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HbA_{1c} in relation to incident diabetes and diabetes-related complications in non-diabetic adults at baseline

Patricia Anne Metcalf [a,b,*], Cam Kyle [c], Tim Kenealy [d], Rod T. Jackson [a]

[a] Department of Epidemiology & Biostatistics, School of Population Health, University of Auckland
[b] Department of Statistics, University of Auckland
[c] LabPlus, Auckland City Hospital, and Department of Molecular Medicine, University, of Auckland, Private Bag 92019, Auckland Mail Center, Auckland 1010, New Zealand
[d] South Auckland Clinical School, University of Auckland, Private Bag 92019, Auckland Mail Center, Auckland 1010, New Zealand

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ABSTRACT

Aims: We compared the utility of glycated hemoglobin (HbA_{1c}) and oral glucose tolerance (oGTT) in non-diabetic patients for identifying incident diabetes; all-cause mortality; cardiovascular disease (CVD) mortality; CVD, coronary heart disease (CHD), and ischemic stroke events; and diabetes microvascular complications.

Methods: Data from a New Zealand community setting were prospectively linked to hospitalization, mortality, pharmaceutical and laboratory test results data. After applying exclusion criteria (prior laboratory diagnosis or history of drug treatment for diabetes or hospitalization for diabetes or CVD event), there were 31,148 adults who had an HbA_{1c} and 2-h 75 g oGTT. HbA_{1c} was measured by ion-exchange high-performance liquid chromatography, and glucose using a commercial enzymatic method. We compared glycemic measures and outcomes using multivariable Cox proportional hazards regression.

Results: The median follow-up time was 4 years (range 0 to 13). The mean age was 57·6 years and 53·0% were male. After adjusting for other glycemic measures (fasting glucose, 2-h glucose and/or HbA_{1c} where relevant) in addition to age, sex, ethnicity and smoking habit, the hazard ratios for incident diabetes and diabetes complications of retinopathy and nephropathy were highest for 2-h glucose levels, followed by HbA_{1c} and lastly by fasting glucose. However, all-cause mortality and CHD were significantly associated with HbA_{1c} concentrations only, and ischemic stroke and CVD events with 2-h glucose only. Circulatory complications showed a stronger association with HbA_{1c}.

Conclusion: Apart from neuropathy, HbA_{1c} showed stronger associations with outcomes compared to fasting glucose and provides a convenient alternative to an oGTT.

1. Introduction

Glycated hemoglobin (HbA_{1c}) has recently been accepted for diagnosing diabetes in New Zealand (NZ).[19] A 2-h 75 g oral glucose test (oGTT) was used previously and remains an alternative for diagnosis. Cardiovascular disease (CVD) is a major long-term complication and the most common cause of preventable death in people with diabetes.[15] While CVD mortality rates have decreased considerably in NZ over the past 30 years,[16] the prevalence of type 2 diabetes has been rising rapidly.[15] All ethnicities show this trend internationally, however, the increase in NZ is greatest in non-Europeans that include Maori, Pacific and South Asians.[28] The increasing dysglycemic prevalence driven by an aging population and unfavorable trends in obesity and lifestyle, may lead to an increase in the total number of CVD events and diabetes-related macro- and microvascular diseases.

The advantages of HbA_{1c} as a diagnostic test compared to the oGTT or fasting glucose alone are that a non-fasting blood sample can be taken, it has lower intra-individual variation,[22] and it is the most common test for monitoring glucose control.[18] Previous studies in predominantly non-diabetic populations have reported HbA_{1c} optimal cut-off levels for diagnosing diabetes,[5,8] retinopathy,[23,29,30,33] and CVD.[12] Others have reported linear or curvilinear associations between elevated HbA_{1c} levels and diabetes diagnosis,[17,21,27] retinopathy,[5] microalbuminuria,[29] ischaemic heart disease,[11] CVD morbidity and/or mortality,[7,10,11,27,31] and all-cause mortality.[2,4,10,11,27]

The aim of this study was to compare the utility of HbA_{1c} and the oGTT in non-diabetic patients for identifying risk of diabetes, all-cause and CVD mortality, CVD, coronary heart disease (CHD) and ischemic stroke events and diabetes microvascular complications.

There are no conflicts of interest.

* Corresponding author at: Division of Epidemiology and Biostatistics, School of Population Health, Tamaki Campus, University of Auckland, 261 Morrin Road, St Johns, Auckland 1072, New Zealand.
E-mail address: p.metcalf@auckland.ac.nz (P.A. Metcalf).

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Table 1
Selected characteristics of study subjects according to HbA_{1c} in mmol/mol (mean ± SD or percent).

Value	All	<40	40 to 42	43 to 44	45 to 50	≥51
Number	31,148	5884	5780	5214	7734	6536
HbA_{1c} (mmol/mol)	46.6 ± 11.4	36.5 ± 2.8	41.1 ± 0.8	43.5 ± 0.5	47.1 ± 1.8	62.5 ± 15.2
Fasting glucose (mmol/L)	6.2 ± 1.7	5.3 ± 0.7	5.6 ± 0.7	5.6 ± 0.7	6.0 ± 0.9	8.2 ± 2.6
2-h glucose (mmol/L)	9.0 ± 4.4	6.5 ± 2.5	7.1 ± 2.6	7.4 ± 2.8	8.8 ± 3.1	14.2 ± 4.9
Age (years)	57.5 ± 11.7	57.4 ± 11.7	58.8 ± 11.4	58.5 ± 11.4	58.4 ± 11.7	55.0 ± 12.2
Male sex (%)	53.0	60.1	54.9	50.4	48.4	52.5
Ethnicity (%)						
European[1]	45.0	27.5	22.7	16.9	20.0	12.9
Maori	10.4	11.9	15.2	17.1	28.4	27.4
Pacific	19.4	8.0	18.9	17.8	27.8	29.1
Asian	11.2	16.1	18.9	17.8	27.8	19.4
Indian	12.0	12.4	13.6	17.0	27.9	29.1
Other	2.0	21.6	20.0	15.1	24.2	19.1
Fasting cholesterol (mmol/L)	5.05 ± 1.09	5.11 ± 1.10	5.13 ± 1.08	5.13 ± 1.08	5.03 ± 1.07	4.90 ± 1.11
Cholesterol/HDL ratio	4.18 ± 1.23	4.06 ± 1.25	4.17 ± 1.20	4.17 ± 1.18	4.21 ± 1.21	4.29 ± 1.29
Systolic blood pressure (mm Hg)	132.6 ± 17.1	132.2 ± 16.9	132.9 ± 16.9	132.6 ± 17.0	133.0 ± 17.1	132.3 ± 17.3
Diastolic blood pressure (mm Hg)	80.6 ± 10.5	80.0 ± 16.9	80.4 ± 10.2	80.6 ± 10.3	80.6 ± 10.5	81.1 ± 11.1
BMI (kg/m^2)	31.5 ± 7.2	29.6 ± 6.4	30.7 ± 6.5	31.4 ± 7.0	32.1 ± 7.3	33.1 ± 7.7
Smoking status (%)						
Current smoker[1]	10.4	14.9	16.3	17.2	24.7	26.9
Former smoker	17.5	19.3	19.8	16.3	24.7	19.9
Never smoker	72.1	19.4	18.6	16.8	24.9	20.4
NZ deprivation score	3.2 ± 1.5	2.8 ± 1.5	2.9 ± 1.5	3.1 ± 1.5	3.3 ± 1.5	3.5 ± 1.5

BMI = body mass index.
[1] 'All' column has column percentages, HbA_{1c} quintiles are row percentages.

2. Subjects, materials and methods

2.1. Participants

We used the common participants in 2 sources: i) the Auckland region Diagnostic-Medlab (DML) laboratory data (2000–2010) that included 96,470 individuals with an oral glucose tolerance test (oGTT) and 336,924 individuals with an HbA_{1c} test(s); and ii) Auckland and Northland primary care data of 272,682 adults with cardiovascular disease (CVD) risk assessments (2002–2012) from the PREDICT cohort. From these 2 data sources there were 35,810 adults who had a CVD risk assessment and an oGTT and HbA_{1c} measured within 60 days of the oGTT. These data were linked anonymously to pharmaceutical payment data supplied by the New Zealand Ministry of Health (MOH).

Of the 35,810 on the combined PREDICT-DML database, exclusion criteria included 1033 adults taking diabetes medication(s) prior to the oGTT, 576 with diabetes-related hospital admissions prior to the oGTT, and 3053 with a previous CVD hospital admission (leaving 31,148). The New Zealand Ministry of Health Auckland Ethics Committees provided ethical approval (NTX/12/EXP/008/AM03).

2.2. Variables

For a 75 gram oGTT, participants fast from 10 pm the evening before the test and 75 g glucose (Glucaid drink) was given in the

Table 2
Adjusted hazard ratios for incident diabetes (n = 13,274) according to the glycaemic quintiles with median concentration and number of cases out of the total.

Variable	Model 1	Model 2	Model 3	Model 4	Median	Cases/Total
HbA_{1c}						
< 40 mmol/mol	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	37	910/5884
40 to 42 mmol/mol	1.85 (1.70–2.02)	1.77 (1.62–1.92)	1.67 (1.54–1.82)	1.67 (1.53–1.82)	41	1310/5780
43 to 44 mmol/mol	2.51 (2.31–2.73)	2.36 (2.17–2.56)	2.16 (1.99–2.35)	2.15 (1.98–2.34)	43	1477/5214
45 to 50 mmol/mol	5.56 (5.16–5.99)	4.93 (4.58–5.31)	4.07 (3.78–4.38)	4.02 (3.73–4.33)	46	3816/7734
≥ 51 mmol/mol	17.85 (16.61–19.21)	11.27 (10.40–12.18)	6.87 (6.33–7.45)	6.86 (6.33–7.44)	56	5761/6536
Model 1: adjusted for age, sex, ethnicity and smoking history; model 2: model 1 plus fasting glucose; model 3: model 1 plus 2-h glucose; model 4: model 1 plus fasting and 2-h glucose.						
Fasting glucose						
< 5.1 mmol/L	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	4.8	690/5370
5.1 to 5.4 mmol/L	1.60 (1.45–1.76)	1.50 (1.36–1.65)	1.54 (1.40–1.70)	1.49 (1.36–1.65)	5.3	1027/5654
5.5 to 5.9 mmol/L	2.94 (2.70–3.21)	2.47 (2.27–2.70)	2.75 (2.52–3.00)	2.49 (2.28–2.71)	5.7	2119/6836
6.0 to 6.7 mmol/L	5.98 (5.52–6.50)	4.13 (3.81–4.49)	5.26 (4.85–5.71)	4.19 (3.86–4.56)	6.3	3658/6648
≥ 6.8 mmol/L	15.46 (14.29–16.75)	5.73 (5.25–6.26)	9.60 (8.85–10.45)	5.73 (5.25–6.26)	7.7	5780/6640
Model 1: adjusted for age, sex, ethnicity and smoking history; model 2: model 1 plus 2-h glucose; model 3: model 1 plus HbA_{1c}; model 4: model 1 plus 2-h glucose and HbA_{1c}.						
2-h glucose						
< 5.4 mmol/L	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	4.5	651/6034
5.4 to 6.8 mmol/L	1.69 (1.53–1.86)	1.62 (1.47–1.79)	1.62 (1.47–1.79)	1.62 (1.47–1.78)	6.1	1085/6118
6.9 to 8.9 mmol/L	3.76 (3.45–4.11)	3.46 (3.18–3.79)	3.47 (3.18–3.79)	3.45 (3.16–3.77)	7.8	2244/6330
9.0 to 12.1 mmol/L	8.44 (7.77–9.19)	7.26 (6.69–7.91)	7.32 (6.75–7.97)	7.24 (6.66–7.88)	10.5	3884/6423
≥ 12.2 mmol/L	20.28 (18.70–22..04)	12·72 (11.68–13.90)	12.66 (11.64–13.82)	12.23 (11.21–13.35)	14.6	5410/6243
Model 1: adjusted for age, sex, ethnicity and smoking history; model 2: model 1 plus fasting glucose; model 3: model 1 plus HbA_{1c}; model 4: model 1 plus fasting glucose and HbA_{1c}.						