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Glycaemic trajectory and predictors of suboptimal glycaemic control in people with type 2 diabetes

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Abstract

We aimed to describe glycaemic trajectory and define characteristics associated with suboptimal glycaemic control in the type 2 diabetes clinic. Higher HbA1c at one year was associated with higher baseline HbA1c, concurrent anti-depressant or antipsychotic medication, higher body weight and low treatment adherence. These characteristics may help identify patients unlikely to attain HbA1c treatment targets and be better served by a different model of care.

Introduction

Optimal glucose control in type 2 diabetes (T2D) decreases the risk of long-term complications, particularly retinal, kidney and cardiovascular disease [1]. A glycosylated haemoglobin (HbA1c) target of <7% (53mmol/mol) is recommended for most T2D patients [2]. However, despite broad availability of diabetes care teams and glucose-lowering drugs in developed nations, a significant proportion of T2D patients do not achieve this target [3].

In prior studies conducted mostly in Europe and the U.S., suboptimal glucose control has been associated with multiple factors, including longer duration of diabetes, younger age, low medication adherence, depression and clinical inertia [4-9]. We sought to determine the relevance of these factors to our clinic population as a basis for identifying strategies to improve outcomes.

Methods

This retrospective cohort study was approved by the Melbourne Health Human Research Ethics Committee as a quality assurance project (QA2016118) that did not require patient consent. Clinical and biochemical data from patients aged over 18 years who first attended Royal Melbourne Hospital Specialist Diabetes Clinic between January 2008 and December 2013 were downloaded from the Biogrid diabetes electronic medical record. Data from patients with type 2 diabetes who had at least 3 clinic attendances over the first year were included. The clinic is supported by diabetes nurse educators and dieticians, but does not involve psychologists or exercise physiologists.

Treatment intensification was defined as prescription of additional oral or injectable glucose lowering medication during the first year of clinic attendance. Treatment non-adherence was defined as less than 50% compliance with 1 or more prescribed glucose-lowering medication, as noted by the treating clinician.

Micro- and macroalbuminuria thresholds were 3.5 and 35mg/mmol respectively for women and 2.5 and 25mg/mmol respectively for men. Retinopathy was defined as documented non-proliferative or proliferative change, and neuropathy was defined as reduced monofilament sensation in the toes.

Data completeness is summarised in Supplemental Table 1. Statistical analyses were performed using Prism software (v7; GraphPad, San Diego, CA) and R software (www.r-project.org). Continuous data were compared using the Kruskal Wallis test with Dunn's correction for multiple comparisons. HbA1c values up to 2 years after the initial value were interpolated at monthly intervals using the Approxfun function of the R software package. Categorical data were compared using the chi-square test for trend and Fisher's exact test. Linear models to identify factors associated with HbA1c at one year were

created using the lm function within R software after the group median was used to impute missing data.

Results

From a total of 835 patients with type 2 diabetes who entered the Royal Melbourne Hospital Specialist Diabetes Clinic from 2008 to 2013, we identified 284 (61% male, median age 61 years, median duration 10 years) who attended clinic for at least one year. Figure 1 shows the mean HbA1c trajectory of these 284 patients and for subgroups stratified according to the HbA1c one year after clinic attendance. The mean HbA1c of 8.4% at baseline decreased to 7.5% at 12 months, with most of the decrease occurring over the first 3 months of clinic attendance (Figure 1A). Thirty-seven, 62, 99 and 86 patients, respectively, had 1-year HbA1c values of >9%, 8-9%, 7-8% and <7%. Patients with HbA1c>9% at one year initially improved before deteriorating, whereas the other groups had similar starting points that decreased divergently over the year of follow up (Figure 1B).

The baseline characteristics for each of the four HbA1c outcome groups and their prescribed diabetes therapy are summarised in Supplemental Table 2. When compared to the 185 patients comprising the 1-year HbA1c groups of <7% and 7-8%, the 37 patients in the HbA1c>9% group had a higher median [Q1, Q3] baseline HbA1c (9.9 [8.7, 12.0] vs 8.1 [7.2, 9.6] percentage units; p<0.0001) and baseline body mass index (35.7 [32.2, 41.2] vs 29.4 [27.4, 33.3] kg/m^2; p=0.002). Compared to patients who attained HbA1c<7%, those who attained HbA1c>9% were diagnosed with diabetes at a younger age (43.5 [32.1, 48.9] vs 51.9 [41.9, 59.4] years, p=0.0128), more likely to take medication for depression and schizophrenia (8 (22%) vs 4 (5%); p=0.0067), more likely to have been prescribed additional glucose-lowering therapy (14 (78%) vs 17 (30%); p=0.0007) and less likely to adhere to medication (8 (22%) vs 0; p<0.0001).

To identify baseline and treatment factors associated with HbA1c at one year, linear models were generated using the following measures as inputs: smoking status, gender, use of anti-depressant or

anti-psychotic therapy, injectable glucose-lowering medication at baseline, number of clinic visits in the first year, treatment intensification during the first year, compliance with glucose-lowering medication, age, age of diabetes diagnosis, body weight and baseline HbA1c. Measures that were independently associated with 1-year HbA1c were: baseline HbA1c; use of anti-depressant or anti-psychotic medication; low treatment adherence; higher body weight; and recommendations to intensify treatment during the first year (model coefficients presented in Supplemental Table 3). Combined, these factors explained 22% of the variance of 1-year HbA1c.

Discussion

This longitudinal analysis of 'real world' HbA1c outcome data has identified several findings that could be used to improve patient care. In the population overall, attending diabetes clinic for one year was associated with a significant reduction in median HbA1c from 8.4 to 7.5 percentage units, with most of this decrease occurring in the first few months of attendance. The one-year glucose outcome is somewhat lower than the Australian average within hospital diabetes clinics of 8.2% [10]. Despite this however, a significant minority (13% of our population) recorded HbA1c >9% after one year. This population was characterised by younger age, higher baseline HbA1c and obesity. On the other hand, the association between mental illness and treatment non-compliance with suboptimal glucose control implies a need to address both issues. One effective approach to address this would be to employ diabetes 'case managers' to provide mental health support and assistance to overcome treatment barriers [11].

We confirm the association between higher baseline HbA1c and worse glycaemic outcomes described previously in type 1 [12] and type 2 diabetes [13]. One practical implication would be to consider setting a higher HbA1c target (e.g. 7.5 or 8.0%) in cases where the HbA1c exceeded 9% on clinic entry and could not be reduced to the conventional target of 7% despite treatment adherence. This approach is consistent with recent guidelines advising personalised diabetes care [14].

The observation that obesity was associated with suboptimal glucose outcomes has been described previously [15] and presents an opportunity to consider placing more emphasis on weight management in the clinic. Because weight loss through lifestyle modification dramatically improves glucose control in type 2 diabetes [16,17], resources to deliver similar programs in the clinic could be considered.

Some limitations of this study should be noted. Firstly, missing data decreased our ability to identify associations between patient characteristics and glucose outcomes. This was particularly relevant to missing height data, which prevented analysis based on body mass index rather than body weight. Second, the observation that the available characteristics could only explain 22% of the variance in 1-year HbA1c indicates a need for clinic staff to identify and address other determinants of glucose outcome, such as self-management behaviour [18]. Finally, the generalisability of these findings from the tertiary hospital outpatient setting to the broader type 2 diabetes population is uncertain and will require further study.

In summary, suboptimal glycaemic control after 1 year of attending the clinic was associated with higher baseline HbA1c, obesity, mental illness and low adherence. Modification of the HbA1c target based on starting HbA1c and strategies to improve weight management and psychosocial health are likely to improve patient outcomes.

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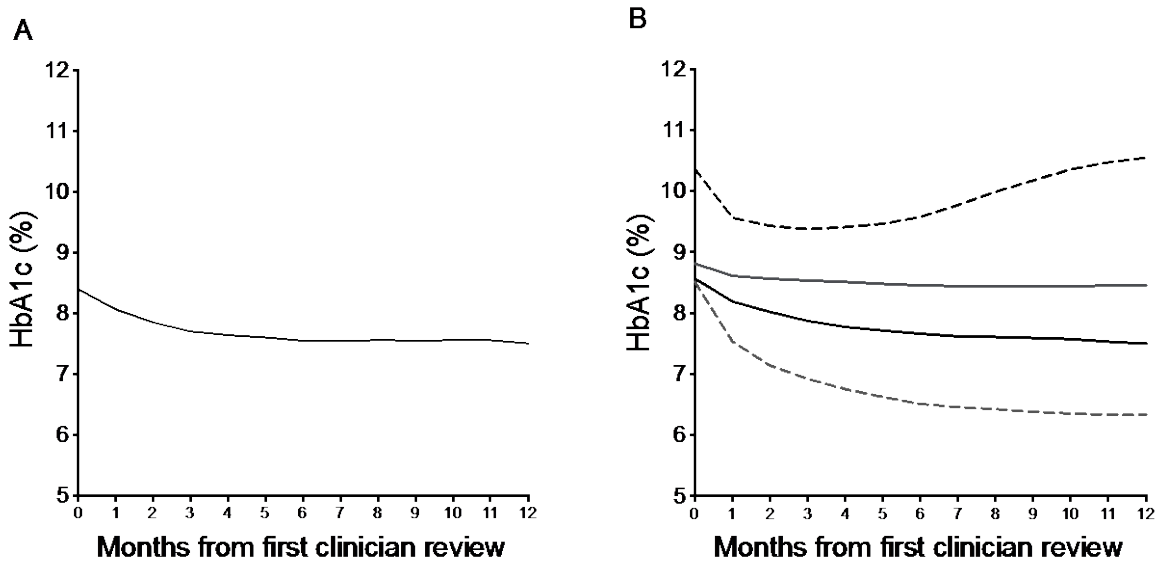
Figure 1: HbA1c trajectories for all 284 patients (A) and stratified according to HbA1c attained after one year of clinic attendance (B).

Data are the mean of each treatment group. Black dashed line: HbA1c>9%; Grey solid line: HbA1c 8-9%; Black solid line: HbA1c 7-8%; Grey dashed line: HbA1c<7%.



Supplemental Table 1

Number of patients with data for each variable (Total number of patients in study= 284)

Variable	**N**
Age (years)	283
Male	284
English second language	284
Smoker	284
Diabetes Duration (years)	189
Diabetic Retinopathy	284
Peripheral Neuropathy	284
Microalbuminuria	224
Macroalbuminuria	224
Macrovascular complications	284
Using injectable glucose lowering medication	283
Using ACEi or ARB	284
Using lipid lowering medication	284
Taking oral steroid	284
Taking antidepressant and/or antipsychotic	284
Weight	247
Height	96
Body mass index	96
Systolic blood pressure (mmHg)	238
Diastolic blood pressure (mmHg)	238
HbA1c (%)	284
Total cholesterol (mmol/L)	246
Triglycerides (mmol/L)	246
HDL (mmol/L)	240
LDL (mmol/L)	233
Albumin creatinine ratio (mg/mmol)	223
eGFR (ml/min.1.73m^2)	268
Number of clinic visits	284
Treatment intensified	168
Commenced Injectable	168
Treatment non-adherence	284

Supplemental Table 2: Baseline and treatment factors stratified to 1-year glucose outcome

	All Patients	HbA1c <7	HbA1c≥7 and ≤8	HbA1c>8 and ≤9	High HbA1c >9
	N=284	N=86	N=99	N=62	N=37
Baseline					
Age (years)	60.5 [51.4, 68.7]	59.2 [50.6, 67.5]	63.0 [53.7, 70.3]	60.9 [53, 70.5]	52.3 [45.8, 62.6]
Male	173 (61%)	54 (63%)	58 (59%)	37 (60%)	24 (65%)
English second language	74 (26%)	22 (26%)	33 (33%)	13 (21%)	6 (16%)
Smoker	45 (16%)	14 (16%)	17 (17%)	9 (15%)	5 (14%)
Diabetes Duration (years)	9.6 [3.9, 15.9]	5.0 [0.2, 11.4]	12.2 [7.3, 19.5]	8.8 [4.3, 15.6]	9.6 [4.6, 13.7]
Diabetic Retinopathy	31(11%)	7 (8%)	12 (12%)	7 (11%)	5 (14%)
Peripheral Neuropathy	17 (6.0%)	6 (7.0%)	5 (5.1%)	3 (4.8%)	3 (8.1%)
Microalbuminuria	106 (47%)	34 (55%)	33 (40%)	22 (46%)	17 (53%)
Macroalbuminuria	95 (42%)	23 (37%)	40 (49%)	20 (42%)	12 (38%)
Macrovascular complications	41 (14%)	10 (12%)	15 (15%)	11 (18%)	5 (14%)
Using injectable glucose-lowering medication*	115 (41%)	29 (34%)	42 (43%)	25 (40%)	19 (51%)
Using ACEi or ARB	152 (54%)	37 (43%)	56 (57%)	34 (55%)	25 (68%)
Using lipid-lowering medication	169 (60%)	39 (45%)	61 (62%)	45 (73%)	24 (65%)
Taking oral steroid	21 (7%)	7 (8%)	7 (7%)	5 (8%)	2 (5%)

Taking antidepressant and/or antipsychotic	18 (6%)	4 (5%)	4 (4%)	2 (3%)	8 (22%)
Weight (kg)	87 [74.4, 103]	86 [77, 102.5]	83 [70.4, 96.8]	89 [77.4, 107]	98 [83, 119]
Systolic blood pressure (mmHg)	130 [120, 140]	130 [120, 140]	128 [113, 140]	129 [120, 140]	130 [120, 148]
Diastolic blood pressure (mmHg)	75[70, 80]	80 [70, 80]	70 [70, 80]	75 [70, 80]	80 [70, 80]
HbA1c (%)	8.4 [7.5, 9.9]	8 [6.7, 10.0]	8.1 [7.6, 9.2]	8.5 [8.0, 10]	9.9 [8.7, 12.0]
Total cholesterol (mmol/L)	4.2 [3.5, 5]	4.2 [3.6, 5.1]	4 [3.4, 4.7]	4.2 [3.5, 4.9]	4.7 [3.9, 5.4]
Triglycerides (mmol/L)	1.9 [1.3, 2.5]	1.95 [1.2, 2.5]	1.8 [1.3, 2.4]	1.9 [1.5, 2.8]	1.8 [1.2, 2.7]
HDL (mmol/L)	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1 [0.9, 1.2]	1.0 [0.9, 1.3]
LDL (mmol/L)	2.1 [1.6, 2.9]	2.1 [1.7, 2.8]	2.0 [1.6, 2.5]	2.1 [1.6, 2.9]	2.8 [2.0, 3.1]
Albumin creatinine ratio (mg/mmol)	18 [5.6, 70]	17 [6.0, 59.5]	24.5 [5, 96]	12 [4.8, 69.3]	18.5 [5.1, 109.7]
egfr >90 (ml/min.1.73m^2	102 (38.1%)	39 (48.1%)	31 (34.8%)	15 (24.6%)	17 (45.9%)
egfr 60-89	94 (35.1%)	29 (35.8%)	29 (32.6%)	23 (37.7%)	13 (35.1%)
egfr 45-59	37 (13.8%)	6 (7.4%)	14 (15.7%)	12 (19.7%)	5 (13.5%)
egfr 30-44	21 (7.8%)	2 (2.5%)	11 (12.4%)	7 (11.5%)	1 (2.7%)
egfr 0-29	14 (5.2%)	5 (6.2%)	4 (4.5%)	4 (8.2%)	1 (2.7%)
Treatment-related					
Number of clinic visits	4 [3,5]	4 [3,5]	4 [3,5]	4 [3,5]	4 [3,5]
Treatment intensified	85 (51%)	17 (30%)	26 (46%)	28 (76%)	14 (78%)
Commenced injectable*	58 (35%)	10 (18%)	15 (27%)	22 (60%)	11 (61%)

Treatment non-adherence	24 (9%)	0	7 (7%)	9 (15%)	8 (22%)

*: injectables were insulin and GLP-1 analogues. Some variables had missing data. The N for each variable can be found in Supplemental Table 1.

Supplemental

Title

The Midland NIV score: A tool to predict Non-Invasive Ventilation failure in people with acute hypercapnic respiratory failure

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Non-invasive ventilation (NIV) is an effective tool to manage acute hypercapnic respiratory failure without the need for invasive mechanical ventilation. NIV decreases mortality in acute exacerbations of Chronic Obstructive Pulmonary Disease[1] (COPD) with acute hypercapnic respiratory failure and reduces intubation during Acute Pulmonary Oedema (APO).[2,3] NIV is often used outside of these indications to manage acute hypercapnic respiratory failure due to other, or a combination, of aetiologies[1]. Predicting the risk of failure of NIV at initiation in hospital may be useful to plan for location of care (Intensive care or high dependency area vs lower acuity medical ward) and to anticipate short-term failure. The Simplified Acute Physiology Score III (SAPS3) is a generic prognostic tool in ICU to predict mortality within the first hour of admission using patient demographics, comorbidities, and biochemical and physiological abnormalities.[4] Martinez-Urbistondo *et al*. adapted the SAPS3 score by including haemoglobin, carbon dioxide tension (PCO2), lactate, do not resuscitate (DNR) orders and aetiology of respiratory failure to create the SAPS3-CNIV score

specifically for individuals treated with NIV.[5] However, the SAPS3-CNIV score only predicts mortality and not intubation, was not superior than SAPS3 when externally validated in our St John of God Midland Public and Private Hospital (SJGMPPH) cohort and is arguably too complex for routine use.[6] Therefore, we aimed to develop a simple risk score to predict NIV failure at initiation in people with acute hypercapnic respiratory failure.

We retrospectively collected SAPS3 data points on all individuals managed with NIV at SJGMPPH between November 2016 and March 2018. Those with acute hypercapnic respiratory failure, defined as arterial blood gas with pH <7.35 & pCO2 ≥45mmHg, were included. NIV failure was defined as intubation or in-hospital death. Re-presentations requiring NIV were excluded. A logistic regression model was developed including all SAPS3 variables using stepwise exclusion criteria of p value >0.1. Beta-coefficients of the final model were multiplied by 10 and rounded to the nearest integer to create the NIV score. Discriminatory accuracy was assessed by the Area under the Receiver Operating curve (AUC) and calibration was assessed with the Hosmer-Lemeshow Goodness-of-Fit test. Statistical analysis was performed on SAS University Edition (SAS Studio 3.6, SAS 9.4M4). The study was approved by the St. John of God Healthcare Human Research Ethics Committee (reference: 1214).

228 individuals total were managed with NIV in this time period, of whom 150 (66%) had acute or acute-on-chronic hypercapnic respiratory failure and were included in the study. Mean ±SD age was 70.9±12.9 years. 73% (110) had a known history of COPD and 34% (51) were managed for APO. NIV failure occurred in 23% (35). The mortality rate was 17% (25) and 8.7% (13) of patients were intubated. The final multivariate adjusted logistic model for NIV failure is shown in table 1. The model AUC was 0.75 (95%CI 0.67-0.84) with acceptable calibration (Hosmer-Lemeshow Chi-Squared 2.96, P=0.8). The Midland NIV score had similar accuracy to the SAPS3-CNIV score (AUC 0.71, 95%CI 0.62-.881, comparison p=0.4), yet contains only five variables compared to 34 for SAPS3-CNIV (Figure 1).

Discussion

Identifying individuals at high risk of NIV failure at admission may be clinically useful to plan for the location of care and anticipate NIV failure, both in people who are suitable for invasive ventilation and those with limits of medical care.

The Midland NIV score is a simple tool that may identify those at increased risk of NIV failure and, in our cohort, is as accurate as the SAPS3-CNIV score. Individuals with a Midland NIV score of ≤11 (average 13% NIV failure) may be suitable for general ward care based on our data, compared to intensive care for those with a Midland NIV score ≥12 (average 66% NIV failure rate). Such a simple score could be implemented in acute settings so that clinicians can make simple calculations of the patients' risk at initiation of NIV.

We endeavoured to determine how Midland NIV score variables compared to those known to be associated with NIV failure. Dave *et al.* reported that in a cohort of individuals with COPD admitted with a first admission with acute hypercapnic respiratory failure, predictors of in-hospital mortality were increasing age, arterial pH <7.15, reduced lung function and persistent acidaemia after four hours of treatment.[7] A notable comparison is that our score determines the absence of a diagnosis of COPD to be a negative prognostic indicator, in keeping with findings by Phua *et al.* who determined the risk of endotracheal intubation to be much higher in those without a diagnosis of COPD in their large prospective study.[8] Also noted in the same study, a diagnosis of pneumonia with hypercapnic ARF was the most significant prognostic indicator which count be in keeping with elevated white cell count being significant in our patient cohort.

Recently the HACOR score has been developed which uses bedside physiological parameters at presentation in determining the risk of NIV failure in COPD patients alone.[9] Their findings determine arterial pH and level of consciousness to be the highest predictors of failure, neither of which we have included in our score. We determine COPD to be a good prognostic indicator in our patient cohort, thus we postulate the scores aren't directly comparable without doing specific subgroup analysis. The same group supported this observation in another study[10]. The HACOR score was assessed for validity in those with acute hypoxemic respiratory failure with results showing a marked difference in NIV failure depending on underlying diagnosis of which pulmonary oedema is a positive prognostic marker of successful NIV similar to our findings.

Increasing age is known to be associated with intubation and death in individuals with critical illness and respiratory failure.[4,5,7] We preferred to categorise this usually continuous variable of age as this allows straightforward comparison of beta-coefficients and therefore derivation of the Midland NIV score. In reality, the role of age in risk of NIV failure does not suddenly increase when individuals

turn 70 years old. A larger development or validation cohort may be able to more precisely describe the NIV failure risk attributed to increasing age.

Our study is limited by the retrospective nature also the variables used were based on pre-existing SAPS3 definitions. Some variables, such as presence of COPD or APO were subjectively defined by clinical suspicion rather than objective measures such as airflow obstruction, echocardiogram parameters or B-type naturetric peptide. While these definitions allow rapid utility of the score, it may limit generalisability to other populations. The sample size was determined by feasibility of the study rather than *a priori* power calculations. The fact it was a single centre study automatically leads to possible bias related to the local population. Lastly the AUC of 0.75 represents moderate discriminatory accuracy only. Risk predication models must undergo independent external validation and clinical impact analysis prior to implementation in routine care. The above mentioned HACOR score was noted to have discrepancies in results of NIV failure between their external and internal validation cohorts reducing its predictive power.[9] Hence, we welcome expressions of interest for collaboration from colleagues who manage acute respiratory failure in developing a prospective cohort to externally validate and/or refine the Midland NIV score, especially to identify a clinically useful threshold that leads to meaningful changes in management of this patient group.

In conclusion, the Midland NIV score, developed at SJGMPPH, is a simple score that includes age, presence of COPD and/or APO, creatinine and white cell count to predict the risk of NIV failure in those with acute hypercapnic respiratory failure. Further prospective independent validation is required before it can be used routinely to guide clinical practice.

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3. Coefficients for the model to predict HbA1c at one year. Shown are estimates of β, standard errors (se) and β/se

Variable	β	se(β)	β / se(β)
Baseline HbA1c (%)	0.177	0.0391	4.52
Use of anti-depressant or anti-psychotic	1.32	0.326	4.04
Compliance with treatment	-1.02	0.281	-3.65

Baseline weight (kg)	0.0102	0.00364	2.80
Intensification of glucose-lowering medication	0.389	0.165	2.36
Intercept	5.99	0.559	-