HbA1C was 8.59% with SD 2.57.
- 90% of subjects had UACR < 33.2 mg/day. 10% of subjects had UACR ≥ 33.2 mg/day. Mean UACR was 10.9 mg/day with SD 15.76.
- 50% of subjects had diabetes mellitus < 4 years at time of testing. Mean duration was 5.1 years with SD 2.98.

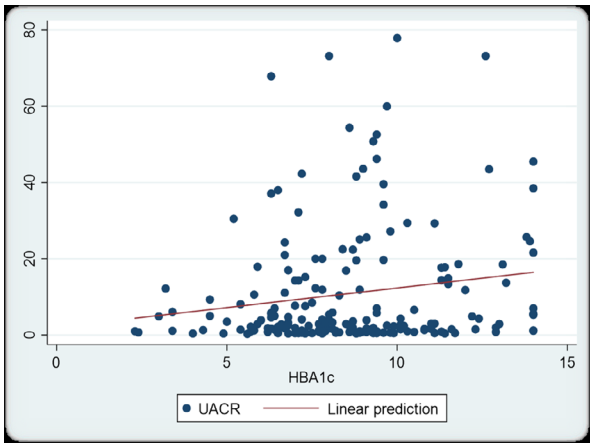
Variable	p-value	95% Confidence Interval
HbA1C (%)	0.056	0.02 - 1.98
Gender	0.467	-10.15
Weight (Kg)	0.112	-0.33
Duration (Years)	0.01	0.19 - 1.40
Age (Years)	0.606	-0.47
Systolic BP (mmHg)	0.459	0.11 - 0.26
Systolic BP >140 (mmHg)	0.88	5.75 - 6.70
n = 190		
R2 = 0.43		

Table 2: Multivariate linear Regression on UACR.

- Significant (marginal) correlation between HbA1C and UACR in multivariate regression (p-value = 0.056, 95% CI 0.02-1.98, R2 = 0.43), after controlling for weight, systolic BP, gender, duration of diabetes, age, and systolic hypertension.
- Statistically significant correlation between diabetes duration and UACR in multivariate model (p-value = 0.010, 95% CI 0.19-1.40), after controlling for confounding.
- R2 is regression coefficient indicating strength of association between individual variable (HbA1C, duration) and outcome (UACR). R2 = 0.43 means a unit change in HbA1C or diabetes duration will entail a corresponding 0.43 (43%) unit change in UACR.



Graph 1: Scatter plot showing relationship between UACR and HbA1C values.



Graph 2: Scatter plot with best-fit line showing predicted linear relationship between UACR and HbA1C values.

Discussion

HbA1C

The mean HbA1C was high 8.6% (5.7- 6.4 %)19 with a standard deviation of 2.6, whilst UACR had a low mean value of 10.9 mg/day with SD 15.76 (Table 1). 90% of the UACR values were below microalbuminuria threshold (< 33.2mg/day) whilst 90% of HbA1C readings were above optimal level (5.8%). This means 90% of the participants had poor glycemic control in the preceding 3-4 months before testing, highlighting the potential for glycosylation reactions with subsequent micro- and macro-vascular diabetic complications including microalbuminuria and diabetic nephropathy. The observed normoalbuminuric status in most patients with diabetes of more than 1-year

(90% with UACR < 33.2 mg/day, Table 1) may not necessarily exclude the presence or progression of insidious diabetic nephropathy, as existing evidence also suggest possible non-albuminuric pathways accounting for development of kidney disease in diabetes of many years [20-23].

The regression model (Table 2) showed a significant, though weak, positive correlation between HbA1C and UACR readings (p-value=0.056, 95% CI 0.02-1.98, R2=0.43). Regression coefficient (R2) = 0.43 means a 1% increase in HbA1C would entail only a 0.43 mg/day corresponding increase in UACR. This weakness in association may be owing to either confounding or a type two error (β) from a small sample size of 190. Underpowering of the study would statistically reduce the strength and measure of the association between the variable (HbA1C) and outcome (UACR > 30mg/day). Hence, larger prospective cohorts would be ideal to further explore and/or ascertain the observed association. Nevertheless, relevant literature supports an association between microalbuminuria and HbA1C variability or high persistence [9,10,24,25]. Scatter Graphs 1&2 further illustrate a positive correlation between HbA1C and UACR readings, although with fewer data points above the microalbuminuria threshold (UACR > 30 mg/day). The low prevalence of microalbuminuria amongst study participants with high HbA1C levels, and a weak HbA1C -UACR association may imply that microalbuminuria is not singularly influenced by high or variable HbA1C levels, although they may share pathophysiological mechanisms [11-16]. This would support multifactorial causality in the development of microalbuminuria and diabetic kidney disease, including glomerular hyperfiltration, oxidative stress, hypertension, inflammatory mediators, and collagen alteration alongside endothelial dysfunction [14,26-29]. A High HbA1C level, initial or progressive, may therefore not be a strong independent predictor of microalbuminuria and diabetic nephropathy in adult diabetics with at least 1-year duration. However, in resource-constrained settings without the capacity for microalbuminuria testing, high or variable HbA1C levels can still be used as a proxy to suspecting presence or progression of microalbuminuria, given the linear association and supporting evidence, to prompt timely and appropriate interventions towards preventing further deterioration of glomerular function [17]. Prospective cohorts with larger sample sizes are necessary to further ascertain the strength of the observed association between high HbA1C levels and UACR.

Duration

The mean duration of diabetes was 5.1 years with SD=2.99. 50% of participants were at less than 4 years disease duration. This may explain the observed low prevalence of microalbuminuria amongst participants studied as half of them were diagnosed less than 5 years. However, related studies have shown presence of microalbuminuria in diabetics in as early as 1-3 years with incidence increasing with increasing duration [30-32]. Time of diagnosis in our Melanesian subjects may not necessarily reflect duration of illness, as late presentation and/or diagnosis are common in clinical practices in the developing world, owing to logistic and resource limitations coupled with unsupportive patient behavior [33,34]. The disease may have progressed undetected to variable stages with subclinical or overt complications at the time of a definitive diagnosis. Therefore, a high index of suspicion for microalbuminuria and/or diabetic nephropathy, as well as related vascular complications (micro/macro), is necessary even at the time of diagnosis or in recently diagnosed diabetics. A follow-up study involving a cohort of newly diagnosed diabetics would be ideal to ascertain time-to-event outcomes for microalbuminuria and diabetic nephropathy in our Melanesian population.

A significant positive correlation between duration of diabetes and microalbuminuria was observed (p-value = 0.010, 95% CI 0.19-1.40) in the multivariate model (Table 2). A year increase in duration of diabetes would entail a corresponding 0.43 mg/day increase in UACR in the subjects. This outcome agrees with existing evidence in support of a strong association between diabetic complications and duration of illness [35-38], and further highlights the need for heightened clinical suspicion with timely action for diagnosis, treatment and prevention of diabetic complications at earlier stages to reduce morbidity and death.

Hypertension

There was no significant association between single-point systolic hypertension and UACR levels on the multivariate model, which highlights the fact that single blood pressure readings do not reliably reflect long-term blood pressure status, and therefore may not necessarily represent the effect of long-term blood pressure variability on microalbuminuria development or independent renovascular disease, as suggested by literature on the association of hypertension and microalbuminuria or kidney disease [39-42].

Conclusion

A significant, though weak, positive correlation was observed between high HbA1C levels and UACR (p-value = 0.056, 95% CI 0.02-1.98, R2=0.43). Whilst high HbA1C levels may not be a strong independent predictor for microalbuminuria in this study, it can serve as a proxy to heighten clinical suspicion of microalbuminuria and/or subclinical diabetic nephropathy in resource-poor settings, in order to prompt timely and appropriate therapeutic and preventative interventions. A significant positive correlation between duration of

diabetes and UACR was observed (p-value=0.010, 95% CI 0.19-1.40), which emphasizes the need for heightened suspicion for presence or progression of subclinical diabetic nephropathy in patients with diabetes of many (≥5) years. The high prevalence of undiagnosed adult diabetics amongst local Melanesian populations with subclinical vascular complications further highlights the need for anticipation of microalbuminuria and diabetic nephropathy even at the time of diagnosis.

Ethics

Ethical consideration and approval was granted by the Ethics Review Committee of the Angau Memorial Hospital.

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