



Glycaemic control and antibody status among Waikato, New Zealand patients with newly diagnosed Type 1 diabetes

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Abstract

Aim To compare the risk of admission to hospital and poor glycaemic control by antibody status among newly diagnosed patients with type 1 diabetes in the Waikato Province of New Zealand.

Method A cohort aged under 25 years at diagnosis was identified from the Waikato Diabetes Service database. Patient information was extracted from the database, hospital information system and patient's paper records. The primary outcomes of interest were: admission to hospital, admission for diabetic ketoacidosis (DKA) and most recent HbA1c.

Results The cohort included 164 people with predominantly either Type 1 (133, 81%) or Type 2 (27, 16%) diabetes, diagnosed between 1997 and 2002. Twenty-four (18%) patients with Type 1 diabetes had one or more admissions for DKA. Logistic regression suggested male gender was associated with subsequent poorer glycaemic control whereas a positive anti-IA2 status was associated with HbA1c less than 10%.

Conclusion Admission to hospital with DKA was uncommon. We did not show an association between antibody status and subsequent admission to hospital. In view of its association with better glycaemic control, high levels of anti-IA2 may be a good, rather than a poor, prognostic feature in newly diagnosed patients with Type 1 diabetes.

The classification of children and young adults presenting with symptoms of diabetes mellitus has become more difficult with the increase in Type 2 diabetes in young patients¹ (including in New Zealand).²

Type 2 diabetes among children and young adults has increased due to their increasing obesity and associated insulin resistance.¹ Type 1 diabetes is categorised as either being positive or negative for various auto-antibodies related to pancreatic function.³ Although most patients with Type 1 diabetes are autoantibody positive, ethnicity confers notable differences and may make confirmation of Type 1 diabetes more difficult.

Studies have shown that up to 90% of those of Northern European origin have raised levels of at least one antibody at diagnosis⁴ whilst they are less frequently found in black Africans or African Americans.⁵⁻⁸ In the last 10 years it has become routine to measure anti-GAD and anti-IA2 antibodies to establish the type of diabetes in a given patient.

While such measurements remain imperfect diagnostic tools, the results are of use in the management of individual patients. It has not been established whether the actual titres of anti-GAD or anti-IA2 antibodies at diagnosis have prognostic implications

although the presence of anti-GAD is believed to be indicative of beta-cell destruction.⁹

Admission to hospital with DKA is a serious and potentially life-threatening situation. Whilst it is rare in children, it is an important cause of premature death in young adults with diabetes.¹⁰ If we can identify those most at risk and through more intensive management prevent admission with DKA then this is a worthwhile goal.

The WDHB (Waikato District Health Board) catchment area includes 339,100 people (8.3% of New Zealand's population), of which 74,110 (22%) are Māori and 7,300 (2%) are Pacific people (mostly of Samoan, Tongan, Niuean, or Cook Islands origin).

Previous studies have shown that Māori in New Zealand have a prevalence and incidence of Type 1 diabetes lower than that in the New Zealand European population^{11,12} whilst Type 2 diabetes is more common in Māori.² The use of antibodies is becoming increasingly important to differentiate between Type 1 and Type 2 diabetes in the province, particularly among Māori.

The primary aim of the study was to observe the relationship between antibody status in newly diagnosed patients with Type 1 diabetes and the incidence of hospital admission. A secondary aim was to compare antibody status with long term glycaemic control as measured by HbA1c.

Method

Study design and subjects—An inception cohort of newly diagnosed patients with diabetes between 1997 and 2002, under the age of 25 at diagnosis and resident in the WDHB area was identified from the Waikato Diabetes Service diabetes database. A starting year of 1997 was chosen because this is when anti-GAD and anti-IA2 measurements began to be used. Including patients diagnosed up until 2002 assured a minimum of 3 years of follow-up.

Patients were identified as Type 1, Type 2 and other. Type 1 patients were differentiated from Type 2 patients based upon their symptoms, insulin dependence, and autoantibody and glucose test results. Patients with gestational diabetes without diabetes postnatally, drug-induced diabetes, and diabetes related to surgery were excluded from the study.

Where the type of diabetes was not clear two independent clinicians reviewed the patient file and provided a clear diagnosis. Where there was disagreement between clinicians, the case was discussed until a final diagnosis was reached.

Other patient information extracted from the diabetes database included: gender, date of birth, ethnicity, year of diagnosis, age at diagnosis, initial and current treatment, and HbA1c data. Where information and data was missing from the database, the WDHB electronic database and local pathology laboratory's database was used to find these details. If this did not provide the needed information the patient file was requested from Waikato Hospital.

Anti-GAD and anti-IA2 data were obtained from the WDHB and local pathology laboratory's electronic databases and paper records. Because two different laboratories were used to measure the antibody levels in different patients, there were two different units and reference ranges in our database: units/ml (measured by a radioimmunoassay by the Waikato Hospital laboratory) and Units (used by Diatranz laboratory).

Consequently results were categorised into normal (as indicated in the relevant reference range for each laboratory), weakly positive, positive, or strongly positive as categorised in tertiles of the positive tests. The primary outcomes of interest identified were: admission to hospital admission for diabetes related conditions; DKA subsequent to being diagnosed with diabetes; and most recent HbA1c levels. Death was initially considered as a possible outcome of interest, but no patients in the cohort died during the study period.

Information on hospital admissions for diabetes-related complications (DKA, hypoglycaemia, and infections) were obtained from the WDHB electronic patient database. This records the date of all

admissions and discharges and the reason for the admission. The results of all laboratory tests are also available. Follow-up of all those Type 1 patients included in the final database was through accessing the hospital electronic patient records, through the laboratory database or by accessing the paper notes.

Statistics and analysis—The incidence of diabetes by type and ethnicity was calculated. Population figures were obtained from the WDHB and were based on estimates from the 1996 and 2001 censuses. Ethnic categories for these populations were given as Māori, Pacific people, and Others (approximately 5% of the non-Māori, non-Pacific population are of Asian descent. Each outcome of interest (number of hospital admissions, number of hospitalised episodes of DKA and latest HbA1c level) was plotted against a number of independent variables, including: age, gender, ethnicity, age at diagnosis, body mass index (BMI), total cholesterol, triglyceride, and autoantibody status to investigate any correlation. Logistic Regression analysis using backward elimination was used with a significance level of 0.05. Analysis was performed using STATA version 8 software (STATA Corp., College Station, TX, USA).

Results

A total of 164 people (84 males and 80 females) under the age of 25 residing in the WDHB area were diagnosed with diabetes between 1997 and 2002. Of the 164, 133 (81%) were diagnosed with Type 1 diabetes and 27 (16%) with Type 2 diabetes. Four (2%) had diabetes due to other causes, including maturity onset diabetes of the young (MODY), cystic fibrosis, and pancreatitis.

Mean age at diagnosis in those with Type 1 diabetes was 13.0 years (14.8 in Māori and 12.6 in European), 67/133 (50.4%) were female and the mean BMI was 22.9 kg/m². The average incidence of Type 1 and Type 2 diabetes in the Waikato region are shown in Table 1 and indicate the incidence of Type 1 diabetes was as expected lower in Māori than non-Māori whilst the reverse was true in Type 2 diabetes.

Table 1. Incidence (%) of people with diabetes (per 100,000 per year) in the Waikato DHB area, by diabetes type as well as ethnicities and ages of people affected

Variables	All (%)	Māori (%)	European/Others*
Type 2 0–24 years	3.5 (2.2–4.8)	8.0 (4.3–11.7)	1.5 (0.5–2.5)
Type 1			
0–24 years	17.4 (14.4–20.4)	6.7 (3.3–10.1)	21.9 (17.9–25.9)
0–14 years	17.9 (14.1–21.7)	5.3 (1.6–9.0)	24.3 (18.8–29.8)
15–24 years	16.8 (12.0–21.6)	9.3 (2.4–16.2)	20.1 (13.9–26.3)

Data are crude incidence rates (95% confidence interval) based on average Waikato population for the period 1997–2002; *The 2 patients of Pacific origin are included in the total population but are not included in the column headed European/others.

Of the 133 patients with Type 1 diabetes, 85/133 (64%) had anti-GAD results available and 68/133 (51%) had an anti-IA2 result. Of those that had both tests, 59/68 (87%) had either anti-GAD, anti-IA2, or both positive. Seventy-six percent were anti-GAD positive and 65% were anti-IA2 positive. The antibody status of patients by ethnicity is shown in Table 2 and Table 3.

Fifty-nine (44%) of the 133 Type 1 patients had been admitted to hospital for a diabetes-related complication since their diagnosis. The main reason for admissions were hypoglycaemia, infections, or DKA. There were 51 episodes of DKA among 24 patients. Of the 20 patients who had a negative anti-GAD result, 1 (5%) had an episode of DKA—this compares to the 10 (15%) patients who had an episode of DKA

from the group of 65 patients who had a positive anti-GAD result (OR=1.46, p=0.226). Of the 48 patients who did not have anti-GAD measured, 13 (27%) had an episode of DKA.

Table 2. Anti-GAD measurements by ethnic group

Variables	All	Māori	European/Others*
Anti-GAD Positive	65/85 (76%)	9/10 (90%)	55/74 (74%)
Anti-GAD Negative	20/85 (24%)	1/10 (10%)	19/74 (26%)
Not Tested	48/133	5/15	42/116

Table 3. Anti-IA2 measurements by ethnic group

Variables	All	Māori	European/Others*
Anti-IA2 Positive	43/67 (64%)	6/9 (67%)	37/58 (64%)
Anti-IA2 Negative	24/67 (36%)	3/9 (33%)	21/58 (36%)
Not Tested	66/133	6/15	58/116

*The 2 patients of Pacific origin are included in the total population but are not included in the column headed European/others.

Almost all the patients (97%) had HbA1c measurements available. The mean HbA1c at diagnosis was 10.3% and after 3 or more years of treatment the mean was 9.4%.

The current patient characteristics that are influencing DKA, number of hospital admissions, and recent HbA1c >10% were investigated using logistic regression analysis. The dependent variables used included most recent HbA1c, current age, gender, duration of diabetes, Māori (Y/N), anti-GAD positivity, and anti-IA2 positivity in the initial models.

Non-significant variables (p<0.10) were excluded using backward stepwise regression. The most recent HbA1c was found to be a significant predictor of DKA (OR=1.5 [1.23–2.01], p=0.001) and hospital admission (OR=1.24 [1.01–1.57], p=0.039). Male gender and anti-IA2 positivity were significant predictors of most recent HbA1c >10 (OR=4.34 [1.39–13.54], p=0.012 and OR=0.278 [0.09–0.88], p=0.029 respectively).

Table 4. Anti-GAD levels of patients who had an episode of diabetic ketoacidosis

Anti-GAD Levels (Units)	N (%)
Normal	1/20 (5%)
Weak positive	5/20 (25%)
Positive	4/23 (17%)
Strongly positive	1/22 (5%)
Not Tested	13/48 (27%)
Total	24/133 (18%)

Discussion

Our study shows that admission to hospital with DKA was a relatively rare event and only occurred in 24/133 (18%) of patients. Other common reasons for admission included hypoglycaemia and infections such as candidiasis, infected pilonidal sinuses, and urinary tract infections.

We did not show any statistically significant associations between antibody status and subsequent admission for DKA, but there was a negative association between anti-IA2 positivity and poor glycaemic control as indicated by a HbA1c > 10%. Unsurprisingly, a current HbA1c > 10% was also associated with risk of hospital admission or of admission with DKA.

Zanone et al also found an inverse relationship between autoantibody levels and HbA1c.¹³ They hypothesised that patients with higher anti-IA2 levels had more functioning islet cells, which led to more endogenous insulin synthesis and hence less dependence on exogenous insulin. Our findings support this in that those patients with positive anti-IA2 were less likely to have a HbA1c > 10%.

We did not show any association between anti-GAD levels and HbA1c, hospital admission or DKA. This is in contrast to the small study of 35 patients by Hoeltke et al who showed an association between positive anti-GAD status and risk of poor glycaemic control.⁹

The incidence rates of under-25 year olds with Type 1 and Type 2 diabetes residing in the WDHB catchment area averaged 17.4 and 3.5 per 100,000 people per year, respectively.

The incidence for the under 15 age group was 17.9 per 100,000, which is the same as that found by Campbell-Stokes et al in their study¹¹ which covered all of New Zealand during the 1999–2000 period. Rates for the Māori and non-Māori 0–14 subpopulations (5.3 and 24.3 per 100,000, respectively) are also similar to that found by Campbell-Stokes et al. (5.6 and 21.7 per 100,000, respectively).

It should be noted that the classification of ethnicity in hospital records is not entirely consistent with self-identified ethnicity or that used in the New Zealand census.¹⁴ Whilst this may have introduced a bias into the estimate of the incidence of Type 1 diabetes in Māori, the consistency with the rate found by Campbell-Stokes is reassuring and suggests substantial misclassification is unlikely to have occurred.

A significant difference in incidence by ethnicity was noted for Type 2 diabetes, with Māori having a much higher incidence rate. These results are further evidence that the incidence of Type 1 diabetes has increased since the 1980s.^{15,16} It also supports the belief that Type 2 diabetes is becoming a more significant health issue among younger people, especially Māori.¹⁷

Of those Type 1 patients that had two autoantibody measurements done, 87% tested positive for one or more autoantibody. Of the 85 patients that had an anti-GAD measurement done, 65 (76%) had a positive result. This is a similar result to that found in other studies.^{9,18,19}

Some studies have ignored those with idiopathic Type 1 diabetes and only include those insulin-dependent patients who are antibody positive. However in all other respects these idiopathic Type 1 patients are similar to those that have positive anti-

GAD or anti-IA2. Of those that had both an anti-GAD and anti-IA2 59/68 (87%) tested positive to one or other. This result is slightly below the 94% who tested positive in the study by Campbell-Stokes et al.

Because our study covered an initial period when antibody levels for anti-GAD and anti-IA2 were not always done, the proportion of patients that had their antibody status tested was lower in the earlier years of the study. This may have introduced a bias to our findings. However in those that did have their antibody status tested the proportions of New Zealand Europeans and Māori with positive autoantibody results were very similar. Thus the findings from the USA and South Africa where a higher proportion of African/African Americans with Type 1 diabetes are antibody negative does not seem to be true for Māori.

We believe this is the first time this finding has been reported. Whilst a larger study is needed to confirm this finding it does suggest that there maybe aetiological differences in the development of Type 1 diabetes in Africans and African Americans compared with other ethnic groups including Māori.

Some methodological problems included having two laboratories that used different auto-antibody measurements. This meant that we had to categorise the level of antibodies rather than treat them as a continual variable. Despite their benefits, the immunoassay techniques used are not perfect and so can still quantify auto-antibody levels incorrectly²⁰ and so our categorisation maybe a reasonable approach.

Another potential problem is that there may be under-reporting of hospital admissions due to patients moving out of the WDHB area or being out of the area when medical assistance was needed. Bias may have come from clinicians only having auto-antibody measurements done on patients where they were not confident of their diagnosis. Such a bias may be one explanation why 27% (13/48) of those Type 1 patients who did not have their anti-GAD levels measured had a subsequent episode of DKA compared to 15% (10/65) of those who had their anti-GAD measured and had a positive result.

This study provided an overview of diabetes in children and young adults in the Waikato Province. It has shown that the most important predictor of subsequent admission to hospital for newly diagnosed patients with Type 1 diabetes is poor glycaemic control. If there is evidence of antibodies to IA2 present then this is a predictor of better glycaemic control and it maybe that these patients will have less complications than those who are anti-IA2 negative.

Whilst anti-GAD is an important marker indicating the likely subsequent need for long-term insulin therapy in adults,²¹ it does not help predict risk in newly diagnosed Type 1 patients.

As previously found by Scott et al, good glycaemic control is hard to achieve in adolescents and young adults with Type 1 diabetes²² but concentrating on improving glycaemic control in all newly diagnosed patients with Type 1 diabetes would seem to be the most important factor in reducing hospital admissions and other complications.

Competing interests: None.

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