ORIGINAL RESEARCH PAPER

ORIGINAL RESEARCH: CLINICAL

The Royal New Zealand College of General Practitioners
Te Whare Tohu Rata o Aotearoa

Metformin adherence in patients with type 2 diabetes and its association with glycated haemoglobin levels

Lynne Chepulis BSc, MSc, MPhil, PhD;[1,4] Christopher Mayo Student;[2] Brittany Morison BASc, MSc;[1] Rawiri Keenan MbChB, FRNZCGP;[1] Chunhuan Lao BSc, MSc, PhD;[1] Ryan Paul MbChB, FRACP, PhD;[2,3] Ross Lawrenson MBBS, MD, FRCGP, FFPH, FAFPHM[1,3]

[1] Medical Research Centre, University of Waikato, Hamilton, New Zealand
[2] Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[3] Waikato District Health Board, Hamilton, New Zealand
[4] Corresponding author. Email: lynnec@waikato.ac.nz

J PRIM HEALTH CARE
2020;12(4):318–326.
doi:10.1071/HC20043
Received 6 May 2020
Accepted 29 September 2020
Published 5 November 2020

ABSTRACT

INTRODUCTION: Metformin is the initial medication of choice for most patients with type 2 diabetes. Non-adherence results in poorer glycaemic control and increased risk of complications.

AIM: The aim of this study was to characterise metformin adherence and association with glycated haemoglobin (HbA1c) levels in a cohort of patients with type 2 diabetes.

METHODS: Prescription and dispensing data were used for this study. Primary care clinical and demographic data were collected from 10 general practices (October 2016–March 2018) and linked to pharmaceutical dispensing information. Metformin adherence was initially measured by calculating the proportion of patients who had optimal medication cover for at least 80% of days (defined as a medication possession ratio (MPR) of ≥0.8), calculated using dispensing data. Prescription adherence was assessed by comparing prescription and dispensing data. The association between non-adherence (MPR <0.8) and HbA1c levels was also assessed.

RESULTS: Of the 1595 patients with ≥2 metformin prescriptions, the mean MPR was 0.87. Fewer Māori had an MPR ≥0.8 than New Zealand European (63.8% vs. 81.2%). Similarly, Māori received fewer metformin prescriptions ($P = 0.02$), although prescription adherence did not differ by ethnicity. Prescription adherence was lower in younger patients ($P = 0.002$). Mean HbA1c levels were reduced by 4.8 and 5.0 mmol/mol, respectively, in all and Māori patients with an MPR ≥0.8. Total prescription adherence reduced HbA1c by 3.2 mmol/mol (all $P < 0.01$).

DISCUSSION: Ethnic disparity exists for metformin prescribing, leading to an overall reduction in metformin coverage for Māori patients. This needs to be explored further, including understanding whether this is a patient preference or health system issue.

Keywords: Type 2 diabetes; medication adherence; general practice; inequality

Introduction

Type 2 diabetes is a growing health issue in New Zealand (NZ) that affects twice as many Māori as non-Māori and an increasing number of younger people.[1–3] Type 2 diabetes is associated with a range of microvascular and macrovascular complications, chronic kidney disease and cardiovascular disease; the latter being the greatest cause of morbidity and mortality in this patient group.[4–6] Patients with good glycaemic control have fewer complications.[7,8]

To achieve optimal outcomes and reduce the chance of diabetes-related complications, patients should aim to have their glycated haemoglobin (HbA1c) measurement <53 mmol/mol.[9]

Type 2 diabetes is mainly managed in general practice with the aim of achieving good glycaemic control and reducing cardiovascular risk factors. Management primarily involves the use of diet and exercise along with medication.[10] Typically, metformin is the initial medication of choice as it has been shown to reduce insulin resistance, cardiovascular disease and mortality, while demonstrating a good safety profile at a low overall cost.[11] Many studies have demonstrated significant improvements in glycaemic control with metformin use, either alone or in combination therapy.[12–14] However, the efficacy of metformin depends on patients' adherence to prescribed medication.[15,16] Many factors contribute to diabetes medication adherence, including cost, health literacy and disease awareness.[17,18] Many patients may also be non-adherent to metformin prescribing because of gastrointestinal side-effects.[19,20]

Adherence to metformin and other oral hypoglycaemic agents is sub-optimal in NZ patients with type 2 diabetes.[21,22] Non-adherence is higher in patients receiving combination oral hypoglycaemic therapy and in patients who are male, of Māori ethnicity and who have high socioeconomic deprivation.[21] In these studies, non-adherence was assessed using medication dispensing data and there was no record of whether this was because patients failed to receive a prescription or did not visit a pharmacist. This is important to know because there may be disparities between Māori and non-Māori in the medications that are prescribed rather than medications dispensed.[23] Therefore, the primary aim of this study was to characterise metformin adherence in a cohort of NZ patients with type 2 diabetes using both primary care prescription and dispensing data. This study also evaluates associations between metformin non-adherence and HbA1c levels as this has not previously been reported in NZ.

WHAT GAP THIS FILLS

What is already known: Metformin adherence is suboptimal in New Zealand patients with type 2 diabetes, particularly in Māori, males and people with higher social deprivation.

What this study adds: Ethnic disparity in metformin use appears to be due to fewer prescriptions for Māori than for New Zealand Europeans. A medication ratio of ≥0.8 (80% of days covered) is associated with a reduction in HbA1c of 4.8 and 5.0 mmol/mol in all and Māori patients, respectively.

Methods

Study design

This study was part of a larger project aiming to assess the quality of diabetes care in primary care using demographic and clinical data collected from 10 general practices in the Waikato region. The full project was granted ethics approval by the New Zealand Health and Disability Ethics Committee (ref: 19/CEN/8).

Data sources

In June 2019, primary care data were collected directly from the electronic patient management systems of study general practices for the period of October 2016 – March 2018. National Health Index (NHI)-identified patient information was extracted for all patients who had a confirmed diagnosis (≥12 months) of diabetes (read code C10) and were aged ≥15 years on 1 October 2016. Extracted data included age (at time of data collection in June 2019), gender, ethnicity, HbA1c values and metformin prescription data for the study period. HbA1c values were averaged to provide a mean value for each patient for the study time period. General practices were coded as rural or urban using the NZ Department of Statistics database Urban Rural Profile Categories.[24]

Patient records were checked against the Waikato District Health Board clinical records to retrieve missing demographic and diagnosis information. Patients with type 1 diabetes were then excluded from the dataset.

Data processing

Patients with type 2 diabetes who had received at least two dispensings of metformin were included for analysis. Primary care prescribing data were analysed for this cohort to determine how many metformin prescriptions were written for each

patient during the 18-month study period (the 'Prescribing Period'). These data were then linked by patient NHI to the Ministry of Health Pharmaceutical Collection database to determine how many prescriptions were dispensed. Each dispensing could be matched to only one prescription and needed to be within 3 months of the prescription date. The pharmaceutical dataset included the 21-month period between October 2016 and June 2018 ('Dispensing Period'). The extra 3 months allowed for the dispensing of prescriptions that were written towards the end of the Prescribing Period (medications can be dispensed up to 3 months after being prescribed, while remaining valid for government subsidy).[25] A 90-day quantity dispensing was assumed for each prescription.

For this study, metformin adherence is characterised in two ways: (1) using medication dispensing data to define the number of days that patients had medication cover (the medication possession ratio (MPR)); and (2) by comparing the number of prescription and dispensing events to calculate the proportion of prescriptions being filled. Using the pharmaceutical dispensing data, an MPR of ≥0.8 indicated 'good adherence' (medication cover for at least 80% of days).[26] Metformin adherence was considered 'poor' where the MPR was <0.8.[26] MPR was calculated by summing the days of medication supply from the first to the last prescription (inclusive) divided by total number of days of the prescription period.[26]

To calculate the proportion of prescriptions being dispensed, we analysed data from a subset of patients who had been prescribed metformin two to seven times during the 18-month prescribing period. These patients were classified as either having 100% prescription adherence (every metformin prescription could be linked to a dispensing event) or <100% prescription adherence (at least one prescribed medication could not be linked to a dispensing event).

Statistical analyses

Metformin adherence was described by gender, age group, ethnicity, rural or urban practice location and concurrent diabetes medications. Subgroup differences were analysed with chi-square test and Student's *t*-tests, and logistic regression was used to estimate the odds ratio of a patient having 100% prescription adherence or having good adherence, adjusting for gender, age, ethnicity, rurality and diabetes treatment regimen. The average number of prescription and dispensing events is reported as mean ± standard deviation (s.d.).

Factors influencing HbA1c levels were also analysed. Student's *t*-tests were used to compare the differences in means of various subgroups, and linear regression was used to determine the adjusted associations of HbA1c with metformin adherence, ethnicity, age, gender, medication regimen and rurality.

All data analyses were performed in Python 3.7 (Python Software Foundation, Beaverton, USA) using the Pandas 0.25.3, Scipy 1.3.2, and Statsmodels 0.10.2 libraries, with significance accepted at $P < 0.05$.

Results

A total of 3716 patients with type 2 diabetes were initially identified in the primary care dataset, including 1595 patients (42.9%) who had at least two metformin dispensings during the prescription period. The mean number of metformin prescriptions during this period was 6.1 ± 1.7.

The demographic characteristics of this group of 1595 patients are shown in Table 1. Their median age was 65 years, with a slightly higher proportion of male patients (55.5% vs. 44.5%; $P < 0.001$). Nearly half of all patients (49.0%) were prescribed metformin monotherapy, with the remainder prescribed combination therapy (Table 1).

Metformin adherence using pharmaceutical dispensing data

For the 1595 patients who had received at least two dispensings of metformin, the mean overall MPR was 0.87, and three-quarters of all patients had an MPR of ≥0.8, which did not differ significantly by gender, rural or urban practice location or medication regimen (Table 2). Māori and Pasifika patients had poorer metformin adherence than patients of other ethnicities, with 63.8% and 59.6% of patients, respectively, having ≥80% medication adherence, compared to 73.8–81.2% of other ethnic groups (Table 2). This difference remained for Māori compared to NZ Europeans after adjusted analysis

(OR 0.41; 95% CI 0.30–0.56; $P < 0.001$). Older patients were more likely to have reduced adherence ($P < 0.001$), although this association did not remain significant after adjustment for gender, rurality, ethnicity, and medication regimen.

Comparison of prescription to dispensing data

Overall, 1127 (70.7%) of the 1595 patients with two or more metformin prescriptions received five to seven metformin prescriptions in the prescribing period, indicating full prescription coverage. The proportion of patients given five to seven prescriptions of metformin was lower for Māori and Pasifika patients (Table 3).

For patients given five to seven metformin prescriptions, the majority were then dispensed, with 86.2% of patients overall having 100% prescription adherence. No significant differences in prescription adherence were seen by gender, ethnicity, rurality, or medication regimen. However, prescription adherence differed significantly with age ($P < 0.001$), with older patients being more likely to have 100% prescription adherence. After adjustment for other factors, patients aged 45–59 years also had a significantly lower rate of 100% prescription adherence than patients aged 60–74 years (OR 0.51; 95% CI 0.33–0.77; $P = 0.002$).

For patients who received less than five prescriptions of metformin during the 18-month period ($n = 438$), prescription adherence was still high, with more than 75% of patients having 100% prescription adherence (Figure 1).

Prescription adherence and HbA1c

HbA1c values were available for 1560 of the 1595 patients with two or more metformin prescriptions (97.8%). Compared to patients who had an MPR of ≥0.8 and 100% prescription adherence, mean HbA1c was significantly higher in patients with an MPR <0.8 (67.6 vs. 59.8 mmol/mol, $P < 0.001$) and in patients who had <100% prescription adherence (64.1 vs. 59.7 mmol/mol, $P < 0.001$). Mean HbA1c was also higher in Māori (65.4 mmol/mol) than in non-Māori patients (60.5 mmol/mol; $P < 0.01$).

Table 1. Demographic and clinical characteristics of patients with type 2 diabetes receiving at least two prescriptions of metformin during the 18-month prescribing period

Characteristic	
Age (mean ± s.d.) (years)	65 ± 8.6
- <44	107 (6.7)
- 45 – 59	440 (27.6)
- 60–74	699 (43.9)
- ≥75	349 (21.9)
Gender	
- Male	886 (55.5)
- Female	709 (44.5)
Rurality	
- Urban	830 (52.0)
- Rural	765 (48.0)
Medication regimen*	
- Metformin Only	782 (49.0)
- Metformin + Sulfonylureas	501 (31.4)
- Metformin + Insulin	192 (12.0)
- Metformin + Insulin + Sulfonylureas	120 (7.5)
Ethnicity	
- New Zealand European	926 (58.1)
- Maori	378 (23.7)
- Asian	149 (9.3)
- Pasifika	47 (2.9)
- Other	95 (6.0)
Total	1595

Data are presented as *n* (%) unless otherwise stated. s.d., standard deviation.
*Medication regimen at beginning of the 18-month period.

After controlling for other factors, we found that, compared with patients with an MPR of <0.8, having an MPR ≥0.8 was associated with a mean reduction in HbA1c of 4.83 overall ($P < 0.001$; 95% CI 3.08–6.57) and 5.00 mmol/mol for Māori ($P = 0.008$; 95% CI 1.30–8.70). Furthermore, having 100% prescription adherence was associated with an overall mean reduction in HbA1c of 3.20 mmol/mol ($P = 0.004$; 95% CI 1.01–5.38) compared with patients who had <100% prescription adherence.

The association between metformin adherence and HbA1c differed by age. In patients aged <60 years (mean age 50.6 years, mean HbA1c 67.9 mmol/mol), an MPR of ≥0.8 and 100% prescription

Table 2. Metformin adherence using the medication possession ratio (MPR) calculated from pharmaceutical dispensing data

Subgroup	*n*	Mean MPR	MPR <0.8 *n* (%)	MPR ≥0.8 *n* (%)	*P*-value
Gender					
- Male	886	0.88	211 (23.8)	675 (76.2)	0.636
- Female	709	0.87	177 (25.0)	532 (75.0)	
Age band (years)					
- <44	107	0.78	51 (47.7)	56 (52.3)	<0.001
- 45–59	440	0.83	143 (32.5)	297 (67.5)	
- 60–74	699	0.89	141 (20.2)	558 (79.8)	
- ≥75	349	0.93	53 (15.2)	296 (84.8)	
Ethnicity					
- Asian	149	0.89	39 (26.2)	110 (73.8)	<0.001
- Māori	378	0.82	137 (36.2)	241 (63.8)	
- New Zealand European	926	0.90	174 (18.8)	752 (81.2)	
- Others	94	0.88	19 (20.0)	76 (80.0)	
- Pasifika	47	0.81	19 (40.4)	28 (59.6)	
Rurality					
- Rural	765	0.88	179 (76.6)	586 (76.6)	0.441
- Urban	830	0.87	209 (74.8)	621 (74.8)	
Medication regimen*					
- Metformin Only	782	0.86	203 (26.0)	579 (74.0)	0.148
- Metformin + Sulfonylureas	501	0.87	122 (24.4)	379 (75.6)	
- Metformin + Insulin	192	0.89	43 (22.4)	149 (77.6)	
- Metformin + Insulin + Sulfonylureas	120	0.91	20 (16.7)	100 (83.3)	
TOTAL	1595				

*Calculated from prescription data.

adherence were associated with a mean reduction in HbA1c of 7.44 mmol/mol ($P < 0.001$; 95% CI 4.12–10.77) and 4.32 mmol/mol ($P = 0.031$; 95% CI 0.41–8.24), respectively. In contrast, in patients aged ≥60 years (mean age 71.7 years, mean HbA1c 58.5 mmol/mol), good metformin adherence was associated with a smaller reduction in HbA1c: MPR ≥0.8 (2.90 mmol/mol; $P = 0.004$; 95% CI 0.94–4.85) and 100% prescription adherence (2.66 mmol/mol; $P = 0.045$; 95% CI 0.06–5.26).

Discussion

Our study showed disparity between Māori and New Zealand European (NZE) for metformin coverage and this is likely due to access to prescriptions rather than medication dispensing. Māori were less likely to receive the five to seven prescriptions needed to maintain 100% medication cover (and more likely to have an MPR of <0.8 and a higher mean HbA1c level); however, once prescribed, metformin dispensing was not different from other ethnic groups.

This finding of fewer metformin prescriptions for Māori patients agrees with previous reports that, in general, Māori are prescribed fewer medications than people of other ethnic groups.[21,27] This may be a result of the westernised model of health care used in NZ not being appropriate for use by many Māori,[28] such that Māori have been reported to be less satisfied with their access to health care in this country.[29] However, it is also possible that Māori may be less adherent to metformin because of other reasons such as a higher rate of side-effects.

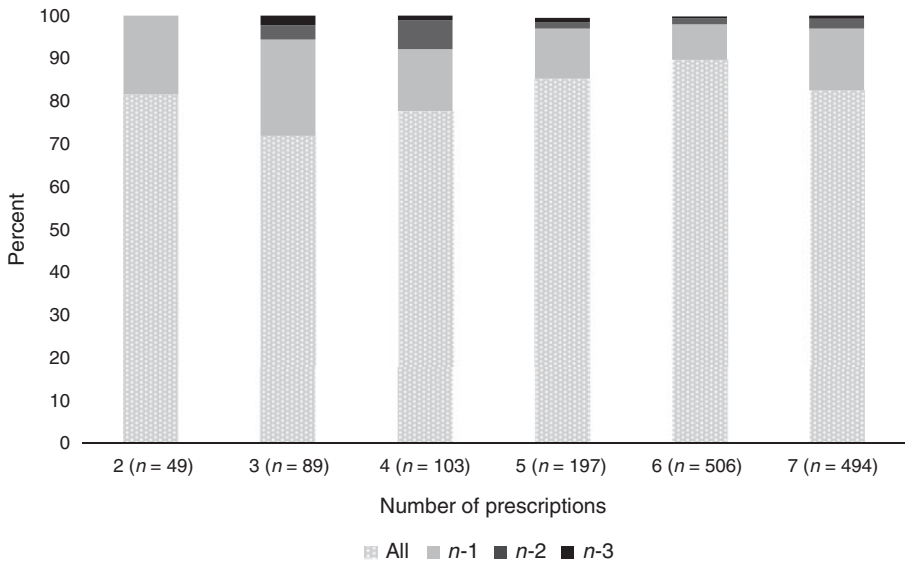
Table 3. Dispensing adherence to metformin prescriptions for patients with type 2 diabetes who were regular metformin users (5–7 prescriptions; n = 1127).

Subgroup	*n*	Proportion of patients with 5–7 scripts (%)*	*P*-value (for % patients with 5–7 scripts)	100% prescription adherence† *n* (%)	<100% prescription adherence† *n* (%)	*P*-value (for adherence)
Gender						
- Male	640	72.2	0.127	557 (87.0)	83 (13.0)	0.430
- Female	487	68.7		415 (85.2)	72 (14.8)	
Age group (years)						
- <44	71	66.4	0.078	233 (79.5)	60 (20.5)	<0.001
- 45–59	293	66.6		456 (89.4)	54 (10.6)	
- 60–74	510	73.0		53 (74.6)	18 (25.4)	
- ≥75	253	72.5		230 (90.9)	23 (9.1)	
Ethnicity						
- Asian	103	69.1	0.022	85 (82.5)	18 (17.5)	0.162
- Māori	247	65.3		202 (81.8)	45 (18.2)	
- NZE	672	72.6		592 (88.1)	80 (11.9)	
- Others	77	81.9		68 (88.3)	9 (11.7)	
- Pasifika	27	57.4		24 (88.9)	3 (11.1)	
Rurality						
- Rural	540	70.6	0.965	472 (87.4)	68 (12.6)	0.317
- Urban	587	70.7		500 (85.2)	87 (14.8)	
Medication regimen						
- Metformin Only	554	70.8	0.453	471 (85.0)	83 (15.0)	0.516
- Metformin + Sulfonylureas	348	69.5		301 (86.5)	47 (13.5)	
- Metformin + Insulin	133	69.3		117 (88.0)	16 (12.0)	
- Metformin + Insulin + Sulfonylureas	92	76.6		83 (90.2)	9 (9.8)	

*Calculated as (the number of patients with five to seven scripts divided by the number of patients with two or more metformin prescriptions [Table 2])*100.
†Prescription adherence is deemed to have occurred where a prescription (primary care record) has a matched dispensing record in the pharmaceutical dataset. 100% adherence = five to seven prescriptions in the 18-month prescribing period (each for 90 days cover) and a matched number of dispensing events in the 21-month pharmaceutical dispensing data.

Importantly, our study did show that if metformin was prescribed, Māori were just as likely as others to have the medication dispensed. This is a positive finding, though it disagrees with the Statistics New Zealand Family, Income and Employment survey from 2010 that reported that Māori had greater odds than European NZers of not having medication dispensed because of cost.[30] The reasons for this study showing a different result are unknown, but could be because of the implementation of the Māori Health Strategy in recent years[31] or because Māori patients in this study were not from a socially deprived area and cost was not their primary concern. Alternatively, it is possible that our subset of patients is not representative of the larger regional population. In a large national review of 85,066 patients with type 2 diabetes who recently initiated metformin monotherapy, a mean MPR value of 0.81 for Waikato patients was reported.[22] This is lower than the overall mean MPR of 0.88 seen in our study. However, our study includes all patients and not only patients who have recently commenced metformin therapy. We also report that older patients (who are likely to have had type 2 diabetes for longer) have higher metformin

Figure 1. Proportion of metformin prescriptions that were associated with a pharmaceutical dispensing event during the 18-month study period. 'All' = every prescription was matched to a dispensing evening; 'n-1', 'n-2' and 'n-3' = all except one / two / three prescriptions were matched to a dispensing event.



adherence. Therefore, our data are likely to be similar to that used in previous reports.

Up to one-quarter of all patients did not have continuous cover of metformin during the study period. The reasons for this will vary, but may include reduced health literacy, lack of disease awareness and acceptance,[17,18] and gastrointestinal disturbances.[20] Where possible, these factors need to be addressed, particularly as our study corroborates other reports that higher HbA1c levels are associated with poorer glycaemic control.[32] In particular, general practitioners should take care to monitor prescription frequency for patients with less severe disease and younger patients, to minimise disease progression. Escalation or change of therapy should also be considered in patients with elevated HbA1c levels, particularly if metformin adherence is low because of adverse events.

Several diabetes medication adherence programmes have been tried with varying degrees of success.[33–35] Integrated approaches have been shown to be the most effective, though even low-cost solutions such as SMS reminders have been improved adherence rates.[33] Māori patients may not receive appropriate diabetes education as diabetes health literacy is lower in this group despite the same provision of resources.[36] Any diabetes intervention designed to improve adherence must be delivered in a culturally appropriate way. Further, diabetes education and intervention programmes must be age and gender appropriate. Younger patients and women, for example, have been shown to be more likely to respond to diabetes management that is associated with improvements in weight.[37] In contrast, older patients are often more concerned about diabetes complications.[38]

The main strength of our study was that we were able to evaluate both primary care prescribing data and pharmaceutical dispensing data to determine where disparity in the use of metformin in primary care occurs. This has not been reported on previously and offers advantages over studies using only dispensing data as a proxy for medication use. Our study also included HbA1c levels, which allowed us to directly compare the effect of metformin non-adherence on glycaemic control.

The primary limitation of our study was that an MPR of 0.8 was used as an indicator of good adherence, suggesting that patients are taking their medication at least 80% of the time. This may not

actually be the case as some studies do report that some patients choose to stockpile their medications or share them with additional family members.[39,40] Second, the assumption was made that prescriptions were all for 90 days, whereas this may not have always been the case. Third, matching of prescription to dispensing records was not an exact process, as patients who required an additional prescription because of legitimate reasons (i.e. because they lost it or if it was prescribed outside of our study practices) will appear to have less than 100% prescription adherence, and patients prescribed metformin elsewhere may have a data mismatch. Similarly, patients may also have had HbA1c tests that were not recorded in their primary care records; these would have been identified if we had also linked to laboratory data. These circumstances may skew the overall findings, although we believe that the rigour of our methodology should have reduced the incidence of these events. Finally, we suggest that it would be useful in future studies to include the number of visits that patients make in general practice to determine whether disparity in prescribing is due to differences in the number of health-care visits.

In conclusion, primary care data are invaluable for understanding medication adherence, demonstrating here that there appear to be differences in metformin use by Māori, likely as a result of them having fewer prescriptions.

Competing interests

The authors have no competing interests to declare.

Author contributions

LC, RL, RK and RP all contributed to the conception and design of the study, as well as interpretation of data. BM collected the data and CM and CL analysed it. LC, CM, RP and RL drafted the article for publication. All authors revised it for critically important intellectual content. All authors give their approval for publication.

Acknowledgement

We would like to thank the New Zealand Society for the Study of Diabetes for funding a summer studentship to Mr Mayo to undertake this study.

References

1. Atlantis E, Joshy G, Williams M, Simmons D. Diabetes among Māori and other ethnic groups in New Zealand. In: Diabetes Mellitus in Developing Countries and Underserved Communities. S. Dagogo-Jack, ed. Cham, Switzerland: Springer; 2017. p. 165–90.
2. Ministry of Health. Diabetes; Table 28: Indicators by gender, Māori and non-Māori. Wellington, Ministry of Health; 2018. [cited 2018 August 22]. Available from: https://www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/diabetes
3. Best Practice Advocacy Centre New Zealand. A rising tide of type 2 diabetes in younger people: what can primary care do? Dunedin: BPAC; 2019. [cited 2019 August]. Available from: https://bpac.org.nz/2018/diabetes.aspx
4. Fowler M. Microvascular and macrovascular complications of diabetes. Clin Diabetes. 2011;29(3):116–22. doi:10.2337/diaclin.29.3.116
5. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12:73–81.
6. Mulnier HE, Seaman HE, Raleigh VS, et al. Mortality in people with type 2 diabetes in the UK. Diabet Med. 2006;23(5):516–21. doi:10.1111/j.1464-5491.2006.01838.x
7. Khalil H. Diabetes microvascular complications—A clinical update. Diabetes Metab Syndr. 2017;11:S133–39. doi:10.1016/j.dsx.2016.12.022
8. Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. Diabetologia. 2008;51(9):1639–45. doi:10.1007/s00125-008-1076-y
9. New Zealand Guidelines Group. Guidance on the management of type 2 diabetes. Wellington: Ministry of Health; 2011. [cited 2019 January]. Available from: https://www.moh.govt.nz/notebook/nbbooks.nsf/0/60306295DECB0BC6CC257A4F000FC0CB/$file/NZGG-management-of-type-2-diabetes-web.pdf
10. Best Practice Advocacy Centre New Zealand. Managing patients with type 2 diabetes: from lifestyle to insulin. Best Pract J. 2015;72:32–42.
11. Best Practice Advocacy Centre New Zealand. HbA1c targets in people with type 2 diabetes - do they matter? Dunedin: BPAC; 2010. [cited 2020 Mar]. Available from: https://bpac.org.nz/BPJ/2010/August/docs/BPJ_30_hba1c_pages8-15.pdf
12. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab. 2012;14(9):810–20. doi:10.1111/j.1463-1326.2012.01606.x
13. Scheen AJ, Paquot N. Metformin revisited: a critical review of the benefit–risk balance in at-risk patients with type 2 diabetes. Diabetes Metab. 2013;39(3):179–90. doi:10.1016/j.diabet.2013.02.006
14. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016;164(11):740–51. doi:10.7326/M15-2650
15. Aikens JE, Piette JD. Longitudinal association between medication adherence and glycaemic control in type 2 diabetes. Diabet Med. 2013;30(3):338–44. doi:10.1111/dme.12046
16. Raum E, Krämer HU, Rüter G, et al. Medication non-adherence and poor glycaemic control in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2012;97(3):377–84. doi:10.1016/j.diabres.2012.05.026

17. Farahani Dastjani F, Shamsi M, Khorsandi M, et al. To study the factors affecting medication adherence in diabetic patients based on health belief model in Arak, 2014. J Arak Univ Med Sci. 2016;19(2):49–58.
18. Petrenchik L, Loh FE. Factors affecting noninsulin antidiabetic drug adherence in patients with type 2 diabetes. Diabetes. 2018;67(Suppl 1):. doi:10.2337/db18-806-P
19. Florez H, Luo J, Castillo-Florez S, et al. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. Postgrad Med. 2010;122(2):112–20. doi:10.3810/pgm.2010.03.2128
20. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes Obes Metab. 2017;19(4):473–81. doi:10.1111/dom.12854
21. Kharjul MD, Cameron C, Braund R. Using the Pharmaceutical Collection Database to identify patient adherence to oral hypoglycaemic medicines. J Prim Health Care. 2019;11(3):265–74. doi:10.1071/HC19017
22. Horsburgh S, Barson D, Zeng J, et al. Adherence to metformin monotherapy in people with type 2 diabetes mellitus in New Zealand. Diabetes Res Clin Pract. 2019;158:107902. doi:10.1016/j.diabres.2019.107902
23. Horsburgh S, Norris P. Ethnicity and access to prescription medicines. N Z Med J. 2013;126(1384):7–11.
24. Statistics New Zealand. Urban/Rural Profile Categories: North Island. Wellington: Statistics New Zealand, 2001. [cited 2018 May 16]. Available from: www.stats.govt.nz
25. New Zealand Pharmaceutical Schedule. Pharmac; 2018. Report No. 1. Wellington: Pharmac; 2018.
26. Karve S, Cleves MA, Helm M, et al. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25(9):2303–10. doi:10.1185/03007990903126833
27. Wong MC, Kong AP, So WY, et al. Adherence to oral hypoglycemic agents in 26 782 Chinese patients: a cohort study. J Clin Pharmacol. 2011;51(10):1474–82. doi:10.1177/0091270010382911
28. Reid J, Cormack D, Crowe M. The significance of socially-assigned ethnicity for self-identified Māori accessing and engaging with primary healthcare in New Zealand. Health. 2016;20(2):143–60. doi:10.1177/1363459315568918
29. Lee CH, Sibley CG. Demographic and psychological correlates of satisfaction with healthcare access in New Zealand. N Z Med J. 2017;130(1459):11–24.
30. Jatrana S, Crampton P, Norris P. Ethnic differences in access to prescription medication because of cost in New Zealand. J Epidemiol Community Health. 2011;65(5):454–60. doi:10.1136/jech.2009.099101
31. Ministry of Health. He Korowai Oranga. Wellington: Ministry of Health; 2019. [cited 2020 April]. Available from: https://www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga
32. Doggrell SA, Warot S. The association between the measurement of adherence to anti-diabetes medicine and the HbA1c. Int J Clin Pharm. 2014;36(3):488–97. doi:10.1007/s11096-014-9929-6
33. Zullig LL, Gellad WF, Moaddeb J, et al. Improving diabetes medication adherence: successful, scalable interventions. Patient Prefer Adher. 2015;9:139–49. doi:10.2147/PPA.S69651
34. Omran D, Guirguis LM, Simpson SH. Systematic review of pharmacist interventions to improve adherence to oral antidiabetic medications in people with type 2 diabetes. Can J Diabetes. 2012;36(5):292–9. doi:10.1016/j.jcjd.2012.07.002
35. Odegard PS, Carpinito G, Christensen DB. Medication adherence program: adherence challenges and interventions in type 2 diabetes. J Am Pharm Assoc. 2013;53(3):267–72. doi:10.1331/JAPhA.2013.12065
36. Lawrenson R, Joshy G, Eerens Y, Johnstone W. How do newly diagnosed patients with type 2 diabetes in the Waikato get their diabetes education? J Prim Health Care. 2010;2(4):303–10. doi:10.1071/HC10303
37. Mosnier-Pudar H, Hochberg G, Eschwege E, et al. How do patients with type 2 diabetes perceive their disease? Insights from the French DIABASIS survey. Diabete Metab. 2009;35(3):220–7. doi:10.1016/j.diabet.2009.02.001
38. Murray CM, Shah BR. Diabetes self-management education improves medication utilization and retinopathy screening in the elderly. Prim Care Diabetes. 2016;10(3):179–85. doi:10.1016/j.pcd.2015.10.007
39. Beyene KA, Sheridan J, Aspden T. Prescription medication sharing: a systematic review of the literature. Am J Public Health. 2014;104(4):e15–26. doi:10.2105/AJPH.2013.301823
40. Ellis J, Mullan J. Prescription medication borrowing and sharing: risk factors and management. Aust Fam Physician. 2009;38(10):816–19.