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Original Research

Effect of chronic kidney disease on A1C in individuals being screened for diabetes

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ABSTRACT

Objective: Glycated haemoglobin (A1C) has been recommended for the diagnosis of type 2 diabetes mellitus. Chronic kidney disease (CKD) is reported to increase A1C. The prevalence of CKD and its association with A1C as a diagnostic test for type 2 diabetes screening in a community population was studied.

Research design and methods: Age, gender, ethnicity (white/South Asian), haemoglobin, A1C, fasting glucose and fructosamine were compared in participants with estimated glomerular filtration rate (eGFR) 30–59 (CKD 3) and ≥60 ml/min/1.73 m^2 using chi-squared or *t*-tests. Multivariable linear regression analyses were performed with A1C as the dependent variable; remaining variables were forced into a model to identify correlates with A1C. Data were parametric and expressed as means.

Results: Of 949 participants 83.7% had eGFR ≥60, 16.3% had CKD 3 and only 2 had eGFR <30 (CKD ≥4). Compared with eGFR ≥60, patients with CKD 3 were older [$p < 0.001$], had higher A1C [6.0% vs. 5.8%, $p < 0.001$], fasting glucose [5.4 vs. 5.2 mmol/L, $p = 0.003$] and fructosamine [233.7 vs. 225.8 μmol/L, $p < 0.001$] but lower haemoglobin [$p = 0.006$]. After adjustment, gender and CKD stage were not associated with A1C. A1C was associated ($p < 0.05$) positively with age, South Asian ethnicity, fasting glucose and fructosamine and inversely with haemoglobin levels.

Conclusions: Severe CKD (stage ≥4) is rare in primary care patients being screened for type 2 diabetes and its impact on A1C could not be evaluated. Although A1C is higher among patients with CKD stage 3 compared to those with eGFR ≥60, this appeared to be due to the confounding effect of other variables rather than the presence of CKD.

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1. Introduction

Glycated haemoglobin (A1C) is the product of non-enzymatic glycation of the N-terminal valine of the haemoglobin beta chain formed at a rate proportional to the intracellular glucose concentration. Red cell intracellular glucose concentration directly reflects extracellular glucose concentration due to the presence of constitutively active glucose channels (GLUT1). Due to the 3-month life span of red blood cells, A1C has been widely used to reflect long-term glycaemic control and has also recently been widely adopted for the diagnosis of type 2 diabetes mellitus. Use of A1C for diabetes diagnosis avoids the need for patient fasting and correlates with microvascular complications at least as well as fasting plasma glucose or the oral glucose tolerance test (OGTT) [1]. It, however, is not widely appreciated that non-glycaemic factors may affect A1C including chronic kidney disease (CKD) [2], gender [3], age [4] and ethnicity [5–7].

Stages 3–5 CKD occurs in 3–5.5% of men and 7% of women in England [8]. Renal impairment, defined as those with dipstick proteinuria or an eGFR <60 ml/min/1.73 m^2, affects up to 10.4% of those aged 60–64 years in Britain [9]. The prevalence of CKD increases with age, and accumulation of renal insults, reported to affect 27.5% of those with diabetes (Middleton). Severe CKD is associated with factors affecting haemoglobin production such as reduced erythropoietin production, which may result in functional iron deficiency [10].

The mechanisms underlying the association of CKD and A1C are unclear. Proposed mechanisms include reduction in erythropoietin production, increased glycation or carbamylation [3] or iron factors [2]. Carbamylation, addition of urea-derived cyanate ion onto haemoglobin chains, produces a similar charge to glycation therefore interfering with HbA1c measurement by electrical means (ion-exchange chromatography) but not chemical (affinity chromatography) [11] or immunological methods [12]. Iron deficiency, however, has been linked to both elevations [13] and reductions in A1C [14]. Iron replacement has been reported to increase [14], decrease [2,15] or have no effect on A1C [16]. Haemoglobin concentration itself affects A1C, A1C differing as much as 0.2% with haemoglobin levels at either end of the normal spectrum [17]. Red cell life span, a multifactorial variable, also affects A1C level and may account for some of the effects of CKD, both renal insufficiency and diabetes being associated with increased rates of eryptosis [18].

Due to the high prevalence of CKD in those with diabetes [19] great interest has been shown in the interpretation of A1C for monitoring in this group. The impact of CKD on A1C when used for diagnosis of type 2 diabetes mellitus in primary care patients is, however, unknown. We, therefore, studied the prevalence of CKD in a primary care population screened for type 2 diabetes mellitus and whether CKD is independently associated with A1C.

2. Research design and methods

Samples were collected from 1006 consecutive primary care patients from the Wolverhampton area, West Midlands, UK, from December 2012 to April 2013. Inclusion criteria consisted of adult white and South Asian patients with the required sample types in whom A1C had been requested for type 2 diabetes mellitus diagnosis. Exclusion criteria included pregnant women, children aged less than 16 years, those with diabetes and haemoglobinopathies and those whose ethnicity was unknown and not white or South Asian. Further exclusion criteria were biochemical and haematological including B12 levels > upper limit of detection and haemoglobin ≤90 g/L. This resulted in a final study population of 949 patients. Data were anonymised prior to analyses. Permission for data to be published has been granted by the Royal Wolverhampton NHS Trust Caldicott Guardian.

Table 1 – Sample characteristics (n = 947).

Variable	n (%)	Mean (SD)
Age (years)	–	55.0 (18.2)
Gender		
Male	402 (42.5)	–
Female	545 (57.6)	–
Ethnicity		
White	710 (75.0)	–
South Asian	237 (25.0)	–
CKD stage		
<3 (eGFR ≥60 ml/min/1.73 m^2)	793 (83.7)	–
3 (eGFR <60 ml/min/1.73 m^2)	154 (16.3)	–
Haemoglobin (g/L)	–	141.9 (15.0)
A1C (%) [mmol/mol]	–	40.1[a] (6.4)
Fasting glucose (mmol/L)	–	5.2 (0.9)
Fructosamine (μmol/L)	–	227.1 (23.3)

[a] 40.1 mmol/mol is equivalent to 5.8%.

The presence of CKD and the level of A1C were considered outcome measures. CKD stage was based on the estimated glomerular filtration rate (eGFR), calculated using the four variable modification of diet in renal disease formula [20]. CKD stages <3, 3, 4 and 5 were based on eGFR levels of ≥60, 30–59, 15–29 and <15 ml/min/1.73 m^2, respectively. Independent variables included demographic and laboratory data. Age, gender and ethnicity (white or South Asian) were taken from the sample request form, laboratory computer system and hospital electronic medical records. Data on haemoglobin, fasting glucose and fructosamine were collected from the laboratory computer system.

Haemoglobin was measured using flow cytometry (Sysmex XN-10®, Sysmex Corporation, Kobe, Japan). A1C was measured using an automated cationic non-porous ion exchange HPLC method certified by National Glycohemoglobin Standardisation Program (G7 HPLC analyser, Tosoh Corporation, Kanagawa, Japan). Fasting glucose (hexokinase), creatinine (compensated kinetic Jaffe with rate-blanking) and fructosamine (nitrotetrazolium-blue) were measured with Roche methodology and reagents (MODULAR® P analyser, Roche Diagnostics GmbH, Mannheim, Germany). All measurement methods behaved within acceptable limits according to external quality assurance schemes throughout the study and were performed in a fully accredited laboratory.

Descriptive analyses on patients and laboratory information were expressed as frequencies for categorical data