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THE NEW ZEALAND MEDICAL JOURNAL

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THE NEW ZEALAND MEDICAL JOURNAL
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SUMMARIES

This Issue in the Journal

The prevalence of low vitamin B12 status in people with type 2 diabetes receiving metformin therapy in New Zealand—a clinical audit

Sylvan Haeusler, Amber Parry-Strong, Jeremy D Krebs

The prevalence of low vitamin B12 in people with type 2 diabetes taking metformin is 18.7%. The likelihood of a low B12 increased with age and higher dose of metformin. It is recommended that people over 50 taking metformin should be screened for B12 levels.

Intensification of blood pressure treatment in Pasifika people with type 2 diabetes and renal disease: a cohort study in primary care

Jasmine Tan, Fifita McCready, Fiona Noovao, Oketi Tepueluelu, John Collins, Tim Cundy

This paper investigated the efficacy of blood pressure lowering conducted in primary care practice in Pasifika patients with type 2 diabetes and chronic kidney disease over 2 years. The integrated model of care involving a diabetologist, primary care physicians and nurses in an ethnic-concordant primary care setting was successful in improving patients' medication adherence and blood pressure. This translated to improved cardiac outcomes and slower decline in kidney function especially in those who have a reduction in the urinary protein excretion (which is a surrogate for kidney injury).

Observational study of the visibility of branded tobacco packaging and smoking at outdoor bars/ cafés in Wellington, New Zealand

Natasha Martin, Hugh McHugh, Jono Murtagh, Connor Oliver-Rose, Div Panesar, Harriet Pengelly, Scott Rieper, Henry Schofield, Vidit Singh, Amanda Speed, Rhona Strachan, Te Kahui Tapsell, Sara Trafford, Stefan van Ryn, Ethan Ward, Rosie Whiting, Merryn Wilson-van Duin, Zhou Wu, Gordon Purdie, Frederieke S van der Deen, George Thomson, Amber L Pearson, Nick Wilson

This study aimed to collect data on tobacco brand visibility on packaging on outdoor tables at bars/cafés prior to New Zealand's proposed plain packaging law. Observational data were systematically collected at 55 bars/cafés with outdoor tables (in Central Wellington City). A total of 19,189 patrons, 1707 tobacco packs and 1357 active smokers were observed. One tobacco pack was visible per 11.0 patrons and the active smoking prevalence was 7.1%, similar to Australian results (8.3%). Eighty percent of packs were positioned face-up (showing the brand), 8% face-down (showing the large pictorial warning), and 12% in other positions. Pack visibility per patron was significantly greater in areas without child patrons (RR=3.1, $p<0.0001$). In summary, tobacco branding on tobacco packaging was frequently visible because of the way smokers position their packs. These results highlight the residual problem posed by this form of marketing. The results also provide baseline data for the future evaluation of plain packaging if a proposed law is implemented in New Zealand.

Variation in gout care in Aotearoa New Zealand: a national analysis of quality markers

Gary Jackson, Nicola Dalbeth, Leanne Te Karu, Doone Winnard, Peter Gow, Catherine Gerard, Nikolai Minko

We used health data to determine that for New Zealanders aged 20–79 years with gout, 57% were dispensed allopurinol in 2010/11. Of these, 69% were receiving allopurinol regularly, and only 34% of people dispensed allopurinol had serum urate testing in a 6-month period. The annual

hospitalisation rate was 1% of people with gout. Māori and Pacific people with gout were less likely to be on regular allopurinol treatment, despite having more than twice the chance of being hospitalised with acute gout. We conclude that primary care initiatives that focus on ensuring a continuous supply of urate-lowering therapy to achieve therapeutic serum urate targets are required to improve the impact of gout in Aotearoa New Zealand.

A descriptive study of urethral discharge among men in Fiji

Lavenia Gaunavinaka, Dashika Balak, Sumanthla Varman, Sharan Ram, Stephen M Graham

An evaluation of the medical records of men presenting to clinics in Fiji with urethral discharge over recent years found that this form of sexually transmitted infection is very common. There were also cases of repeated infection. There was also no association between 'risky sexual behaviours' and recurrence and this may be due to the fact that the reported behaviours were totally dependent on the subjective view of the clients. We need to know more about the causes and risk behaviours for this disease in order to provide the most effective treatment, but also to educate the public in order to reduce the burden of sexually transmitted diseases in Fiji.

Barriers to early initiation of antenatal care in a multi-ethnic sample in South Auckland, New Zealand

Sarah Corbett, Carol Chelimo, Kara Okesene-Gafa

It is recommended that women commence maternity care before 10 weeks of pregnancy. This study looked into barriers to initiation of antenatal care before 19 weeks of pregnancy in over 800 women in South Auckland. Findings indicated that women were more likely to book late (after 18 weeks) for care if they had limited resources (e.g. no transport), no tertiary education, were not living with a partner, or were of Māori or Pacific ethnicity.

The importance of measuring unmet healthcare needs [viewpoint article]

Robin Gauld, Antony Raymont, Philip F Bagshaw, M Gary Nicholls, Christopher M Frampton

Objective assessment of the outcomes of health system restructuring is rare. In the absence of comprehensive objective data, the success or otherwise of health reforms has been inferred from narrowly-focussed data or anecdotal accounts. A recent example relates to a buoyant King's Fund report on the quest for integrated health and social care in Canterbury, New Zealand which prompted an equally supportive editorial article in the British Medical Journal (BMJ) suggesting it may contain lessons for England's National Health Service. At the same time, a report published in the New Zealand Medical Journal expressed concerns at the level of unmet healthcare needs in Canterbury. Neither report provided objective information about changes over time in the level of unmet healthcare needs in Canterbury. We propose that the performance of healthcare systems should be measured regularly, objectively and comprehensively through documentation of unmet healthcare needs as perceived by representative segments of the population at formal interview. Thereby the success or otherwise of organisational changes to a health system can be better documented.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-17-oct-2014/6340

Pathways to health and wellbeing for Pacific children—how are we tracking? [viewpoint article]

Fa'asisila Savila, Elaine Rush

The government's 5-year strategy for improving Pacific people's health and wellbeing, 'Ala Mo'ui Pathways to Pacific Health and Wellbeing 2010–2014, emphasised disease prevention and improvements in health systems as priority outcomes. Actions that would contribute to disease prevention included reducing barriers to health in structural mechanisms (such as better access to healthy housing) and improving health service systems. However, after 4 years since its release, not only have important structural barriers remained but so have the poor health outcomes of Pacific peoples in New Zealand.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-17-oct-2014/6325

EDITORIAL

A safe and effective drug?

Matthew P Doogue

A safe drug is an oxymoron. Any substance with pharmacological effects can cause harm and if a substance is harmless it has no effect. The potential harms of a medicine is one of two factors that limits medicine use, the other being cost. Knowing the potential harms (adverse effects) of a medicine and mitigating the risk of harm in individual patients is at the core of therapeutics.

In New Zealand there are about 1700 registered medicines, each medicine capable of causing several effects. The probability of each of those effects occurring is dependent on patient factors and drug exposure. Identifying circumstances of increased risk is codified in "contraindications" and "precautions". Of particular difficulty for prescribers is that those who are most likely to benefit from a drug are often also those at greatest risk of harm.

Of these 1700 medicines only a handful can be generally described as effective, safe and cheap, and one of these is metformin. Metformin is effective and stands alone as first-line pharmacotherapy for type 2 diabetes. Metformin is cheap with the New Zealand community pharmaceutical schedule price $1:23 for 100 500 mg tablets, about $20 a year per patient.[1]

Metformin is mostly safe with the most common harm of metformin being nausea and diarrhoea affecting up to one-third of patients. This can be monitored by symptoms and managed by dose titration in most patients. Discontinuation is required in 1–5% of patients.[2] The most feared harm of metformin, lactic acidosis, is very rare and can be avoided by avoiding metformin use in those at highest risk.[3] The third notable harm of metformin, less well known to prescribers is vitamin B12 deficiency.

In this issue of the *Journal*, Haeusler and colleagues report a 17% prevalence of B12 deficiency in a cross-sectional study of New Zealand patients.[4] While one could quibble about methodology (e.g. the lack of a comparator group) the primary finding is strong and important to clinical practice. It is strong because no matter the confounders this result is likely to be statistically and clinically significant. It is important because we can do something about it, vitamin B12 deficiency is easily diagnosed, easily treated and treatment improves outcomes.

That metformin causes malabsorption of vitamin B12 was demonstrated more than 40 years ago.[5] Authors at the time advocated annual laboratory measurement of vitamin B12 and this has been included in the product information continuously since the 1970s. Subsequent clinical studies have demonstrated megaloblastic anaemia associated with metformin can be easily diagnosed and treated with vitamin B12 without stopping metformin.[6]

Despite this, current international and regional guidelines for treating diabetes seldom comment on the risk of B12 deficiency and metformin, although they often mention checking for vitamin B12 deficiency in the differential diagnosis of peripheral neuropathy.[7–9] Most drug formularies, including the New Zealand Formulary, mention B12 deficiency as an adverse effect but provide no guidance for clinicians about risk mitigation, including testing.

What are the implications for prescribers in New Zealand? Firstly metformin-induced B12 deficiency is an adverse drug reaction with a high prevalence, 17% in this study and similar in many other studies. Secondly B12 deficiency is asymptomatic early on and when symptomatic one of the manifestations, peripheral neuropathy, is also a complication of the disease being treated. Hence, unlike gastrointestinal (GI) intolerance, it won't be detected by symptoms alone. Thirdly the neurological effects of vitamin B12 deficiency are permanent. Fourthly vitamin B12 deficiency can be detected readily by cheap widely available blood tests. Fifthly vitamin B12 is safe, cheap, effective and familiar to most GPs. All in all Haeusler and colleagues make a compelling case for screening.

However annual measurement of serum vitamin B12 concentration, as recommended in the data sheet, may not be justified as the onset of B12 deficiency is gradual and less frequent testing is likely to be effective. Further the threshold to define vitamin B12 deficiency is not universally agreed and measurement of vitamin B12 in serum is not the only test option, with serum homocysteine and/or methylmalonic acid being sensitive biomarkers of B12 deficiency. Measurement of a baseline serum vitamin B12 concentration and a full blood count around the time of initiation of metformin is pragmatic. In most cases other blood tests will also be indicated and the incremental cost of these tests is modest. How often to perform subsequent tests, in the absence of symptoms is not clear and further guidance is needed. In the absence of guidelines, rechecking serum vitamin B12 every 2–5 years in a patient treated with metformin seems reasonable.

The real cost of drug treatment is never just the price of the drug. Monitoring the effects (beneficial and harmful) and managing harms is necessary for all drug treatments. Several new drugs have come to market, notably the new oral anticoagulants, claiming minimal monitoring is required and claiming consequent savings for the health system.

The reality is that even the safest drugs require careful monitoring to mitigate patient harm. While harms from medications can never be completely avoided, we have a duty to reduce them where we can.

Competing interests: Nil.

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ORIGINAL ARTICLE

The prevalence of low vitamin B12 status in people with type 2 diabetes receiving metformin therapy in New Zealand—a clinical audit

Sylvan Haeusler, Amber Parry-Strong, Jeremy D Krebs

Abstract

Aim Metformin, the most common hypoglycaemic agent used in type 2 diabetes, is associated with reduced serum vitamin B12 concentrations. This cross sectional observational study determines the prevalence of low vitamin B12 status in people with type 2 diabetes on metformin therapy in both primary and secondary care in New Zealand.

Method All eligible patients seen in a secondary-care clinic over a 15-month timeframe were screened for low serum vitamin B12 concentrations. Additionally, patients from four primary health care providers were identified using metformin prescription data and offered the chance to participate in the audit.

Results Prevalence of serum Vitamin B12 level <220 pmol/L was 18.7%. Positive correlations were observed between B 12 concentration, age and dosage and duration of metformin treatment. Māori and Pacific Islanders had higher mean serum B12 concentrations than Europeans but no difference in prevalence of low serum B12 concentrations.

Conclusion Low serum B12 concentration is a common occurrence in people with type 2 Diabetes treated with Metformin. Age is an important factor which explains some of this association. Systematic screening in those receiving metformin is advisable, particularly for patients older than 50 years.

Metformin is the first-line medication for patients with type 2 diabetes.[1] Vitamin B12 (B12) is one of eight B group vitamins and plays an important role in haematopoiesis as well as key roles in brain and nerve function.

The association between metformin treatment and impaired serum B12 concentration was first reported in the 1970s.[2] The prevalence of metformin associated vitamin B12 deficiency has generally been estimated to be 10–20% of treated patients,[3,4] though the range is as low as 5% of treated patients[5] and levels higher than 30%.[6]

The mechanism for metformin-induced vitamin B12 deficiency remains unclear.[5] Current evidence supports an effect of metformin on calcium channels and resultant impairment of calcium-dependent membrane activity in the ileum leading to malabsorption of vitamin B12 bound to intrinsic factors.[7] A measurable reduction in serum vitamin B12 concentration can occur as quickly as 3–4 months after the initiation of the metformin therapy, while symptomatic deficiency may take as long as 5–10 years to manifest.[7] The clinical consequence of B12 deficiency is macrocytic anaemia, but changes in cognitive function have been observed in 28–52% of patients with low B12 but no evidence of anaemia.[8,9]

The prevalence of low serum B12 concentration in people using metformin in New Zealand is unknown. Furthermore, there are no data on rates of B12 deficiency in Maori or Pacific groups taking metformin, nor whether there are differences between those seen in a primary or secondary care environment.

The aim of this study was to estimate the prevalence of low serum B12 concentrations (<220 pmol/L) in those taking metformin and to compare this between ethnic groups and between primary and secondary care in New Zealand.

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Methods

This is a cross sectional observational study of serum vitamin B12 concentration in patients taking metformin for management of type 2 diabetes, in primary and secondary care settings in New Zealand.

All patients attending the diabetes outpatient clinics at Wellington Regional Hospital and Kenepuru Hospital between February 2013 and April 2014 were reviewed. Additionally, patients enrolled in four primary health providers were included.

Through the practice management system (Medtech) an initial screen was conducted on the patient database of each practice for: *Diagnosis of type 2 diabetes and prescription of metformin hydrochloride between February 2012 and February 2013*. This produced a list of patients with a diagnosis of Type 2 diabetes who had received a prescription for metformin within the last year. These individuals were posted an invitation to join the study which included an explanation about the observed association between metformin and vitamin B12. In both groups patients were included if they had a diagnosis of type 2 diabetes and treatment with metformin for a minimum duration of 12 months. Those on current B12 treatment were excluded.

Data collected included age, duration and current dose of metformin therapy (mg/day), vitamin B12 concentration. Ethnicity was coded using the New Zealand Ministry of Health ethnic identifiers. Participants were grouped into 3 categories based on clinical relevance of serum vitamin B12 concentration: Vitamin B12 deficiency (<150 pmol/L), lowered vitamin B12 (150–219 pmol/L), and normal vitamin B12 (≥220 pmol/L). Outcomes assessed were prevalence of serum vitamin B12 <220 pmol/L, and factors predicting B12 status. Comparisons between primary and secondary care and between patient ethnicities were conducted.

Data were analysed using SPSS v20.0 software. The primary outcome results are presented as arithmetic means. Assessment for significance between means was tested through application of t-test. Univariate analysis of variance (ANOVA) was used to assess between group interactions. Correlation was assessed using Pearson (for normal distribution, linear correlation) and Spearman (for non-normal, non-linear correlation) tests as specified. Continuous variables were log transformed wherever possible before running tests that require normal distribution of the data.

All tests were two-sided and p values of <0.05 were considered to be statistically significant. Logistic regression analysis was used for comparison of prevalence data due to the dichotomous property of the outcome variable. Stepwise forward multiple regression analysis was applied to identify variables that predict serum vitamin B12 concentration.

Ethics approval for the study was obtained from the Central Health and Disability Ethics Committee (reference: 12/CEN/65/AM02). The study was undertaken as a clinical audit and therefore did not require individual patient consent.

Results

Demographics

A total of 19,857 patients were reviewed from four primary health providers in the Wellington region and the Diabetes Outpatient Clinic at Wellington Regional Hospital (Figure 1).

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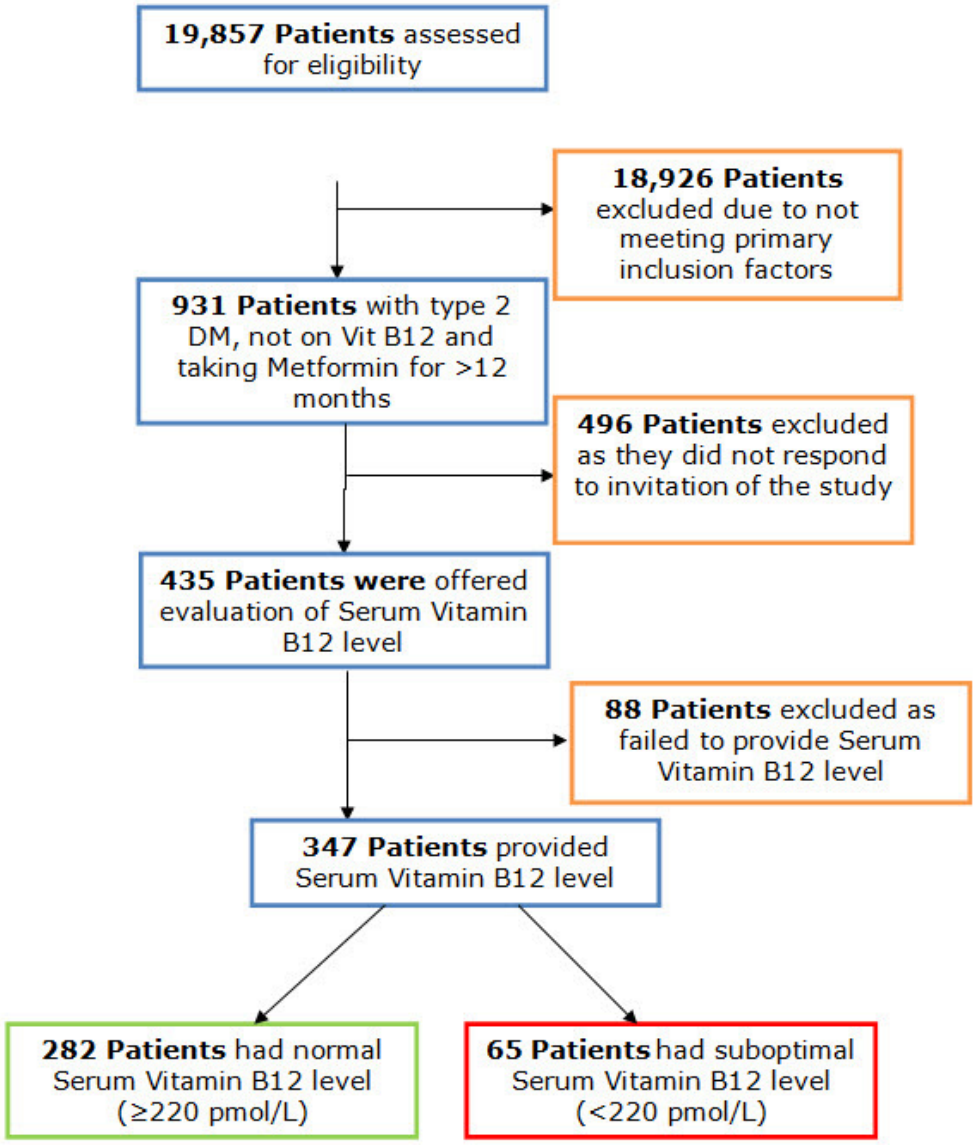
Figure 1. CONSORT diagram of audit to assess prevalence of lowered serum vitamin B12 level in primary and secondary health



The two study groups were similar in demographic composition but different in overall group size (Table 1). Patients screened from secondary healthcare were significantly younger than from primary health (p=0.008).

Both groups had a higher percentage of men than women. There were no differences in distribution of ethnicity between the groups.

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Table 1. Demographics of patient groups included in prevalence study. Mean (SD)

	Primary Health n = 101	Secondary Health n = 246	Total Group n = 347
Age (years)	63.76 (10.55)	60.56 (11.28)*	61.50 (11.16)
Men - n (%)	59 (58%)	125 (51%)	184 (53%)
Duration of metformin treatment (years)	7.65 (4.35)	7.60 (4.20)	7.61 (4.24)
Dosage of metformin (mg/day)	1848.51 (686.97)	2002.64 (775.69)	1957.78 (753.24)
Serum vitamin B12 (pmol/L)	348.98 (175.95)	363.83 (182.10)	359.51 (180.21)
Ethnicity:			
NZ European	46 (45.5%)	107 (43.5%)	153 (46.0%)
Other European	10 (9.9%)	23 (9.3%)	33 (9.5%)
NZ Maori	13 (12.9%)	27 (11.0%)	40 (11.5%)
Pacific Islander	10 (9.9%)	27 (11.0%)	37 (10.7%)
Indian	9 (8.9%)	29 (11.8%)	38 (11.0 %)
Other	13 (12.9%)	33 (13.4%)	46 (13.3%)

** $p<0.05$*

Vitamin B12 concentration

The distribution of serum vitamin B12 concentration was skewed towards the lower range, with the peak located slightly higher than the 220 pmol/L level of lowered vitamin B12 status. The prevalence of lowered B12 concentration (<220 pmol/L) was 18.7% (Table 2).

The median deficient (<150 pmol/L) B12 concentration was 122.5 pmol/L and the median low B12 (150–219 pmol/L) concentration was 183 pmol/L (Figure 2).

Table 2. Number and percentage of patients in each serum vitamin B12 level category

Vitamin B12 Level Status	Number of Patients n (% of group)		
	Primary Health n = 101	Secondary Health Care n = 246	Total Group n = 347
Deficient (<150 pmol/L)	6 (5.9%)	10 (4.1%)	16 (4.6%)
Lowered (150-219 pmol/L)	16 (15.8%)	33 (13.4%)	49 (14.1%)
Normal (≥220 pmol/L)	79 (78.2%)	203 (82.5%)	282 (81.3%)

Note: No significant differences in B12 status between groups

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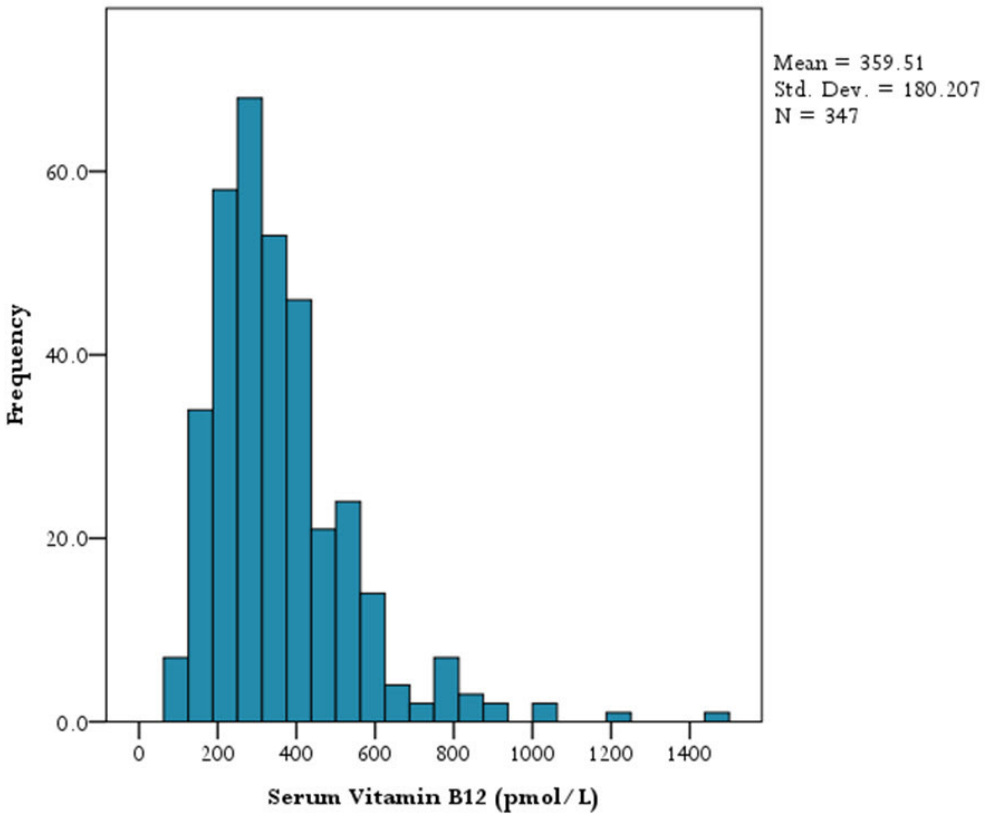
Table 3. Distribution of vitamin B12 values



Effect of metformin dosage and duration

Univariate regression of duration of metformin with B12 concentration shows significant regression (p=0.023).

As metformin dose is dependent on tablet strength, metformin dosages were assigned to six different categories dependant on the gram per day value. Serum vitamin B12 levels decreased progressively as metformin dose increased (ANOVA p=0.007) (Table 3).

Table 3. Effect of metformin dose on vitamin B12 level

Categorised metformin dosage (mg/day)	N (%)	Mean serum vitamin B12 (SD)	Prevalence of lowered level (<220 pmol/L)
<1000	15 (4.32)	446.33 (218.609)	7%
1000 - 1499	67 (19.31)	391.37 (187.287)	12%
1500 – 1999	40 (11.53)	394.88(181.467)	15%
2000 – 2499	129 (37.17)	349.70 (159.201)	19%
2500 – 2999	25 (7.20)	332.04 (165.279)	24%
≥3000	71 (20.46)	318.66 (195.930)	28%

Logistic regression shows significant effect of metformin dosage on prevalence of decreased serum Vitamin B12 level (<220 pmol/L) (p=0.004).

Effect of ethnicity

Vitamin B12 concentrations varied by ethnicity (ANOVA p<0.0005) (Table 4). However, the prevalence of low serum B12 (<220 pmol/L) is not significantly different across all ethnic groups (p=0.854).

Table 4. Ethnicity dependent presentation of mean values of data for study group

	Mean level (SD)			
Ethnicity	**Serum vitamin B12 (pmol/L)**	**Metformin dosage (mg/day)**	**Duration of metformin treatment (years)**	**Prevalence of low vitamin B12 (<220 pmol/L) (%)**
NZ European n = 153	318.51 (129.93)	1908.50 (774.25)	7.58 (4.36)	21%
Other European n = 33	330.94 (164.37)	1692.42 (644.46)	6.71 (3.88)	18%
NZ Maori n = 40	429.70 * (193.11)	2206.25 (768.05)	7.63 (4.46)	13%
Pacific Islander n = 37	472.65 * (188.33)	2022.97 (674.80)	6.84 (3.65)	8%
Indian n = 38	374.63 (279.51)	1988.16 (729.35)	7.77 (4.24)	24%
Other n = 46	351.83 (164.48)	2018.48 (778.77)	8.85 (4.19)	19%

*= p < 0.0005 for comparison with NZ European

Effect of age

Vitamin B12 concentrations reduced with age (ANOVA p=0.044) when patients were allocated into the following age groups: <50, 51–69, >70. Older age (uncategorised) predicted lowered serum Vitamin B12 status (<220 pmol/L) (logistic regression, p=0.011).

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Table 5. Mean serum vitamin B12 (pmol/L) and prevalence of low serum vitamin B12 concentration dependent on age group categorisation

Age range (years)	Number of individuals (% of study group)	Mean serum vitamin B12 level (<220 pmol/L) (SD)	Prevalence (%) of low serum vitamin B12 level (<220 pmol/L) within age group
<50	54 (15.6%)	394.96 (151.22)	5.6 %
51-70	210 (60.5%)	358.91 (192.00)	20.0 %
>70	83 (23.9%)	337.95 (164.29)	24.1 %*

** $p<0.05$*

Age was correlated with both dosage of metformin (mg/day) (Pearson correlation coefficient of -15.75, p<0.0005) and with duration of metformin treatment (years) (Pearson correlation coefficient of 0.259, p<0.0005). After adjustment for age, the effect of dosage remained significant (p<0.001) but the effect of duration of metformin on serum vitamin B12 was no longer significant (p=0.102).

Discussion

The New Zealand Ministry of Health Primary Care Handbook 2012 recommends metformin as the first line therapy for glycaemic control in type 2 diabetes once lifestyle modifications have been deemed ineffective.[10] Although there are recommendations for the annual screening of serum B12 concentration in patients with type 2 diabetes on long-term metformin treatment; it was observed that this is not a common practice in primary health.

Only one of the four medical centres approached for recruitment had a regular serum B12 screening program for patients with type 2 diabetes who are taking metformin. In this study we recruited subjects from primary and secondary care. Subjects from secondary care may be considered to be more at risk due to a greater complexity of issues and co-morbidities. However this was demonstrated not to be the case.

The overall level of prevalence of reduced serum B12 concentration (<220 pmol/L) in patients with type 2 diabetes receiving metformin therapy in this study was 18.7% which is similar to results from other studies reporting between 5 and 36.8%.[5,6,11] At the lower end of this range, in a North American group, Reinstatler et al reported a vitamin B12 deficiency in only 5.8% of patients with type 2 diabetes taking metformin compared to 2.4% of patients with type 2 diabetes not taking metformin.[5] This is in contrast to a study in a Brazilian group by Nervo and colleagues. The threshold for deficiency in this study was higher (250 pmol/L vs 220 pmol/L) which may partially explain the high prevalence of decreased serum B12 of 36.8%.[6] Differences between the two studies are also seen in the subsequent effect of vitamin supplementation. While supplementation with vitamin B12 in the American group did not result in a significant alteration to prevalence, in the Brazilian group an increase in Vitamin B12 intake was positively correlated to serum Vitamin B12 status. This suggests that impairment is linked closely to dietary malnutrition of Vitamin B12.

This study did not have a dietary intake component, however we can use Ministry of Health data to inform the discussion. The median daily dietary intake of B12 in New Zealand in the last National Nutrition Survey was 4.7 mcg for men and 3.3 mcg for women.[12] The daily intake of participants in the Brazilian study was 2.25 mcg, less than the recommended daily intake of 2.4 mcg.[6] While the American study does not include vitamin B12 intakes, it does note that 40% of people with diabetes were taking a supplement containing B12.[5] While this data is not available for New Zealand,

supplement rates here in the general population vary between 2 and 11%, with people in the 31–50 year group reporting the highest supplement use.[12]

The 2003–2006 American National Health and Nutrition Examination Survey (NHANES), reports the mean population serum Vitamin B12 level was 370 pmol/L compared with 355 pmol/L in the present study.[13] Again this may reflect greater use of vitamin supplements in the US.

There are few data on Vitamin B12 status in the general population of New Zealand. Levels in non-vegetarian Seventh Day Adventists were reported to be 245 pmol/L, with an average age of 40.[14] In an older group (age >65 years) 35.5% were observed to have a lowered serum Vitamin B12 concentration (<221 pmol/L).[15] This compares with a rate of 24.1% in patients >70 years in the current study, reflecting again the influence of age alone on B12 status.

One of the unique aspects to this study is the consideration of ethnic differences in the New Zealand population, a factor that has not yet been explored in previous literature. Higher mean serum Vitamin B12 concentrations were seen in NZ Maori and Samoan groups compared to the other groups.

Dietary or genetic determinants may explain this observation.[16] Data from the 2008/2009 New Zealand Adult Nutrition Survey showed that levels of Vitamin B12 consumption from red meat and seafood are higher in the Maori group than in the NZ European group.[12]

A limitation of this study is the lack of a true New Zealand population denominator for prevalence of low vitamin B12 concentrations. Nor were we able to compare our results with those of a group with type 2 diabetes but not taking metformin. Despite this, it is clear that the prevalence of reduced B12 status in those with type 2 diabetes who are taking metformin is high and increases with age.

As this is a cross-sectional study and we do not have B12 concentrations prior to commencement of metformin, it cannot be concluded that metformin is causative of low B12 concentrations. Furthermore, the clinical implications of this are less clear, and whether supplementation of these individuals would be of benefit requires an intervention study.

While it is difficult to diagnose B12 deficiency based on physiological symptoms, further data on cell volume and presence of anaemia would also be useful. This would help to inform whether universal screening of those taking metformin is appropriate. Given the low rate of reduced B12 levels in those less than 50 years, it may be argued that screening could be safely restricted to those older than this.

Competing interests: Nil.

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ORIGINAL ARTICLE

Intensification of blood pressure treatment in Pasifika people with type 2 diabetes and renal disease: a cohort study in primary care

Jasmine Tan, Fifita McCready, Fiona Noovao, Oketi Tepueluelu, John Collins, Tim Cundy

Abstract

Background Chronic kidney disease is common in Pasifika people with type 2 diabetes. Lowering blood pressure (BP) and reducing proteinuria may slow the rate of progression of renal disease.

Method We conducted a 2-year study in patients with type 2 diabetes with estimated glomerular filtration rate (eGFR) ≥40ml/mmin/1.73m^2 and urinary albumin-creatinine ratio (ACR) ≥40 mg/mmol to evaluate a community-based programme aimed at optimising BP. Primary outcomes included BP reduction, remission of albuminuria and change in eGFR.

Results Thirty-nine of 47 patients completed ≥17 months of intervention. The mean age was 53±8 years; 77% were male. An increase in antihypertensive therapy intensity was accompanied by a median (IQR) reduction in BP of 13[-1.5–22.5)/ 12(1–19) mmHg p<0.05] and urinary ACR (51(20-97) vs. 126(65-194) mg/mmol, p<0.05). Twelve (28%) of 43 patients achieving remission of albuminuria had a faster eGFR loss in the first year compared to the non-remitting group [13.6(4.0–16.6) vs. 3.5(-0.97–7.5) ml/min/1.73m^2/year, (p=0.02), but the rate of loss slowed in the second year. Two patients reached ESRF.

Conclusion This community-based programme was effective in lowering BP and urinary ACR. In patients who achieved remission of albuminuria, a slower eGFR decline was observed after 12 months.

Diabetes kidney disease (DKD) defined as the presence of albuminuria and/or chronic renal disease in patients with diabetes,[1] is the most important cause of end-stage renal failure (ESRF) in developed countries. About half the patients starting dialysis in New Zealand suffer from type 2 diabetes and DKD.[2]

Established risk factors such as obesity,[3] smoking,[4] hyperglycaemia[5,6] and hypertension,[7,8] are important targets in slowing the progression of DKD. Attaining remission of albuminuria is also an important treatment goal: remission of albuminuria (variously defined) is associated with a substantial reduction in morbidity and mortality.[9–11] However, achieving this is challenging, with only about 25% of type 2 diabetic patients with proteinuric renal disease attaining and maintaining remission.[10,11]

Specific combinations of antihypertensive treatment (with blockade of the renin-angiotensin system being first-line therapy) have been shown to be more effective than others in reducing albuminuria, slowing the progression of diabetic nephropathy and reducing cardiovascular events and death.[8,12,13] However, it is often difficult to reduce blood pressure (BP) down to target levels particularly in patients with diabetes, raising the question as to whether more intensive antihypertensive therapy might be more effective in inducing remission of albuminuria and preserving renal function.

The incidence of end-stage renal failure (ESRF) is the greatest in Māori and Pasifika people.[14] This is largely attributed to a higher prevalence of obesity, earlier onset of type 2 diabetes, poorer glycaemic control, higher levels of albuminuria, and smoking.[15,16] Cultural and language differences and socioeconomic disadvantage are also significant barriers to accessing health care.

The DEFEND study was a randomised-controlled trial which studied the effectiveness of 12-month community-based intervention in achieving BP target <130/80 mmHg in Māori and Pasifika patients with type 2 diabetes and DKD. It demonstrated that a community-based intervention of regular BP

monitoring and titration of antihypertensive agents using ethnic-concordant health care assistants and supervised by nurses, was more effective than routine primary care in lowering systolic BP after 1 year, with the prospect of improved cardio-renal outcomes.[17] These results were likely a result of improved patient adherence.

Community-based interventions through primary care play a crucial role in modifying risk factors at a population level, and at managing chronic diseases. For example, Russell et al[18] demonstrated that integrated medical care with a specialist and general practitioner (GP) in a primary care setting was successful in achieving improvements in BP, glycaemic and lipid profile in patients with complex type 2 diabetes. Such models of care highlight that a systematic and well-supported practice in primary care may be effective and efficient in complex chronic disease management. Furthermore, primary care is well-positioned to overcome barriers to health care through easier accessibility, providing a supportive, culturally-appropriate environment and continuity of care.[19]

We undertook our study at the Langimalie Tongan Health Centre. This primary care practice serves a large proportion of the Tongan community living in Auckland and is well-connected to the community through its Tongan-speaking staff. Our intervention utilised an integrated model of care involving a primary care physician and nurses and a diabetologist to provide intensive BP management in this high-risk group.

We evaluated the effectiveness of this intervention, delivered through a community-based team, on the remission of albuminuria and on DKD progression.

Methods and study design

We conducted a 2-year prospective uncontrolled cohort study of 47 Pasifika patients who had type 2 diabetes and DKD as defined by the presence of substantial albuminuria. The intervention followed an algorithm which directed a stepwise escalation of antihypertensive therapies to achieve and maintain BP ≤125/80 mmHg.

The first-line therapy included an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) if intolerant. The second-line therapy was the addition of a thiazide; third-line, a calcium-channel blocker and, if necessary, fourth to sixth-line agents were added: loop diuretic, beta-blocker, alpha-blocker or aldosterone-receptor antagonist. The choice of the latter agents was individualised according to cardiac and fluid status, residual renal function and serum potassium.

Antihypertensive treatment was adjusted based on 2–6 weekly office BP readings and regular laboratory results and was predominantly directed by nurses following consultation with the study doctors. Doses of individual drugs were titrated up to maximal recommended doses, unless there was intolerance or side effects. We devised a cumulative scoring system based on the number of different agents and prescribed doses to measure the intensity of therapy (Table 1).

The nurses at the Langimalie Tongan Health Centre leading the programme particularly focused on improving medication adherence. This included a close working relationship with the local pharmacy to provide patients with updated and free medication blister packs. Home visits were made to those unable to visit the clinic (usually because of work commitments) to measure BP, deliver prescriptions and monitor adherence by reviewing medication blister packs.

Lifestyle, dietary and self-care education were provided for all study patients. Patients who had a more complex medical history or required closer medical attention were reviewed regularly at the health centre by the diabetologist or GP, in addition to nurses' home visits.

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Table 1. Antihypertensive scoring based on class and dosage of antihypertensive agents

Score	ACEi		ARB	Thiazide	Loop diuretic	Aldoseterone receptor antagonist	Calcium channel blocker		Beta-blocker	Alpha-blocker	Alpha & beta-blocker
	Cilazapril	Quinapril	Losartan	HCT	Frusemide	Spironolactone	Felodipine/ Amlodipine	Isradipine	Metoprolol	Doxazsoin	Carvedilol
0	0mg	0mg	0mg	0mg	0mg	0mg	0mg	0mg	0mg	0mg	0mg
1	≤2.5mg	≤10mg	≤25mg	12.5mg	≤20mg	≤12.5mg	≤5mg	≤2.5mg	≤23.75mg	1mg	≤12.5mg
2	5mg	20mg	50mg	25mg	40mg	25mg	10mg	5mg	47.5mg	2mg	25mg
3	≥10mg	40mg	≥100mg		≥60mg	≥50mg	≥20mg	≥10mg	≥95mg	≥4mg	≥50mg

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockade, HCT: Hydrochlorothiazide

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Data source and patients—Patients were included in this study if they were 18 to 65 years of age, had a history of type 2 diabetes, a urinary albumin/creatinine ratio (ACR) ≥40 mg/mmol from 2 of 3 consecutive sterile casual urine specimens (normal range 0 – 3.5 mg/mmol), an estimated glomerular filtration rate (eGFR) ≥40 ml/min/1.73m^2, and who had a life expectancy of at least 2 years. Patients were recruited after they were flagged at the Centre's triage who fulfilled the study inclusion criteria. Patients were recruited between October and November 2011. The study was fully explained in Tongan language and informed consent received from all participants.

We recorded patient demographics and clinical data including the duration of type 2 diabetes, hypertension and albuminuria, retinopathy and smoking status, and comorbidities. The severity of retinopathy was collected from the national retinal screening database which have been graded by a trained operator as none, minimal, mild/moderate or severe. Patients were reviewed at the clinics 2–6 weekly for optimisation of BP to a target of ≤125/80 mmHg with titration of antihypertensive medications. Seated systolic and diastolic BP measurements, urinary ACR, serum creatinine, weight, and details of prescribed antihypertensive therapies were documented 4-6 weekly and glycated haemoglobin (HbA_{1c}), 3-monthly. We reported the mean of repeated BP measurements taken over 3 months at baseline, and 4 – 6 weekly nurse-facilitated measurements over the study period. The study was completed in November 2013.

Outcome measures—The main outcome measures were change in BP, eGFR and remission of urinary ACR at the end of the 2-year intervention. Remission of ACR was defined as ≥70% reduction from the peak ACR in the 6 months before the study that was sustained till the end of follow up.[11] Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) equation;[20] and annualised eGFR loss was calculated.

Secondary outcomes included change in HbA1c, non-fatal cardiovascular (acute myocardial infarction (AMI) or congestive heart failure (CHF)), cerebrovascular (ischemic stroke or transient ischemic attack), peripheral vascular (foot ulcers or amputation) events, ESRF (eGFR ≤10 ml/min/1.73m^2 or dialysis) and death.

We explored the relationship between baseline characteristics and eGFR decline. Intergroup comparison of baseline characteristics between patients who achieved remission of albuminuria, and those who did not, was performed to identify variables associated with remission of albuminuria.

Statistical analysis—Statistical analysis was performed using STATA software (version 13.1). Results are expressed as mean±SD unless otherwise stated and were compared using Student's t-test or ANOVA. Median values were compared using Mann-Whitney test or Wilcoxon matched-pairs signed rank test. Proportions were compared using χ^2-test (Chi-squared test). Regression analyses was performed for baseline variables and both eGFR decline, and remission of albuminuria. $P<0.05$ was considered significant. All tests were two-tailed.

Results

Forty-seven patients were enrolled into the programme: 45 were Tongan, one Niuean and one Cook Islander. Of these 47 patients, four withdrew from (2 opted out before commencement, 1 transferred to different GP and 1 moved overseas). The baseline characteristics of the remaining 43 patients is recorded in Table 2.

At the commencement, 30% of patients had no evidence of diabetic retinopathy, in spite of the presence of macroalbuminuria. The median (IQR) eGFR was 68 (50 – 81) ml/min/1.73m^2, including 4 patients with eGFR ≤40ml/min/1.73m^2. All 43 patients were already on ACEi or ARB treatment.

Six patients (14%) had a previous history of vascular events: 2 had both an AMI and CHF as separate events, the other 4 had previous single events—1 AMI, 1 CHF and 2 amputations due to peripheral vascular disease (Table 2).

Patients were followed for up to 2 years. Two patients were referred to Renal Services for worsening renal impairment at 4 months and 18 months, respectively. Thirty-nine patients had 17 – 24 months of intervention. The mean±SD duration of follow-up was 21±5 months.

Table 2. Baseline characteristics of 43 patients

Baseline characteristics	
Male, n (%)	33 (77)
Age (years)	53±8
Residence in New Zealand (years)	23±11
Smoking status, n (%)	
None	13 (30)
Previous	21 (49)
Current	9 (21)
Retinopathy status, n (%)	
None	12 (30)
Minimal	7 (17.5)
Mild/moderate	12 (30)
Severe	9 (22.5)
Duration of type 2 diabetes (years)*	8 (4–12.5)
Patients on insulin, n (%)	20 (47)
Duration of macroalbuminuria (years)*	3 (2–6)
Duration of hypertension*	6 (2–9)
Median eGFR (MDRD equation)* (ml/min/1.72m^2)	68 (50 – 81)
Previous events, n (%)	
Cardiovascular/CHF	4 (9%)
Cerebrovascular events	0 (0%)
Peripheral vascular disease	2 (5%)

*median (IQR).

Primary outcomes—At the final follow up, the antihypertensive score was higher than baseline ($p<0.05$) and mean systolic and diastolic BP were significantly lower. The mean number of classes of antihypertensive agents used at baseline and at 21 months were 2.7±1.1 and 3.5± 0.9 ($p<0.05$) respectively. The proportion of patients achieving the BP target of ≤125/85 mmHg had doubled by the two years. Mean HbA_{1c} values were also significantly lower.

Median (IQR) urinary ACR was significantly reduced at final follow up compared to that at baseline (51 (20–97) vs. 126 (65–194), p=0.003) and a higher proportion of patients achieved remission of urinary ACR to ≤30mg/mmol as the study progressed (19% at 6 months, 25% at 12 months and 33% at end). The number of patients with urinary ACR ≥100mg/mmol was halved (56% at 0 months vs 26% at 21 months, p=0.001) (Table 3).

The median (IQR) eGFR at baseline was 68 ml/min/1.73m^2. At 12 months and at study end it was significantly lower at 59 and 57 ml/min/1.73m^2, respectively ($p<0.05$) (Figure 1). The median (IQR) eGFR loss was 4.6 (0.4–13.6) ml/min/1.73m^2 over the first year and 6.7 (-2.4–12.6) ml/min/1.73m^2 over the second year (p=NS). At baseline there were four patients with eGFR ≤40ml/min/1.73m^2, and at the end there were eight ($p<0.05$).

Secondary outcomes—Four cardiovascular events occurred (1 AMI and 3 episodes of CHF) during the 2 years of follow up. Two patients reached ESRF – one was referred to the renal service 4 months into the study and was established on dialysis 14 months later. The other patient was referred to the renal service at 18 months and reached eGFR <10ml/min/1.73m^2 3 months later: both patients had low renal reserve at baseline with eGFR of 29 and 37 ml/min/1.73m^2, respectively. There were no reported deaths. The change in eGFR was not related to baseline urinary ACR or eGFR, or duration of diabetes.

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Table 3. Blood pressure and renal outcomes during the 2-year follow up

Variables	Baseline N=43	6months N=43	12 months N=39	End N=39
HbA_{1c} (mmol/mol)	81±24	77±33	75±37[b]	71±20[c]
BMI (kg/m^2)	37.6±5.9	38.3±16.5	37.8±11.3	38.4±13.4
SBP (mmHg)	137±17	133±31	129±25[b]	126±16[c]
DBP (mmHg)	84±13	80±20[a]	76±17[b]	74±13[c]
Patients with BP ≤ 125/80 mmHg; n (%)	11 (26%)	9 (22%)	15 (39%)	22[c] (56%)
Antihypertensive score*	5 (3–7)	6 (4–9)[a]	7 (5–11)[b]	9 (6–11)[c,d]
ACR (mg/mmol)*	126 (65–194)	85 (33–154)[a]	67 (29–114)[b]	51 (20–97)[c]
Serum creatinine (µmol/L)*	104 (82–135)	107 (82–135)	116[b] (81–142)	118[c,d] (91–155)
Estimated GFR† (ml/min/1.73m^2)	68 (50–81)	65 (51–82)	59 [b] (46–78)	57 [c,d] (42–73)
ACR, n (%)‡				
<3 mg/mmol	0	0	0	2 (5)
3–30 mg/mmol	0	7 (19)	8 (25)	11 (28)
31–50 mg/mmol	3 (7)	5 (14)	5 (16)	6 (15)
51–100 mg/mmol	16 (37)	11 (30)	10 (31)	10 (26)
>100mg/mmol	24 (56)	14 (38)	9 (28)	10 (26)

ACR: Albumin creatinine ratio; BMI: body mass index; HbA_{1c}: glycated haemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure

Mean±SD except *median (IQR)

† eGFR calculated using MDRD equation[20]

‡ At 6 months and 12 months, there were 37 and 32 available urinary ACR measurements

[a] p<0.05 comparing baseline and 6 months; [b] p< 0.05 comparing baseline and 12 months

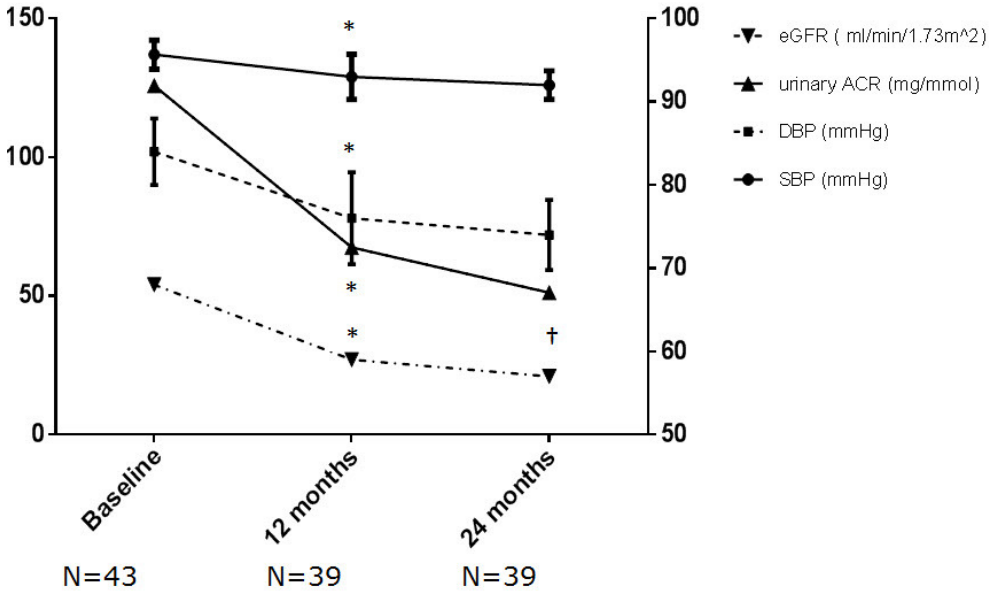
[c] p< 0.05 comparing baseline and 24 months; [d] p< 0.05 comparing 12 months and 24 months

Remission of albuminuria—Twelve (28%) of 43 patients achieved and sustained remission of urine ACR, to a median (IQR) 10.2 (6.1–18.4). Remission was not related to duration of type 2 diabetes, duration or level of albuminuria, HbA1c, eGFR or BP at baseline, or a higher antihypertensive score.

In the first year, eGFR fell more rapidly in the group that achieved remission of albuminuria compared to the group which did not (13.6 (4.0–16.6) vs. 3.5 (-0.97–7.5) ml/min/1.73m^2/year, p=0.02), but in the second year it was significantly slower than in the first (p=0.03). The rate of decline of eGFR in the second year was slower in those achieving remission compared to the non-remitting group (1.7(-2.0–9.7) vs. 8.2(-0.55–14.5) ml/min/1.73m^2/year, p=0.21).

Adverse events—Mild hyponatraemia (serum sodium 130–135 mmol/L), was the most common electrolyte abnormality and affected 12(28%) patients in this study. Severe hyponatraemia (<130 mmol/l) occurred in 2 patients during a period of hospitalisation for concurrent illnesses, which resolved on cessation of diuretics. Mild hypokalaemia was observed in one patient.

Figure 1. Change of systolic and diastolic BP, urinary ACR and eGFR‡



ACR: albumin creatinine ratio; eGFR: estimated glomerular filtration rate; DBP: diastolic blood pressure; SBP: systolic blood pressure; *p<0.05 comparing baseline and 12 months; †p<0.05 comparing 12 and 24 months; ‡ eGFR calculated using MDRD equation[20]

Discussion

In this 2-year prospective cohort study of Pasifika patients with type 2 diabetes and macroalbuminuria, we found that a significant reduction of BP to clinical targets can be achieved through intensification of antihypertensive treatment and promotion of medication adherence in a primary care setting. Although the main management focus was BP reduction, the success of this intervention also extended to reduction in albuminuria and improved HbA_{1c}.

A multi-risk approach targeting BP, glycaemia, dyslipidaemia and weight reduction plays an important role in survival outcomes in patients with type 2 diabetes with metabolic syndrome – with adequate BP lowering BP having the major effect.[21] Blood pressure optimisation delays the progression of cardiovascular and renal diseases,[22] and reduces albuminuria which is an independent factor of premature death.[8]

While it has been debated as to the lowest threshold for BP targets, the general consensus is that a goal <130/80 mmHg should be aimed in patients with DKD without concomitant cardiovascular disease.[23] In a subgroup of patients with overt albuminuria and renal insufficiency however, renal benefits have been observed with lower BP.[24,25] Our BP goal was lower compared to most interventional studies as our cohort comprised of a population with heavy albuminuria and minimal cardiac history. The mean systolic and diastolic BP at the end of this study was lower than that observed in similar studies,[17,18] with more than half of the group attaining the pre-determined BP goal of <125/80 mmHg by 1 year and sustained to the study's end.

These results highlight the importance of patient and provider-specific factors in effective health care delivery. The recognition of these variations allow for meaningful patient-centred management and improved outcomes.[19] Langimalie Tongan Health Centre operates with culturally-appropriate staff who understand the unique cultural and economic barriers and can address these with patient education through community events, home visits and co-operation with local pharmacy to ensure medication adherence. An integrated community-based care involving a specialist, primary care

physician and nurses, and the patient in complex diabetes care has previously demonstrated clinical and process benefits beyond that of tertiary diabetes outpatient care.[18]

Six new events occurred—two cases of ESRF and four cardiovascular events. The two patients who reached ESRF had low eGFR at recruitment and neither had remission of albuminuria. During the follow-up period, 10% of study patients had non-fatal cardiovascular events. This proportion is lower than that reported in larger studies such as the RENAAL (33%) and IDNT (24%) trials which had similar duration of follow up.[8,26] However, the observation period was too short and not sufficiently powered to determine outcome benefit.

In spite of the widespread use of RAS inhibitors, only a third of our patients achieved remission of albuminuria, suggesting that current therapies for DKD may not be adequate. The absence of retinal disease in 30% of patients in this cohort emphasises that non-diabetic kidney disease is prevalent in patients with type 2 diabetes in whom obesity and metabolic syndrome are common.[27] Furthermore familial clustering of nephropathy occurs in Pasifika people regardless of the presence of diabetes.[28]

Overall, the intensification of antihypertensive management did not appear to compromise renal function. The rate of eGFR decline in this cohort was comparable to the trend seen in recent studies with ranges from 4 to 6.5 ml/min/1.73m^2/year.[29] In the group of patients who achieved remission of albuminuria the rate of eGFR decline in the first year was more rapid, but it plateaued and was significantly slower in the second year. This finding is consistent with the notion that aggressive antihypertensive treatment reduces renal function primarily through early haemodynamic effects. A slower progression to ESRF has been reported in diabetic patients who had greater initial GFR decline,[30] hence such an intervention is more likely to benefit patients with higher renal reserve at baseline.

Our findings have limitations. First, the study was small, and a number of our outcomes were surrogates. However, studies in Pacific Island patients are scarce, and collection of medical data is challenging due to infrequent presentations and the lack of continuity of care. The nurse-led programme succeeded in achieving regular follow up for ≥ 22 months in 70% of our patients. There are 849 type 2 diabetic patients (aged 18 to 65) registered at the Langimalie Tongan Health Centre. Our study population of 47 patients indicates a minimal prevalence of macroalbuminuric DKD of 5.5%, similar to the prevalence observed in other population-based studies.[1]

Secondly, eGFR was calculated using the four-variable MDRD study formula which has limitations, particularly in overweight subjects. This was chosen over the Cockcroft-Gault equation as this has been shown to be superior in estimating eGFR in patients with diabetes and chronic kidney disease.[31] Thirdly, BP measurements in this study were based on both clinic and home readings instead of the gold-standard 24-hour automated BP monitoring. The trend in BP however, corresponded closely with the change in antihypertensive score.

Attaining BP targets in clinical practice has often been difficult, with a greater rate of failure in patients with diabetes,[19] notwithstanding the challenges of other clinical and patient factors. This study has shown that a systematic approach of monitored intensification of antihypertensive therapy coupled with promotion of medication adherence, provides a model of care which can be effectively and safely applied in primary care. It also provides a framework for specialist support and up-skilling of primary care practitioners in the management of complex chronic diseases. A longer term follow up is necessary to accurately assess the sustainability, effectiveness and safety of such an intervention on slowing the progression of DKD with specific attention to important clinical outcomes.

Competing interests: Nil.

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ORIGINAL ARTICLE

Observational study of the visibility of branded tobacco packaging and smoking at outdoor bars/cafés in Wellington, New Zealand

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Abstract

Aim To collect data on tobacco brand visibility on packaging on outdoor tables at bars/cafés in a downtown area, prior to a proposed plain packaging law.

Method The study was conducted in the Central Business District of Wellington City in March 2014. Observational data were systematically collected on tobacco packaging visibility and smoking by patrons at 55 bars/cafés with outdoor tables.

Results A total of 19,189 patrons, 1707 tobacco packs and 1357 active smokers were observed. One tobacco pack was visible per 11.0 patrons and the active smoking prevalence was 7.1% (95%CI: 4.9–9.2%), similar to Australian results (8.3%). Eighty percent of packs were positioned face-up (showing the brand), 8% face-down (showing the large pictorial warning), and 12% in other positions. Pack visibility per patron was significantly greater in areas without child patrons (RR=3.1, p<0.0001). Both smoking and pack visibility tended to increase from noon into the evenings on weekends. Inter-observer reliability for key measures in this study was high (Bland-Altman plots).

Conclusion Tobacco branding on packaging was frequently visible because of the way smokers position their packs. These results highlight the residual problem posed by this form of marketing. The results also provide baseline data for the future evaluation of plain packaging if a proposed law is implemented in New Zealand. Other results warrant further research, particularly the reasons for lower pack visibility and smoking when children were present.

There is strong evidence that indicates that tobacco marketing plays a role in maintaining and increasing tobacco smoking.[1] Advertising can prompt smokers, including those intending to quit, to engage in smoking and purchase tobacco products.[2] As such, the regulation of tobacco marketing has been a worthwhile focus in health interventions.[1,3]

With the growing use of tobacco advertising bans in many countries, tobacco packaging has become an important avenue of product promotion for tobacco companies. Indeed, tobacco packaging "assists consumers to select among other relatively homogenous products".[4] Corporate branding is a well-established marketing tool for generating customer loyalty, particularly for tobacco products; "cigarette brands enjoy the highest brand loyalty of all consumer products, with less than 10% changing brands annually".[4]

Legislated changes to the design of tobacco packaging have been associated with changes in quitting behaviours in several countries. For example, the introduction of pictorial health warnings on packages in New Zealand was associated with increased recognition of the national Quitline number amongst all sociodemographic groups, an increase in new callers, and an increase in the proportion of new callers obtaining the number from the health warning printed on their tobacco packaging.[5,6] More recently in Australia in 2012, a study found a 78% increase in national Quitline calls after brand

imagery was effectively eliminated as part of a new plain packaging law (paired with larger pictorial warnings).[7]

Tobacco pack visibility on outdoor tables in public areas (e.g., at cafés or bars) might be a form of indirect tobacco advertising.[8] Repeated (and often unconscious) exposure to brands has been associated with increased ease in brand identification, more positive attitudes towards the brand, and an increased chance of brand selection.[9] Children and adolescents have been shown to be especially vulnerable to tobacco marketing.[10]

Plain (limited branding) tobacco packaging is, therefore, hypothesised to reduce the market influence of tobacco companies, and possibly leading to a reduction in smoking.[4,11] Australia was the first country in the world to implement plain packaging legislation, and New Zealand is currently developing legislation along these lines.[12] In Australia, plain packaging restrictions include large pictorial warnings, unappealing and consistent (across all brands and product types) pack colouring and regular, small font.

A 2011–12 Australian study, before the introduction of plain packaging, found that 11% of patrons at outdoor tables of cafés or bars had a visible pack, with most packs displayed face-up (revealing the tobacco branding).[8] The study was repeated following the introduction of plain packaging with the proportion of visible tobacco packs decreasing by 15%, and the proportion of packs placed face-up decreasing by 12%.[13]

Currently, the levels of tobacco packaging visibility are unknown in New Zealand. Yet this information will prove useful to understand the impact (if any) of the proposed plain packaging law. The specific aims of this study were therefore threefold:

- Measure the level and type of tobacco pack visibility and active smoking at outdoor areas of cafés and bars in an urban area of New Zealand;
- Make comparisons with the 2011–12 Australian study; and
- Investigate relationships between pack visibility, active smoking and the presence of children.

Methods

Study site and venue selection—Three areas within the Central Business District of Wellington City were selected for the observation of tobacco pack visibility, active smoking and numbers of patrons and children at the outdoor areas of bars and cafés. These areas were selected based on pilot observations and local knowledge that they contained a relatively high number of venues with both outdoor seating and relatively high levels of patronage. These selected areas were: Cuba Street, Courtenay Place and the Waterfront.

Eligible venues included cafés, restaurants, bars and pubs with outdoor tables visible from the footpath. Venues were excluded if patrons appeared likely to remain at the tables for under 10 minutes, such as fast food outlets and ice cream shops (as per the 2011–12 Australian study[8]). Thus, the 55 selected venues included: 21 in Cuba Street, 12 in the Waterfront area, and 22 in Courtenay Place.

Pilot test and inter-observer reliability—Prior to data collection, a pilot test of the data collection instrument was conducted, where all observers visited one area at various times and tested the form. Revisions were made to facilitate efficient and unobtrusive data collection. Inter-observer reliability was then investigated using 17 observers in 10 pairs of non-communicating observers (an average of 3.4 pairs per venue, for 54 venues). Observer agreement was compared using Bland-Altman plots for observational variables.

Data collection methods—Observational data were collected over two weeks in March 2014 (early autumn) by 17 medical students of the University of Otago (Wellington). Observers viewed every designated eligible venue along a route in each study area within a 30-minute period, recording observations on a standardised, printed-paper form. Observations were collected 5-8pm on weekdays and 12-8pm on weekends on nine separate days, with the intention to collect data when patronage was highest. Venues which were closed during observation times were recorded as 'missing'.

Observers recorded the air temperature (Celsius) and wind speed (kilometres/hour) from the national weather service (http://www.metservice.co.nz). Observers also discreetly noted, for each venue, the number of: (i) seated (or standing if tables were designed for standing only) patrons, adults and children (12 years or younger) separately; (ii) non-patron children within 10m of the venues' outdoor tables; (iii) active smokers, (including holding/rolling/lighting a cigarette); (iv) tobacco packages (boxes and roll-your-own pouches) visible on tables; and (v) the orientation of visible packages: (a) face-up (showing branding); (b) face-down (larger pictorial health warning); (c) standing on side/top/bottom (boxes only); (d) in a case/tin; (e) largely concealed (e.g., by a wallet or phone, or in a pocket or bag), so that orientation was not ascertained; or (f) with an unknown orientation (e.g., when unable to get close enough to discern orientation).

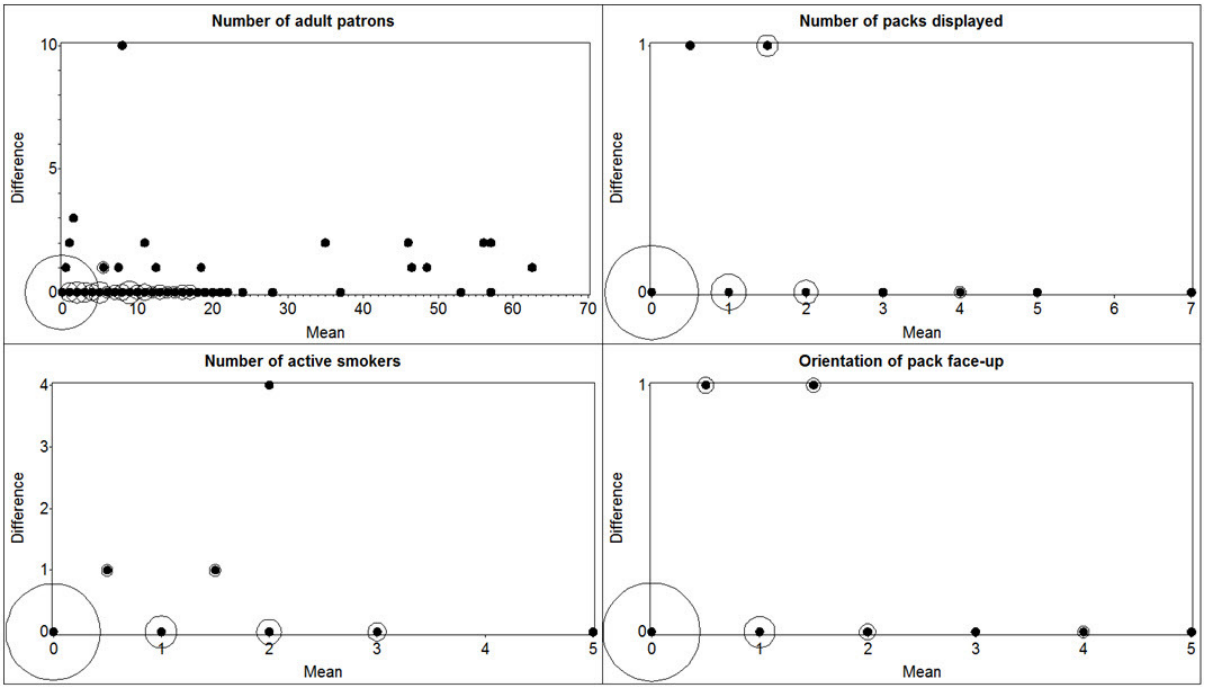
Data processing and analyses—Recorded observations were entered into Microsoft Excel. Data was managed and figures were drawn using SAS v9.2 software (SAS Institute Inc., Cary, NC). Data analyses were performed with STATA v11.2 (StatCorp LP, College Station, TX). Data were treated as clustered by venues using STATA estimation commands for survey data. Confidence intervals for the ratio of visible packs to patrons were calculated by transforming confidence intervals from the binomial distribution using the total of visible packs and patrons.[14]

Ethics approval—Approval for this study was obtained via the University of Otago level B ethics approval process on 12 March 2014 (D14/077).

Results

This observational method appeared to work well in this New Zealand setting. Evaluation of the inter-observer reliability indicated high agreement between observers (see Figure 1 for key variables).

Figure 1. Selected Bland-Altman plots from the study of inter-observer reliability*



* A fuller set of such plots is available from the authors on request.

A total of 2971 venue observations were collected from the 55 venues in this study (Table 1). All observations detailed in Table 1 took place on days without rain, with an average daytime temperature of 18ºC (range: 13–21ºC), and average wind speed of 18 kmph (range: 2–46 kmph). Each venue was observed an average of 54 times.

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Table 1. Descriptive statistics for observed packs, smokers, patrons and non-patron children within 10m of venues for the three study areas in central Wellington City (March 2014)

	Study Areas (N)			
Characteristic	Courtenay Place	Cuba Street	Waterfront	Total
Number of venues	22	21	12	**55**
Average observations per venue	47	59	59	
Total venue observations	1024	1239	708	**2971**
Packs	636	597	474	**1707**
Active smokers	508	504	345	**1357**
Adult patrons	3893	4359	10,476	**18,728**
Child patrons	26	38	397	**461**
Non-patron children (within 10m)	32	105	504	**641**

A total of 19,189 patrons were observed in the outdoor seating areas of the venues, including 461 (3%) child patrons (with another 641 non-patron children within 10m of the venue tables). In total, 1357 (7%) adult patrons were observed actively smoking. The point prevalence of observed active smoking was highest at Courtenay Place (13%), followed by Cuba Street (12%) and the Waterfront area (3%). A total of 1707 packs were visible on tables (one pack per 11.0 adult patrons; or 1.3 packs per active smoker).

The Waterfront area, with 56% of adult patrons, differed greatly from the other areas. It had the majority of all child patrons observed (86%), the lowest percentage of packs visible (28% of all packs) and the lowest proportion of active smokers (25%).

Table 2 shows the percentages of smokers (7.1%) and visible packs (8.9%) per patron. The prevalence rates of active smoking and visible pack per patron for the three areas were significantly different ($p<0.0001$), with the Waterfront area having lower rates than Cuba Street and Courtenay Place. After 5pm, smoking prevalence and visible packs per patron rates were statistically significantly higher during the weekdays, compared to on the weekend ($p=0.004$, $p=0.015$ respectively).

Of the 1707 tobacco packs observed, 80% were oriented face-up (showing the tobacco branding), 8% were face-down (showing the larger pictorial health warning on the back), 2% of the observed packs were standing on either the side, top or bottom, and only 7% of packs were either in a case or tin or concealed so that the labels were not able to be seen but the observer could still see that a pack was present (Table 3). The orientation of 3% of visible tobacco packs was identified as unknown as the observer could not get close enough to discern the orientation of the pack.

Both the levels of smoking and of pack visibility per adult patron at venues with and without children present (either as patrons or within 10m) were significantly higher when there were no children compared to when at least one child was present ($p<0.0001$) (Table 4). This pattern was consistent for each of the three study areas when there were child patrons (Table 5).

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Table 2. Active smoking and visible tobacco packs by area and day of the week (central Wellington City, March 2014)

Area/time	N	People smoking / all patrons ratio % (95%CI)	N	Visible tobacco packs / all patrons ratio % (95%CI)
Total (n=19,189)	1357	7.1 (4.9 – 9.2)	1707	8.9 (6.2 – 11.8)
By area:				
Cuba Street (n=4397)	504	11.5 (8.2 – 14.7)	597	13.6 (8.3 – 19.4)
Waterfront (n=10,873)	345	3.2 (2.1 – 4.2)	474	4.4 (2.8 – 6.0)
Courtenay Place (n=3919)	508	13.0 (9.6 – 16.3)	636	16.2 (12.0 – 20.7)
By day of week (after 5pm):*				
Monday – Wednesday (n=4485)	414	9.2 (6.9 – 11.5)	588	13.1 (10.2 – 16.2)
Thursday – Friday (n=2390)	264	11.0 (8.5 – 13.6)	324	13.6 (9.9 – 17.4)
Saturday – Sunday (n=1821)	111	6.1 (3.7 – 8.5)	151	8.3 (5.1 – 11.7)

* Observations were collected between 5-8pm on weekdays and 12-8pm on weekends, with the intention to collect data when patronage was highest.

Note: calculations of active smokers and visible packs may be more relevant per adult patron, rather than per patron as children <12 years very rarely smoke. However, to facilitate comparability with the Australian study, we used 'per total patrons' in this table (versus 'per adult patrons' in other Tables 4 and 5 and Figure 1).

Table 3. Tobacco pack orientation on the outdoor tables of venues (central Wellington City, March 2014)

Pack orientation	n	% (95%CI)
Face-up (brand imagery side up)	1366	80.0 (77.5 – 82.6)
Face down (pictorial health warning up)	141	8.3 (6.4 – 10.1)
Standing on the side, top or bottom	31	1.8 (1.2 – 2.4)
In a case or tin	29	1.7 (0.7 – 2.7)
Partly concealed (e.g., with wallet, phone, but ignoring lighters)	97	5.7 (4.0 – 7.3)
Unknown	43	2.5 (0.4 – 4.6)
Total	**1707**	**100%**

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Table 4. Comparison of pack visibility and active smoking at venues with and without children (as patrons or within 10 meters of the venue tables, central Wellington City, March 2014)

	Packs or active smokers (n)	Adult patrons (n)	Ratio (%) (95%CI)	Risk ratio (RR)	P-value (two-tailed)
Pack visibility					
No children (n = 2729 venue observations)	1464	12,535	11.7 (9.0 – 14.5)	2.98	<0.0001
One or more children (n = 242)	243	6193	3.9 (2.4 – 5.5)	1.00 (ref)	
Active smoking					
No children (n = 2729)	1159	12,535	9.2 (7.2 – 11.3)	2.89	<0.0001
One or more children (n = 242)	198	6193	3.2 (1.9 – 4.5)	1.00 (ref)	

Table 5. Comparison of pack visibility prevalence rates at venues with and without child patrons by study area and for the total observations in Wellington City (March 2014)

Site		Observations of venues (n)	Packs (n)	Adult patrons (n)	Ratio (%) (95%CI)	Risk ratio (RR)	P-value (two-tailed)
Cuba Street	No child patrons	1215	578	4082	14.2 (9.1 – 19.8)	2.06	0.014
	1+ child patrons	24	19	277	6.9 (0.9 – 13.6)	1.00 (ref)	
Waterfront	No child patrons	557	304	5367	5.7 (4.1 – 7.3)	1.70	0.018
	1+ child patrons	152	170	5109	3.3 (1.6 – 5.1)	1.00 (ref)	
Courtenay Place	No child patrons	1007	620	3723	16.7 (12.8 – 20.8)	1.77	0.086
	1+ child patrons	17	16	170	9.4 (1.0 – 19.3)	1.00 (ref)	
Total	No child patrons	2778	1503	13,172	11.4 (8.8 – 14.2)	3.09	<0.0001
	1+ child patrons	193	205	5556	3.7 (2.2 – 5.3)	1.00 (ref)	

During the weekend there were statistically significantly higher percentages of active smokers per adult patron from 4-6pm compared to 12–2pm (Figure 2). There was also a general upward trend in active smokers from noon to 6pm, with a decrease from 6-8pm. Percentages of visible packs per adult patron steadily increased from noon to 4-6pm, with statistically significantly higher averages from 2-8pm compared to 12-2pm.

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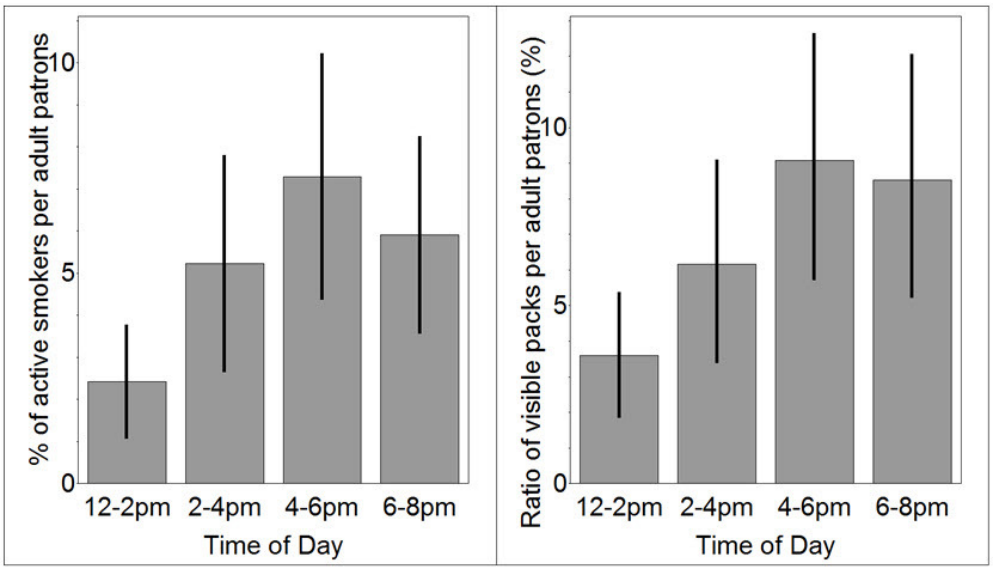
Figure 2. The percentage of active smokers and percentage packs displayed out of all adult patrons, averages (and 95%CI) by time of day on the weekends only (Wellington City, March 2014)



Discussion

Main findings and interpretation—This study identified an overall level of pack visibility of 9%, compared to a slightly larger pack visibility level of 11% found in the similar Australian study.[8] The majority of packs were oriented face-up (80%), showing the branding. Similarly, the Australian study found 81% were face-up.[8]

The face-up orientation hides the larger pictorial health warnings and maximises the "passive marketing" associated with the tobacco brand imagery. Possible reasons for these findings are that smokers could have a negative psychological response to pictorial images on tobacco packs[15] or that other factors, such as this orientation's ease of opening the pack to access cigarettes or rolling tobacco.

Observed point prevalence rates of active smoking in this study were similar to those found in the Australian study (7% and 8% respectively).[8] This is not surprising, given similarities in national adult smoking prevalence rates (15% and 16% respectively).[16,17] The lowest smoking prevalence and pack visibility rates were observed in the Waterfront area, perhaps due to this area's popularity among families and tourists. Conversely, Cuba Street and Courtenay Place are popular areas for adult nightlife, which may relate to higher smoking rates and pack visibility.

We found a pattern of an increased proportion of active smokers and of visible packs in the early evening (relative to noon). This increase could be partly related to greater alcohol consumption as the day progressed, since there is an association between the amount of alcohol consumed and increased smoking behaviour.[18,19] But other explanations are possible, such as more smoking occurring after meals.

Another interesting observation was the significantly lower prevalence rates of active smoking and pack visibility per patron at venues with children present (either as patrons or non-patrons within 10m of venue tables). This contrasts with a previous (albeit much smaller) study in the same city that found no association between smoking prevalence and child presence.[20] Differences between study findings might reflect the protective decisions by parents to reduce secondhand smoke exposure, a different sample of venues, and/or that the presence of children may inhibit smoking behaviour by some smokers.

Strengths and weaknesses of the study—To our knowledge, this study combining pack visibility and smoking behaviour was just the second of its kind in the world. A specific strength was the high level of inter-observer reliability in data observations (see Figure 1), providing accurate measurements and avoiding related biases.[21,22] Data collection on the presence of children, both as patrons as well as nearby non-patrons was a unique feature (not in the Australian study). Children may be particularly vulnerable to the health harms from secondhand smoke exposure, to potential pack-related passive advertising, and to the normalising effects of visible smoking.[23]

A limitation of this study was the lack of examination of differences by neighbourhood socioeconomic status (SES), as we only had the resources to sample three areas in central Wellington (which lacked measurable variation in SES). In contrast, the largely comparable Australian study considered variations across locations of different SES.[8] Future larger, funded studies could potentially include study areas with varying SES. This work could inform the extent to which the future plain packaging law could help address the health inequalities caused by the tobacco epidemic. Another limitation was the subjective element of assessing children "within 10 meters" of venue tables (an issue that could not be assessed objectively as the ethics approval for this study did not include photography).

Possible implications for research—This study may provide robust baseline data for a future follow-up study investigating the effects of plain packaging legislation if implemented in New Zealand (and contributes to further international comparisons). Another implication is the need to further explore the observed association between the presence of children and both lower pack visibility and lower smoking levels. Although this relationship was observed across all three routes, it is possible that other factors (e.g., patron demographics) may have partly been the cause of this observed association and not necessarily changes by smokers when they see children around them. Finally, the diurnal patterns in smoking could be studied further to examine the potential role of alcohol. This study found an association between the presence of children and lower prevalence rates of active smoking and pack visibility.

Conclusion

This study found that tobacco branding on tobacco packaging was frequently visible because of the way smokers position their packs. These results highlight the residual problem posed by this form of marketing. The results also provide baseline data for the future evaluation of plain packaging if a proposed law is implemented in New Zealand. Other results warrant further research, particularly the reasons for lower pack visibility and smoking when children were present.

Competing interests: Nil.

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ORIGINAL ARTICLE

Variation in gout care in Aotearoa New Zealand: a national analysis of quality markers

Gary Jackson, Nicola Dalbeth, Leanne Te Karu, Doone Winnard, Peter Gow, Catherine Gerard, Nikolai Minko

Abstract

Aim To examine whether there was variation in markers for the quality of gout care using national linked data for the entire Aotearoa New Zealand population.

Method Data drawn for the New Zealand Atlas of Healthcare Variation was used to examine regularity of allopurinol dispensing, laboratory testing for serum urate, and acute hospitalisation for gout. Standardised rates by age, gender, ethnicity and District Health Board (DHB) of domicile were calculated.

Results For New Zealanders aged 20–79 years with gout, 57% were dispensed allopurinol in 2010/11. Of these, 69% were receiving allopurinol regularly, and only 34% of people dispensed allopurinol had serum urate testing in a 6-month period. The annual hospitalisation rate was 1% of people with gout. Māori and Pacific people with gout were less likely to be on regular allopurinol treatment, despite having more than twice the chance of being hospitalised with acute gout.

Conclusion We have demonstrated that routinely collected health data can be used to monitor the quality of care for people with gout at a high level. Primary care initiatives that focus on ensuring a continuous supply of urate-lowering therapy to achieve therapeutic serum urate targets are required to improve the impact of gout in Aotearoa New Zealand.

Gout is the commonest form of inflammatory arthritis, caused by deposition of monosodium urate crystals in and around joints, tendons and ligaments. Recent enumerations suggest over 4% of the Aotearoa New Zealand population suffer from gout, with rates particularly high for Māori and Pacific males. [1 2]

An acute attack of gout is extremely painful. While attacks are usually self-limiting, untreated gout or inadequate treatment can lead to tophi, chronic gouty arthritis and joint destruction. Treatment to achieve serum urate levels of <0.36 mmol/L is associated with improved clinical outcomes for people who have more than one attack a year of gout.[3–6] Treatment goals are then to keep serum urate at <0.36 mmol/L.

Gout is predominately managed in primary care. Despite clear guidelines and pathways[3–6] marked variation in gout management exists internationally[7,8] and in Aotearoa New Zealand as shown by the Health Quality and Safety Commission's Atlas of Healthcare variation (www.hqsc.govt.nz/atlas). The Atlas shows that on average 41% of people with gout across New Zealand are regularly prescribed allopurinol, but this ranges from 33% in people residing in the Auckland District Health Board (DHB) area to 47% in Nelson-Marlborough. The question then arises whether this is reasonable variation, or whether it might reflect differing quality of care.

The aim of this study is to examine markers for the quality of gout care in Aotearoa New Zealand primary care that can be assessed using national linked data for the entire Aotearoa New Zealand population. We examined data by gender, ethnicity, and DHB of domicile, looking at potential inter-relationships.

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Methods

The Aotearoa New Zealand national data collections were assessed for their utility to measure the quality of gout care. Three indicators were selected as shown in Table 1.

The Aotearoa New Zealand Health Tracker (ANZHT) provided the denominator gout population, as described in Winnard et al.[1] The ANZHT links the Aotearoa New Zealand national health datasets to cover the entire Aotearoa New Zealand population who have had some contact with the health system. The gout population were identified as people aged 20 to 79 who had a discharge diagnosis of gout [International Classification of Disease (ICD)-9 274, ICD-10 M10] from a public hospital admission from 1988 to June 2011, or who had been dispensed allopurinol or colchicine at least once from a community pharmacy between 2006 and June 2011. Diagnosis of leukaemia or lymphoma was an exclusion criterion for dispensing of allopurinol, and the use of probenecid was not included in the algorithm as it is little used for gout care in Aotearoa New Zealand and gout care not easily distinguished from its other prescribed uses.

Benzbromarone has been available under Section 29 on a named patient basis for several years but use has been limited. Newer agents such as febuxostat and pegloticase were not licensed for use in Aotearoa New Zealand in the period of the study. Only Aotearoa New Zealand residents enrolled in a Primary Health Organisation (PHO) or having had a health event in 2010/2011 and still alive at the end of June 2011 were included (i.e. presumed resident in Aotearoa New Zealand in the period of the study). Allopurinol and colchicine are prescription-only medicines in Aotearoa New Zealand, so near-100% capture in the pharmaceutical collection is expected.

People were assigned to their DHB of domicile; where more than one domicile was recorded, the most recent value was selected. Ethnicity data for this population were taken from the 2011 second-quarter primary care enrolment database and the National Health Index extract for the 2011 second quarter. In keeping with other ethnicity reporting in Aotearoa New Zealand health data, ethnicity was prioritised from multiple ethnic codes in the following order: Māori, Pacific peoples, Asian, European/'Other' New Zealanders.

For people reporting different ethnic groups over the time period the most recent value was used for prioritisation. Rates for the Asian population were similar to the European/other group, and in some DHBs the Asian population was small, so these groups were combined into a group termed 'nonMāori/nonPacific'. Ages were examined in 5-year increments from 20 to 79 years, then grouped into three age ranges: 20–39, 40–59, and 60–79 years.

All collected data were linked together by DHB, age, ethnicity and gender. Means and standard deviations were determined for each variable. Crude rates, standardised ratios (SRs) with 95% confidence intervals, and linear regression between predictor and dependent variables of interest were performed in Statistical Analysis System (SAS) v9.3 software.

Table 1. Assessed quality markers

Marker	Rationale	Aim
1. Of those with gout dispensed at least one allopurinol script, proportion getting at least 3 out of last 4 quarters	Prescribed allopurinol at least once so assume meet the criteria for use of urate-lowering therapy; allopurinol is only effective if regularly taken	As close to 100% as possible
2 Of those with gout, getting allopurinol, proportion getting a serum urate test in the 6 months following dispensing	The key goal of effective gout management is serum urate at <0.36 mmol/l. Cannot do this if not measuring it. Guidelines suggest 6 monthly[4,5]	As close to 100% as possible
3. Hospital admissions for gout—gout as principal diagnosis	Gout flares severe enough to necessitate hospital admission are potentially related to inadequate preventive care	As low as possible

Note: The exact data definitions used for each indicator are noted in Appendix 1. Note that while the fact of a laboratory test being taken is collected, the results are not captured in the national collections. Thus one cannot directly capture those with a serum urate lower than 0.36 mmol/l.

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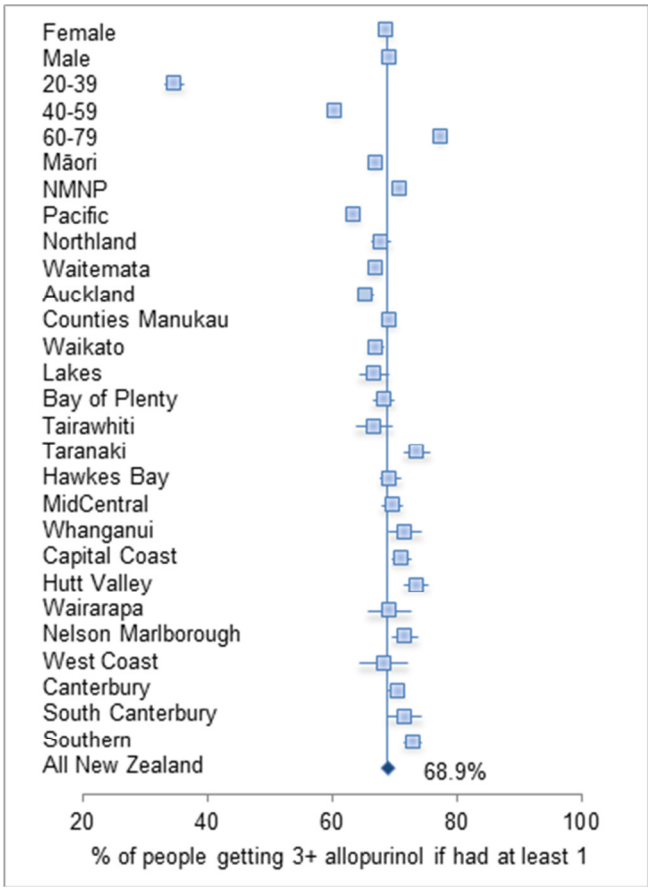
Results

In 2010/11 we identified 114,703 people aged 20–79 years with gout from the national data collections. With 3,032,000 people in the 20–79 year old New Zealand population (Statistics New Zealand estimated resident population), this is a prevalence of 3.8%–1.6% for females and 6.2% for males. Pacific peoples had a prevalence of 9.3% and Māori 7.9%, both significantly higher than the prevalence for nonMāori-nonPacific people at 2.9%. Prevalence rose sharply with age: 0.9% of 20–39 year olds, 3.6% of 40–59 year olds and 10.1% of 60–79 year olds were estimated to have gout.

Allopurinol regularity—Of all people identified as having gout, 65,151 had at least one dispensing of allopurinol in 2010/11, or 57%. Of these, 44,908 were dispensed allopurinol in at least 3 out of 4 quarters in the year—which is 39% of all those with gout, or 69% of those dispensed allopurinol at least once (see Figure 1).

Figure 1. Standardised* rate of those receiving allopurinol regularly as proportion of those getting at least one dispensing per year, 2010/11



'NMNP' = nonMāori/nonPacific; * Each variable standardised for the others – DHB of domicile standardised for gender, age and ethnicity; ethnicity standardised for gender, age and DHB, gender standardised for ethnicity and DHB.

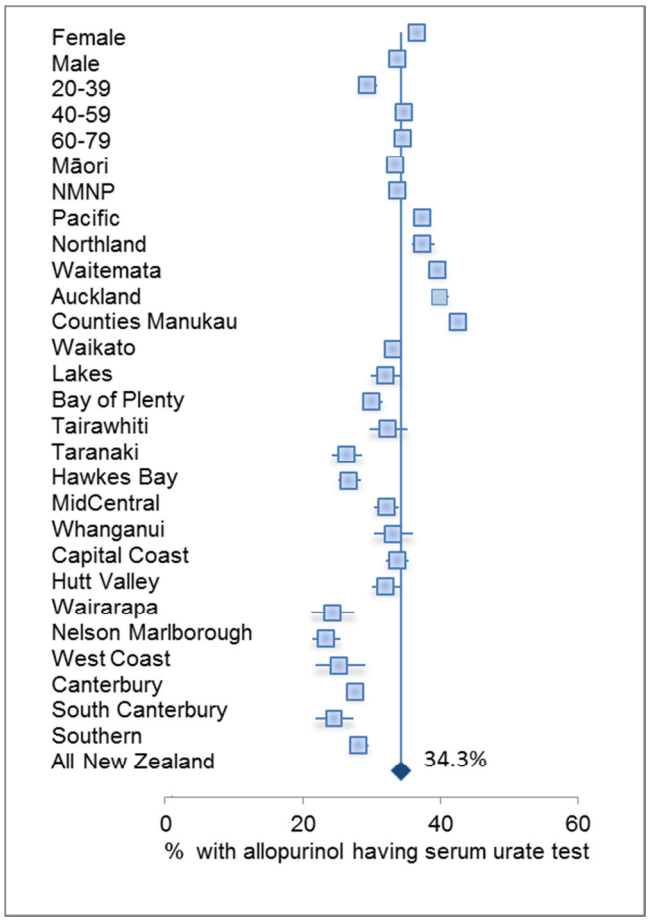
Older people with gout were more likely to receive regular allopurinol than younger (77% for 60–79 compared with 34% for 20–39 year olds), and Māori and Pacific less likely than nonMāori/nonPacific (67% and 63% compared with 71%), but there was little difference by gender (all proportions quoted here are standardised rates). Variation by DHB ranged from 65.2% for people living in Auckland DHB to 73.4% for Hutt Valley DHB.

People living in Waitemata, Auckland and Waikato DHB areas had lower rates of regular use of allopurinol; gout patients in Taranaki, Capital and Coast, Hutt Valley, Nelson Marlborough and Southern had higher rates. A somewhat North–South gradient was observed with rates *higher* in southern regions.

Laboratory testing for serum urate—Of all people with at least one dispensing of allopurinol in 2010/11 only 34% had at least one laboratory test for serum urate levels in the 6 months following dispensing (see Figure 2). Females (37%) were slightly more likely than males (34%) to be tested, and older people (35% for 40–59 and 60–79 year olds) more likely than younger (20–39 year olds 29%). Pacific people dispensed allopurinol were more likely to get a laboratory test (37%) than Māori (33%) or nonMāori/nonPacific (34%). Testing rates varied almost two-fold by DHB, ranging from 43% in people living in Counties Manukau DHB to 23% for those living in Nelson Marlborough.

Rates were higher in the 4 northern region DHBs—Northland, Waitemata, Auckland, and Counties Manukau, and lower in 10, including all the South Island DHBs. An opposite north–south gradient to that of allopurinol regularity was observed with rates lower in southern regions. Of note, if the period was changed to a full 12 months after dispensing then the proportion tested rises from 34% to 50.7% of those with at least one dispensing of allopurinol (DHB range from 33% to 61%—data not shown).

Figure 2. Standardised* rate of those receiving allopurinol getting at least one serum urate laboratory test in the 6 months following dispensing, 2010/11



'NMNP' = nonMāori/nonPacific; *Each variable standardised for the others—DHB of domicile standardised for gender, age and ethnicity; ethnicity standardised for gender, age and DHB, gender standardised for ethnicity and DHB.

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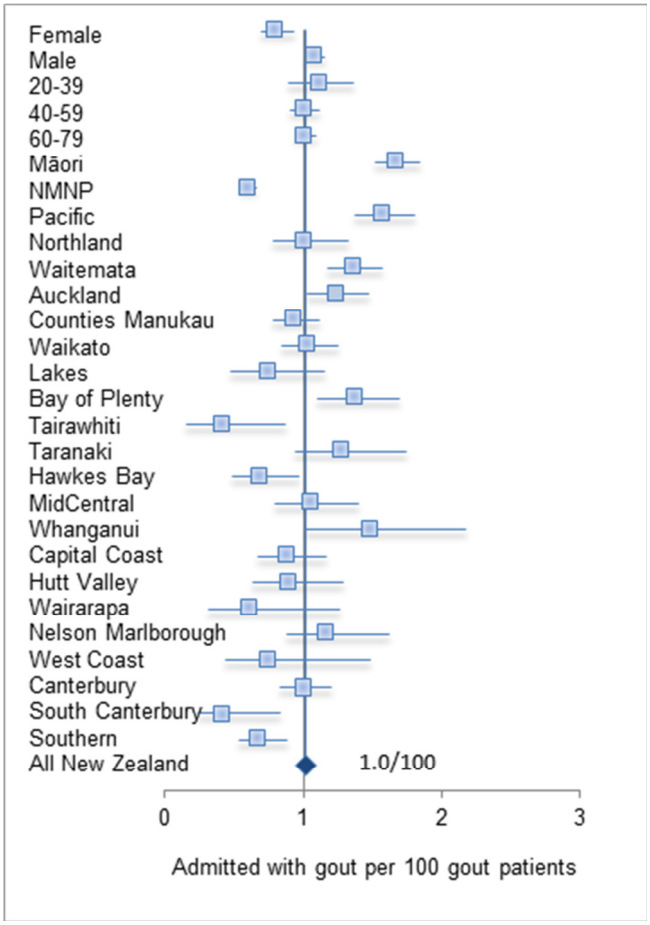
Hospital admission for gout—In 2010/11 there were 1168 acute hospitalisations with a primary diagnosis of gout, or 1.0% of the estimated population with gout (See Figure 3). Females (0.8%) were slightly less likely to be hospitalised than males (1.1%), while age had little effect.

Māori and Pacific people were more likely to be hospitalised (1.7% and 1.6%) than nonMāori/nonPacific (0.6%). Hospitalisation rates by DHB of domicile varied nearly three-fold, ranging from 1.5% in Whanganui to 0.4% for South Canterbury. Rates were high in Waitemata and Bay of Plenty DHBs, and lower in Tairawhiti, South Canterbury and Southern DHBs.

Figure 3. Standardised* rate of hospitalisation for gout as proportion of all with gout, 2010/11



'NMNP' = nonMāori/nonPacific; *Each variable standardised for the others - DHB of domicile standardised for gender, age and ethnicity; ethnicity standardised for gender, age and DHB, gender standardised for ethnicity and DHB. Acute or arranged admissions with a principal diagnosis of gout, ages 20–79 years.

Correlations between quality indicators—Only weak correlations appeared to exist between the quality indicators tested at the DHB level – indeed some were negatively correlated—for example DHBs with higher rates of people regularly receiving allopurinol had lower rates of serum urate testing (r^2=-0.24).

For Māori and Pacific people their relatively low rate of allopurinol regularity fitted with their relatively high rate of hospital admission (r^2=-0.70), but not with their higher rate of serum urate testing (r^2 =-0.64). It is in the age group analyses that we see the most consistency across the indicators, with those in older age groups being more likely to receive allopurinol regularly and to have serum urate tests, while being relatively less likely to be admitted to hospital for gout.

Taking all people with gout in Aotearoa New Zealand aged 20–79 only 39% were being regularly treated with allopurinol. This varied by DHB from 33% to 47%. We compared the variation by DHB to the variation for each of the indicators. There was the expected correlation with allopurinol regularity (r^2=0.63) but a negative correlation with serum urate testing (r^2=-0.54), and no correlation with hospital admission. No measure was particularly correlated with gout prevalence.

Discussion

With an estimated 3.8% of New Zealanders aged 20–79 years having gout, it is important that quality of gout care can be quantified. Maintaining serum urate levels below 0.36 mmol/L is associated with improved clinical outcomes for people who have more than one attack a year of gout. In this analysis, we were particularly interested in exploring system-level effects, where larger population groups vary in care quality indicators. Three indicators have been explored here.

Of all people dispensed allopurinol 69% were receiving it regularly and yet without regular use its benefits on gout would be limited. Only 34% of people dispensed allopurinol had serum urate testing in the guideline-recommended 6-monthly period.[4,5] Combined, only 23% of gout patients considered to require allopurinol treatment were being treated according to best practice. However we are unable to ascertain if dose titration of urate lowering therapy occurred alongside these two important steps.

The third indicator was for acute hospitalisation for gout—1% of gout patients were admitted in 2010/11. At a DHB level the three indicators varied significantly, but seemed to be relatively independent of each other. Each would seem to be measuring a different aspect of care. No measure was correlated with gout prevalence, despite an initial supposition that clinicians working in areas where they saw more gout might be more systematic in their care and demonstrate better quality outcomes.

The higher burden of morbidity related to gout for Māori and Pacific peoples compared to other New Zealanders is highlighted by rates of hospitalisation more than 2½ times that of the nonMāori/nonPacific population (1.7% and 1.6% compared with 0.6%). Despite this higher rate they are no more likely to receive any allopurinol preventive treatment, and are less likely to be receiving regular allopurinol.

This paper suggests that acute flares of gout severe enough to necessitate hospital admission are potentially related to inadequate preventive care, and the higher admissions rates in Māori and Pacific peoples correlate with their being less likely than those identified as nonMāori/nonPacific to be receiving regular allopurinol.

Most people with gout and also the wider public believe that gout is present when there is an acute attack rather than understanding that gout is in fact a long-term (chronic) illness. This misperception makes it hard for people of any ethnicity to understand the need for long-term medication.[9,10] Additionally a New Zealand review of health education resources on gout medication by health literacy professionals, Workbase, found that messages most relevant to Māori and Pacific peoples, are not provided in a manner that is understandable to them.[11,12] An inherited tendency to develop gout[13] for these people is coupled with a lack of prioritisation of resources.[14] They found that the health literacy demands of managing gout are high; that:

> Initially, the medication and management process for gout and gout attacks is complex, with a lot of new information, experiences and decisions for people with gout. It is during this initial phase that managing medication is most complicated and people form incorrect medication habits and beliefs. Poor medication management can lead to a refusal to use preventive medication (p vi, Ministry of Health 2012).[14]

The Workbase review suggested that successful management of gout requires the provision of clear instructions about medication and support for those with gout and their families and whānau to ensure the instructions are understood and followed as part of regular monitoring. This approach will be key

to reducing the current inequities for Māori and Pacific peoples in the quality of gout care demonstrated by this study.

Comparisons—The overall proportion of people with gout regularly receiving allopurinol at 39% was similar to that found in an earlier New Zealand study at 39-42.7%,[15] but higher than the 30% seen in the UK in 2006,[16] 17% over 2 years seen in Israel in 2002 to 2009[17] or 18% over 2 years in the US in 1997/8.[18] In relation to people dispensed allopurinol, general practitioners in the UK saw a 'persistence' of patients on allopurinol at 61% after one year in 2000–2005, while a similar measure for German patients was 31%.[19] Harrold et al found an adherence rate of only 44% in the Northeast US, and noted poorer adherence for younger patients.[20] The equivalent figure reported here at 69%, while compiled from a different metric, compares well.

Proportions of patients on allopurinol getting appropriate laboratory tests for serum urate are not well described in the literature. A practice audit in the UK found 34% had had a test done in the previous year,[21] lower than found here where 50.7% had a test over a 12-month period. Only 32% of general practitioners in Ireland stated that they routinely monitored serum urate levels in patients on allopurinol.[22] Without knowing the level of uric acid in the blood the achievement of the treatment goal of 0.36 mmol/L or below cannot be monitored.

Rates of admission to hospital for gout patients in Aotearoa New Zealand were compared to England by Robinson et al.[23] Their rate for Aotearoa New Zealand of 1.3% of gout patients of all ages for 2008/09 is similar to the 1% shown here for 20–79 year olds, and was compared with estimates from 0.39% (2004) to 1.6% (2007) for England for depending on which gout prevalence estimate was used.

Strengths and limitations—This study covers the entire Aotearoa New Zealand population, and potentially 80% of all gout patients within that.[2] Problems of potential bias from facility-based or region-based studies are avoided. However this study is not based on a clinical diagnosis of gout, nor were we able to otherwise validate the diagnosis. Some people may have been given allopurinol for non-gout reasons.

Evidence for gout flares is imputed from the dispensing data rather than directly measured. There is a lack of direct information about whether a person had more than one attack a year or had tophi – and hence should be offered allopurinol or other urate-lowering medication. Although sustained serum urate levels below 0.36 mmol/L represents the gold standard for optimum gout management, this data is not available at a population level. However, regular use of urate lowering therapy, with monitoring of urate levels to enable adjustment of allopurinol dose to achieve this goal, are useful intermediate outcomes. Urate levels are available in clinical practice records, providing the opportunity for quality audits to explore further issues highlighted by this population study.

Further work—We have demonstrated that it is possible to measure some aspects of quality of care of gout with national data and found little relationship between prevalence and indicators of quality of care. Sometimes neglected in the past, there are now very clear guidelines and treatment goals for gout.[3-6] Practices can audit their care against these treatment goals and recommended processes.[5,20,24-25] A summary of potential aspects of quality of gout care one might measure are shown in Table 2. In addition there is the whole field of appropriate treatment for comorbidities that feature so prominently in gout patients.[26] Further work could explore dose-related measures, particularly around initiation of treatment.

Table 2. Potential indicators for gout quality of care from routinely collected data

Marker	Rationale	Aim
1. Of those with gout, proportion with serum urate levels <0.36 mmol/l	Flares controlled if serum urate levels<0.36 mmol/L, joint damage minimal. [often not available in routinely collected data]	As close to 100% as possible.
2. Of those with gout dispensed at least one allopurinol script, proportion getting at least 3 out of last 4 quarters.	Prescribed allopurinol at least once so assume meet criteria for starting urate-lowering therapy; allopurinol only effective if regularly taken.	As close to 100% as possible.
3. Those with gout getting colchicine dispensed 2 or more times but not allopurinol	Getting more than one attack but not being treated with allopurinol; would likely benefit from allopurinol	As low as possible – some may be getting their first double attack in a year, so prior to initiating allopurinol. Reasons for not taking allopurinol are minimal if people are dosed optimally.
4. Those initiating allopurinol also dispensed colchicine or NSAID	Good practice is to cover initiation of allopurinol treatment with prophylaxis as allopurinol doses are escalated	No target defined.
5. Those initiating allopurinol starting on a low dose (i.e. 100 mg/day or less) then up-titrating if needed	Trying to avoid gout flares on initiation. Guidelines recommend 100mg/day (or less in renal disease) as initiating dose.[4] If possible use eGFR to set starting doses, but this is not usually available in routinely collected data	No target defined.
6. Of those initiating allopurinol, proportion getting a serum urate test within 6 months	Key part of titrating initial treatment is knowing the urate level; guidelines suggests every 2-5 weeks[4]	As close to 100% as possible.
7. Of those with gout on allopurinol, proportion getting a serum urate test in last 12 months	Key marker of potential damage is to keep serum rate below 0.36 mmol/l. Cannot do this if not measuring it. Guidelines suggest 6 monthly [4]	As close to 100% as possible.
8. Proportion of those on allopurinol above 300mg/day	Evidence of dose titration to meet treatment goals.	Non-zero – perhaps 10% or higher
9. Hospital admissions for gout – gout as principal diagnosis	Acute attacks of gout severe enough to necessitate hospital admission are potentially related to inadequate preventive care.	As low as possible.

Source: A distillation from a number of sources including[3–7,15,27,28]

Note it is assumed most urate lowering therapy will be with allopurinol in Aotearoa New Zealand. More generally "urate-lowering therapy" could be substituted for allopurinol in the table.

Conclusion

We have demonstrated that routinely collected health data can be used to monitor the quality of care for people with gout at a high level. Variation by ethnicity and DHB was demonstrated around Aotearoa New Zealand, with lower levels of adequate preventive treatment for Māori and Pacific peoples.

Comparisons using the Atlas of Healthcare Variation may enable DHBs to identify local problems, design interventions, and set appropriate targets. Further work is needed to draw a more comprehensive picture of gout care and development of potential composite scores for monitoring

purposes. In Aotearoa New Zealand, regularity of allopurinol dispensing was less than 70% over 1 year, and laboratory testing for serum urate was low at 34% in 6 months for those taking allopurinol.

Around 1% of all people with gout aged 20–79 years were admitted to hospital in 1 year with gout as the primary cause of admission. Collectively, these data indicate that initiatives that focus on maintaining a continuous supply of urate-lowering therapy to ensure therapeutic serum urate targets are achieved are required to improve the impact of gout in Aotearoa New Zealand.

Competing interests: Nil.

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Appendix 1

Indicator	Numerator	Denominator	Notes on indicators
1. Of those with gout dispensed at least one allopurinol script, proportion getting at least 3 out of last 4 quarters.	Those with an indication of gout who were dispensed allopurinol for at least three of the four quarters of the year in 2010/11	Those with an indication of gout in ANZHT getting at least one allopurinol dispensing in 2010/11	Assumed that gout flares present as received at least one allopurinol dispensing.
2 Of those with gout dispensed allopurinol, proportion getting a serum urate test in the 6 months following dispensing	Those dispensed allopurinol in ANZHT and at least one recorded community laboratory serum urate lab test in the 2010/11 year in the six months following the first allopurinol dispensing of the year	Those dispensed allopurinol at least once	Could extend this to cover all people diagnosed with gout, given they should be monitored. Also could cover the whole year, not just 6 months.
3. Hospital admissions for gout – gout as principal diagnosis	All discharges from public hospitals with a principal diagnosis of gout (ICD10AM M10) in 2010/11	Health care-using population, ANZHT	Acute medical surgical discharges, casemix only; Age-gender-ethnicity standardised
Gout prevalence	Those with an indication of gout in ANZHT-hospitalisation, dispensing of colchicine or allopurinol 2006-2011	Health care-using population, ANZHT	See Winnard et al[1]
Proportion of gout population on allopurinol	Those with an indication of gout who were dispensed allopurinol for at least 3 of the 4 quarters of the year in 2010/11	Those with an indication of gout in ANZHT	

ANZHT = Aoteoroa-New Zealand Health Tracker, a Ministry of Health dataset. All indicators include ages 20–79. 2010/11 refers to the period 1 July 2010–30 June 2011. Prescribing of chronic medication is normally in 3-month increments. Dispensing in 3 out of 4 quarters is roughly equivalent to a Medication Possession Ratio of 80%, often used as a benchmark in compliance work.

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ORIGINAL ARTICLE

A descriptive study of urethral discharge among men in Fiji

Lavenia Gaunavinaka, Dashika Balak, Sumanthla Varman, Sharan Ram, Stephen M Graham

Abstract

Introduction: Urethral discharge is a common presentation of sexually transmitted infection (STI) in men and known pathogens include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. There are no published data of the burden of urethral discharge among men in Fiji.

Objective: To evaluate urethral discharge among men to determine the incidence, the frequency of recurrence and reported at-risk behaviour.

Methods: We conducted a retrospective, descriptive study of clinical records of all men presenting with urethral discharge to two major reproductive health clinics. Data collected included self-reported at-risk behaviours, results of abnormal syphilis serology and antibiotics prescribed. The frequency of recurrence in the following 1–2 years of initial presentation was determined along with microbiological findings from urethral swab in this group.

Results: A total of 748 males presented with urethral discharge to the clinic in one year. This represents an incidence rate of at least 295 per 100 000 adult males per year in the study population. Within the next 1–2 years of the initial presentation, 102 (14%) of these re-presented out of which 42 had urethral swab taken for etiological diagnosis. The commonest isolate was *Neisseria gonorrhoeae*. Results of syphilis tests were available for 560 (75%) of patients and 29 (5%) were positive. Recurrence was not associated with self-reported at-risk behaviours.

Conclusion: The incidence of urethral discharge among males in Fiji is very high and prevention strategies are urgently needed.

Sexually transmitted infections (STIs) are a major cause of morbidity worldwide.[1] A global prevalence survey in 1999 estimated that more than 340 million new cases occurred throughout the world in that year.[2]

Urethral discharge is a common presentation of STI in men and known pathogens causing urethral discharge include *Neisseria gonorrhoeae* (or gonococcus) and *Chlamydia trachomatis*. These infections can also be asymptomatic while on the other hand, urethral discharge may be a clinical presentation of conditions other than STIs. A survey of pregnant women attending antenatal clinics in 2004 found that 29% were infected with chlamydia, 1.7% with gonorrhoea and 2.6% with syphilis.[3] However, there are no peer-reviewed publications of the burden of STIs, including of urethral discharge, among men in Fiji.

STIs are treated syndromically in Fiji according to the national guidelines.[4] Urethral swab and cultures are available but the practice of obtaining a sample is highly variable. There is therefore limited knowledge of the common causes and treatment response of urethral discharge in Fijian men. Further, the demographic profile and risk behaviour associated with urethral discharge in men has not been studied.

The aim of this study was to evaluate urethral discharge among men in Fiji to determine the incidence as well as the frequency of recurrence and reported at-risk behaviour.

Methodology

Study design—We conducted a retrospective descriptive study of urethral discharge among males in Fiji presenting to the reproductive health clinics over a 1-year period.

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Study setting—Fiji is an island nation in the South Pacific Ocean that consists of 322 islands with two major islands and a total population of approximately 837,000. The Ministry of Health divides Fiji into three divisions for administrative purposes: the Central and Eastern Division; the Western Division; and the Northern Division. There are three specialised reproductive health clinics that cater for the majority of STI cases in each division, although patients also present to other general outpatient clinics or private clinics.

Study population—All patients who presented for the first time from January to December 2011 and were recorded with the diagnosis of urethral discharge syndrome in the patient register were included in the study. Upon presentation to these clinics all patient with urethral discharge have a full clinical assessment including history taking and examination of urethral discharge.

Laboratory diagnosis of *N. gonorrhoeae* in Fiji includes microscopy of a direct smear of the discharge stained with Gram stain to reveal Gram-negative diplococci within polymorphonuclear leucocytes. The modified Thayer Martin medium is the selective media used in Fiji to culture *N. gonorrhoeae*. Diagnosis of syphilis in Fiji is made by VDRL (venereal disease research laboratory) and TPHA (*Treponema pallidum* haemagglutination) tests. In the case of *C. trachomatis*, a nucleic acid amplification method (NAAT) is used for detection.

The syndromic treatment guideline for STI recommends single dose of amoxicillin, augmentin, probenecid and azithromycin (AAPA).

Data collection and analysis—Data were collected retrospectively from the clinical files and outpatient register of all initial visits by male patients presenting with urethral discharge to the two reproductive health clinics; Central/ Eastern Hub and Western Hub between 1 January and 31 December 2011. Northern Reproductive Health Clinic data was not included due to insignificant data found during data collection (only 5 clinical data were found).

The following were recorded: name of medical division, patient registration number, age, treatment received, reported at-risk behaviour and result of syphilis test. A patient who was listed more than once in the 2011 register was listed as a recurrent episode. The patient register for 2012 was also reviewed to identify patients who had presented during the study period and have re-presented to the clinics with recurrent episodes. All patients with recurrent episodes had duration between episodes recorded along with result of urethral swab culture where available.

Frequencies were calculated, and Chi-squared test was used to assess differences in proportions between groups with OR and 95% CI indicated where appropriate. The level of significance was set at 5%.

Ethics—Ethics approval was obtained from the Union Ethics Advisory Group (EAG), the National Health Research Committee and the Fiji National Research Ethics Committee.

Results

A total of 748 males presented with new urethral discharge in a 1-year period to the two of the three STI clinics in Fiji. The median age of presenting with urethral discharge was 25 (IQR: 34) years. Using national population census data to obtain the total population of adult males (>14 years) in the Central and Western divisions, it is estimated that the incidence rate of urethral discharge among adult males in Fiji is at least 295 per 100,000 per year.[5]

Table 1 presents characteristics of the study group and the proportion that had recurrent urethral discharge. In the following 1 to 2 years, 102 (13.6%) men presented with recurrence of urethral discharge and 42 (41.2%) of these had urethral swabs for laboratory diagnosis. Only 8 (19%) were positive for *N. gonorrhoeae* alone and an additional one was positive for both *N. gonorrhoeae* and *C. trachomatis*.

First void urine was also collected for recurrent cases and 8 were positive; 5 (56%) for both *N. gonorrhoeae* and *C. trachomatis*, 3 (33%) for *N. gonorrhoeae* alone and 1 (11%) was positive for *C. trachomatis* alone. There were no risk factors for recurrence identified among the study population. Recurrence was significantly more common in those that presented to the clinic for Central Division than those that presented to Western Division (p=0.01).

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Out of the 748, 560(74.9%) were tested for syphilis apart from receiving syndromic treatment for urethral discharge and 29(5.2%) had positive results for syphilis, either VDRL, TPHA or both.

During the study period, the syndromic treatment guideline for STI recommended a single dose of amoxicillin, augmentin, probenecid and azithromycin (AAPA). However, it was noted that AAPD (doxycycline, 100mg twice daily for 7 days) was still widely used by practitioners for the presumptive treatment of gonococcal and chlamydial infection.

Table 1 New urethral discharge cases among men in Fiji in 2011, and recurrent urethral discharge between 2011 and 2012

Characteristics	New urethral discharge cases N (%)		Recurrent urethral discharge N (% of new urethral discharge cases)		P value	Chi² for trend
Divisions						
Central/Eastern	551	(74)	85	(15)	0.01	-
Western	197	(26)	17	(9)		
Age						
14-24	374	(50)	53	(13)	0.06	3.50
25-34	292	(39)	28	(10)		
35-44	57	(8)	13	(23)		
45-54	16	(2)	5	(31)		
≥55	9	(1)	3	(33)		
Sexual Orientation						
Bisexual	20	(3)	4	(20)		
Homosexual	6	(0.8)	1	(17)		
Heterosexual	311	(42)	43	(14)		
Not Recorded	411	(55)	54	(13)		
Number of Partners						
1	32	(4)	2	(6)	0.22	1.5
2-10	459	(61)	69	(15)		
11-20	77	(10)	15	(20)		
≥21	180	(24)	16	(9)		
Condom Use						
Always	45	(6)	11	(24)	0.13	2.3
Sometimes	362	(48)	56	(16)		
Never	199	(27)	27	(14)		
Not Recorded	142	(19)	8	(6)		
Antibiotic Treatment						
AAPD	650	(87)	95	(15)	0.98	0.001
AAPD & Metronidazole	2	(0.3)	1	(50)		
Other Antibiotics	30	(4)	4	(13)		
Not Specified	66	(9)	2	(3)		
AAPA	0	0	-	-		
AAPA & Metronidazole	0	0	-	-		

Discussion

This study provides original data of the very high incidence of urethral discharge among males in Fiji. The majority of cases occurred among young adults (14 to 34 years). The majority of cases reported more than one sexual partner and did not always use a condom. Recurrence was recorded in 14% over the next 1 to 2 years. These data compare to findings of a systemic review by Fung which showed repeat chlamydial infection among men had a median re-infection probability of 11% whereas repeat gonococcal infection among men had a median re-infection probability of 7%.[6]

No association was noted between at-risk behaviors and recurrence. This may be due to the fact that the reported risk factors relied on a subjective view of the client's own sexual behaviors. A large proportion of the men did not disclose sexual orientation or these data were not recorded. Further, it was observed that most specimens sent for laboratory investigation did not identify a pathogen.

Improving specimen collection with efficient Gram staining may improve the aetiological diagnosis of gonococcal infection as the yield from Gram stain is usually higher than from culture for this fastidious organism. Improving specimen collection of first void urine test can also potentially improve the diagnosis of *C. trachomatis*. NAAT of first void urine (FVU) has become the test of choice for the diagnosis of urethral *C. trachomatis* infection in men, since it is noninvasive and allows the detection of infected epithelial cells and associated *C. trachomatis* particles.[7]

It was noted that majority (87%) of the cases were treated with AAPD. It is not known whether adapting the current recommended guidelines of AAPA would reduce the rate of recurrence. There is a need to educate STI clinicians about national guidelines and once practice is changed, it would be worthwhile to conduct a prospective study of recurrence.

There are a number of important limitations. The data do not represent the full national burden of disease in 2011 as the Northern Clinic was excluded due to low availability of records for evaluation. Nonetheless the data do represent the population of the two largest divisions in Fiji, representing 79% of the total male population (301,531) of the age greater than 14. Further, published literature states that reported disease rates underestimate the true burden of infection because the majority of STIs are asymptomatic and because of underreporting.[8]

Data were collected retrospectively and relied on self-reporting, accurate disclosure and clinician accurately entering data. Therefore, there are many potential opportunities for inaccuracy of data that cannot be validated. Data of important risk factors such as HIV infection were not available. The overall prevalence of HIV among adults 15–49 years of age in Fiji is 0.2%,[10] with 0.5% prevalence among men having sex with men.[9]

The large burden of disease suggests that there should be a major focus on strategies that could prevent STIs such as gonococcal and chlamydial infections—known strategies that are also likely to reduce the risk of other important STIs such as syphilis and HIV.

Competing interests: Nil.

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ORIGINAL ARTICLE

Barriers to early initiation of antenatal care in a multi-ethnic sample in South Auckland, New Zealand

Sarah Corbett, Carol Chelimo, Kara Okesene-Gafa

Abstract

Aim To identify barriers to early initiation of antenatal care amongst pregnant women in South Auckland, New Zealand.

Method Women in late pregnancy (>37 weeks gestation) or who had recently delivered (<6 weeks postnatal) completed a questionnaire about their antenatal care. Logistic regression analysis evaluated whether late booking for antenatal care was associated with demographic factors and potential barriers to accessing care.

Results Of the 826 women who participated, 137 (17%) booked for antenatal care at >18 weeks (late bookers). The ethnic composition of the sample was: 43% Pacific Peoples, 20% Māori, 14% Asian, and 21% European or other ethnicities. The multivariate analysis indicated that women were significantly more likely to book late for antenatal care if they had limited resources (OR=1.86; 95% CI=1.17–2.93), no tertiary education (OR=1.96; 95% CI=1.23– 3.15), or were not living with a husband/partner (OR=2.34; 95% CI=1.48–3.71). In addition, the odds of late booking for antenatal care was almost six times higher among Māori (OR=5.70; 95% CI=2.57–12.64) and Pacific (OR=5.90; 95% CI=2.83–12.29) women compared to those of European and other ethnicities.

Conclusion Late booking for antenatal care in the Counties Manukau District Health Board area (South Auckland) is associated with sociodemographic factors, social deprivation, and inadequate social support.

The National Institute for Health and Care Excellence (NICE) guidelines recommend that all women should commence maternity care before 10 weeks gestation.[1] This offers the opportunity to screen for sexually transmitted infections, family violence, maternal mental health issues and congenital abnormalities. It also allows for early recognition of underlying medical conditions that may impact on the pregnancy, as well as an opportunity to provide education about nutrition, smoking and drug use during pregnancy. Under-attendance and non- attendance for antenatal care has been linked to poor pregnancy outcomes, including low birth weight and foetal or neonatal death.[2-4]

The Fifth Annual Report of the Perinatal and Maternal Mortality Review (PMMR) Committee released in July 2011 indicated that barriers to accessing or engaging with maternity and health services were the most common factors contributing to perinatal mortality.[5] This report also found that Māori and Pacific mothers, women from the most deprived socioeconomic quintile, and teenage mothers were more likely to have stillbirths and neonatal deaths.

In overseas studies, demographic factors shown to be associated with late booking for or inadequate antenatal care include: minority ethnic group,[6-8] low educational level,[6,9] age under 20 years or over 35 years,[9] multi-parity,[9] residing in areas with few antenatal care providers (inner city or rural),[10,11] and low socioeconomic status.[12]

There is a paucity of research on barriers to early initiation of antenatal care in the New Zealand (NZ) context. Given New Zealand's unique population and maternity system, conclusions drawn from overseas research may not be generalisable to NZ. In the one study previously conducted in Pacific women residing in the Counties Manukau District Health Board (CMDHB) catchment area, high parity, first pregnancy, unemployment prior to pregnancy and Cook Island ethnicity were associated with late initiation of antenatal care.[13]

CMDHB serves the most economically deprived areas of New Zealand, with a high proportion of young mothers, and women of Māori and Pacific ethnicity. There is a high rate of late booking for antenatal care; in 2000, 26% of mothers of Pacific infants in CMDHB booked after the 15th week of pregnancy.[13] CMDHB also has the highest perinatal mortality rate in New Zealand with a 3-year perinatal-related mortality rate of 13.70 per 1000 births compared with the national rate of 10.75 per 1000 births.[5]

This study aims to identify barriers to early initiation of antenatal care among women utilising CMDHB maternity services, by surveying a sample of women in late pregnancy (>37 weeks gestation) or who have recently delivered (within 6 weeks). Identifying these barriers provides the CMDHB an opportunity to find more targeted approaches in providing antenatal care to women at greatest need in the community it serves.

Methods

This cross-sectional study was undertaken at CMDHB maternity facilities during July to September 2011. In order to ensure recruitment of a representative sample, participants were sought from women attending all CMDHB facilities. A convenience sample comprising of pregnant women at >37 weeks gestation and postnatal women within 6 weeks of delivery were invited to complete the questionnaire. All participants gave informed written consent. The study protocol was approved by the Northern Y Regional Ethics Committee (NTY/11/EXP/026) and the Māori Research Review Committee.

Options for maternity care in CMDHB area at the time of the study included: 1) Lead Maternity Carer (LMC) such as a self-employed midwife, general practitioner (GP) or private obstetrician; 2) DHB bulk-funded primary maternity services (such as community midwives or Shared Care); and 3) Referrals to secondary care for women identified as high risk, which includes both the Obstetric Medical Clinic and Diabetes in Pregnancy Service. Shared Care is a unique system that developed in CMDHB in response to a shortage of self-employed LMCs. Women in the Shared Care model receive most of their antenatal care from a GP who enters into a shared care arrangement with the DHB. In addition, these women are offered three antenatal visits with a DHB-employed community midwife and are delivered at a CMDHB facility by a DHB-employed midwife. GPs providing Shared Care are not currently required to have either specific training in antenatal care or a postgraduate Diploma of Obstetrics and Gynaecology.

Women were eligible to participate if they were >37 weeks pregnant or had delivered within 6 weeks (<6 weeks postnatal). Potential participants were identified for recruitment while seeking antenatal care, or labour and postnatal care. Eligible women were invited to participate by consultants, registrars, house officers, hospital midwives, maternity nurses, breastfeeding educators, health care assistants, and self-employed midwives. Interpreters were offered to women who did not speak English. For eligible women who at discharge had not completed the questionnaire, one was mailed their home address with a prepaid envelope to facilitate its return. Women residing outside the Counties Manukau area who had booked to deliver elsewhere were excluded.

Questionnaire design was guided by a literature review of comparable studies in other countries, as well as clinicians' experiences in CMDHB antenatal care settings. A pilot of the questionnaire was undertaken with 10 women, all of whom were late bookers, with English as a second language. After completing the questionnaire, the women were interviewed about barriers to care and the questionnaire's ease of use and understanding. Responses provided on the questionnaire were compared to qualitative interviews to ensure consistency and comprehension.

The questionnaire collected data on: demographic factors (age, ethnicity, education level, parity, relationship status); National Health Index (NHI) number and date the questionnaire was completed (in order to avoid duplication); gestation when pregnancy was first diagnosed and at booking with a Lead Maternity Carer; the number of visits to a midwife or doctor for pregnancy care; knowledge about the need for care during pregnancy; and specific barriers to antenatal care. In addition, qualitative data was obtained using open-ended questions to allow participants to comment on the difficulties faced in getting antenatal care and what would ease this.

Information obtained from the participants' electronic health records included: due date, baby's date of birth, gravidity, parity, eligibility for free maternity care, date of the initial antenatal booking visit, and with whom women had booked antenatal care (self-employed midwife, shared care, closed unit or case-loading midwife).

Late booking was defined as booking for antenatal care with any healthcare provider after 18 weeks gestation, which was based on self-report. The discrepancy in the gestation at booking obtained through self-report versus that noted in the hospital registration form was determined; this illustrated the unreliability of using hospital registration form data when ascertaining the number of women who book late.

The majority of published studies have used a cut-off of 12 or 14 weeks to define late booking, as it is recommended that antenatal care start in the 1st trimester.[14] However, with the current maternity system at CMDHB, many women see their GP in the first trimester to diagnose pregnancy, and to make arrangements to have blood tests and ultrasound scans before finding a midwife for ongoing care.

Since many midwives will not schedule a booking visit until after 15 weeks gestation (but almost always before 18 weeks), defining late booking as >12 weeks gestation will include a large proportion of women who have had adequate antenatal care. Therefore, in this study 18 weeks was chosen as an appropriate cut-off as by then, women with access to adequate care should have been booked.

The sample size was estimated based on data obtained from an audit of all hospital registration forms completed at CMDHB between 1 August 2008 and 31 July 2009 (n=8423). This audit showed that of the 7093 women registered to deliver at Middlemore Hospital, 2777 (39%) registered after 18 weeks of gestation. It was estimated that a sample of 800 women would be required to detect an odds ratio of 1.75 with 80% power. Sample demographics were compared after recruiting 100, 300, 500 and 800 women to check for consistency.

Demographic characteristics were described for the total study sample (n=826). For participants with information on gestation at booking for antenatal care (n=767), the Chi-squared test was used to assess whether late booking for antenatal care was related to each demographic factor and potential barrier to accessing care. From this analysis, variables significantly associated with late booking for antenatal care were considered as covariates for multivariate logistic regression analysis.

Associations between all covariates were determined to avoid using similar/collinear covariates in the multivariate model. For instance, given the significant positive association between maternal age and parity as well as the higher proportion of missing data on parity than maternal age (10% vs. 1.3%), maternal age (but not parity) was entered into the multivariate model. In addition, a variable ("limited resources") was created using four associated variables to capture information on women's lack of one or more of the following: transport; childcare; phone credit or phone; and money for clinic visits/scans. The most parsimonious multivariate logistic model (n=705) was selected based on Akaike's information criterion and the results summarised using odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed using SAS® version 9.3 software (SAS Institute Inc., Cary, N.C., USA).

Results

Of the 826 women participated in this study, 137 (17%) booked for antenatal care at >18 weeks (late bookers) and 630 (76%) booked at ≤18 weeks; for the remaining 7%, data on gestation at antenatal care booking was unavailable.

The ethnic composition of the sample was as follows: 43% Pacific Peoples, 20% Māori, 14% Asian and 21% European or other ethnicities (Table 1). This was fairly comparable to the ethnicity of women who registered to deliver at Middlemore Hospital in August 2008 through July 2009 (38% Pacific, 22% Māori, 13% Asian and 27% European/other ethnicities). Most of the women had either secondary or tertiary education and were eligible for free maternity services. A little less than a quarter did not live with a husband/partner.

Upon learning about their pregnancy, most women initially sought care from a GP (72%) or midwife (19%). Compared to the overall sample, the group booking late for antenatal care had a higher proportion of women of Pacific ethnicity, aged <20 years, with secondary education, not living with a husband/partner, with ≥3 children, and ineligible for free maternity services.

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In the univariate analysis, late booking for antenatal care was significantly associated with several demographic factors (Table 1) and potential barriers to accessing care (Table 2). Factors unrelated to late booking for antenatal care (Table not shown) were: help from GP to find pregnancy care; the source of initial pregnancy care (GP, midwife or other care); learning about an LMC from friends/family; having the same LMC as in the previous pregnancy; spending a long time in waiting rooms during appointments; and forgetting appointments.

Table 1. Characteristics of the study population

Variable	Total (n=826)	*Late booking for antenatal care		
		No (n=630)	Yes (n=137)	
	n (%)	n (%)	n (%)	†p-value
Ethnicity (prioritised)				
Māori	166 (20.1)	116 (18.4)	40 (29.2)	<0.001
Pacific	357 (43.2)	245 (38.9)	85 (62.0)	
Asian	119 (14.4)	111 (17.6)	4 (2.9)	
European & Other	173 (20.9)	156 (24.8)	7 (5.1)	
Maternal age				
Under 20 years	88 (10.7)	51 (8.1)	29 (21.2)	<0.001
20-24 years	189 (22.9)	141 (22.4)	34 (24.8)	
25-29 years	200 (24.2)	164 (26.0)	28 (20.4)	
30-34 years	187 (22.6)	151 (24.0)	26 (19.0)	
35 years or more	151 (18.3)	121 (19.2)	19 (13.9)	
Maternal education				
Primary / no formal education	40 (4.8)	25 (4.0)	7 (5.1)	<0.001
Secondary (high school)	384 (46.5)	269 (42.7)	91 (66.4)	
Tertiary (University/Tech)	369 (44.7)	325 (51.6)	31 (22.6)	
Living with a husband/partner				
No	163 (19.7)	97 (15.4)	54 (39.4)	<0.001
Yes	649 (78.6)	531 (84.3)	82 (59.9)	
Parity				
Nulliparous	271 (32.8)	209 (33.2)	47 (34.3)	0.001
1-2 children	304 (36.8)	244 (38.7)	36 (26.3)	
3 or more children	169 (20.5)	114 (18.1)	43 (31.4)	
Eligible for free maternity				
No	20 (2.4)	12 (1.9)	8 (5.8)	0.019
Yes	724 (87.7)	553 (87.8)	120 (87.6)	

NOTE: Counts and percentages may not add up to totals due to missing data

* Gestation at antenatal care booking was unavailable for 59 (7%) women

† Chi-squared test or Fisher's exact test

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Table 2. Late booking for antenatal care in relation to potential barriers to accessing care in pregnancy (n=767)

Variable	Late booking for antenatal care		
	No (n=630)	Yes (n=137)	
	n (%)	n (%)	†p-value
Aware of need to choose/register with LMC			
No	144 (22.9)	46 (33.6)	0.006
Yes	483 (76.7)	88 (64.2)	
Experienced difficulty finding an LMC			
No	495 (78.6)	89 (65.0)	0.001
Yes	96 (15.2)	31 (22.6)	
Did not try	37 (5.9)	17 (12.4)	
Hard to understand doctor/midwife			
No	572 (90.8)	116 (84.7)	0.015
Yes	50 (7.9)	20 (14.6)	
Lack of money for clinic visits/scans			
No	590 (93.7)	109 (79.6)	<0.001
Yes	31 (4.9)	25 (18.3)	
Lack of transport (car)			
No	552 (87.6)	92 (67.2)	<0.001
Yes	69 (11.0)	44 (32.1)	
Lack of childcare			
No	572 (90.8)	103 (75.2)	<0.001
Yes	49 (7.8)	33 (24.1)	
No of phone credit/phone to make appointment			
No	574 (91.1)	115 (83.9)	0.002
Yes	45 (7.1)	21 (15.3)	
Too busy to go to appointments			
No	572 (90.8)	106 (77.4)	<0.001
Yes	48 (7.6)	27 (19.7)	
Unable to get appointment at suitable time			
No	555 (88.1)	102 (74.5)	<0.001
Yes	66 (10.5)	34 (24.8)	
Moved house during pregnancy			
No	540 (85.7)	107 (78.1)	0.013
Yes	81 (12.9)	29 (21.2)	

NOTE: Counts and percentages may not add up to totals due to missing data
† Chi-squared test

The multivariate analysis identified factors independently associated with late booking for antenatal care (Table 3). The adjusted analysis indicated that the odds of late booking were approximately two times higher among women with limited resources, with no tertiary education, and not living with a husband/partner. In addition, the odds of late booking for antenatal care was almost six times higher for both Māori and Pacific women compared to those of European and other ethnicities.

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Table 3. Logistic regression analysis for late booking for antenatal care (n=705)

Variable	Late booking for antenatal care		
	Yes (n=121)	Unadjusted OR	Adjusted OR
	n (row %)	(95% CI)	(95% CI)
*Limited resources			
No	73 (13.1)	Reference	Reference
Yes	48 (32.2)	3.14 (2.06, 4.80)	1.86 (1.17, 2.93)
Ethnicity (prioritised)			
Māori	37 (26.2)	9.88 (4.61, 21.20)	5.70 (2.57, 12.64)
Pacific	75 (24.6)	9.06 (4.43, 18.50)	5.90 (2.83, 12.29)
Non-Māori, Non-Pacific	9 (3.5)	Reference	Reference
Maternal education			
None/ Primary/Secondary	90 (24.7)	3.26 (2.10, 5.06)	1.96 (1.23, 3.15)
Tertiary (University/Tech)	31 (9.1)	Reference	Reference
Living with a husband/partner			
No	46 (34.1)	3.41 (2.22, 5.25)	2.34 (1.48, 3.71)
Yes	75 (13.2)	Reference	Reference

NOTE: All variables in the table are adjusted for each other
CI=confidence interval; OR=odds ratio
*Includes lack of one or more of the following: transport; childcare; phone credit or phone; and money for clinic visits/scans

It was not possible to determine the late booking status for 7% (n=59) of the sample as data on gestation at initiation of antenatal care was unavailable. There were no significant difference between women missing data on gestation at initiation of antenatal and those with valid values (Chi-squared test, Table not shown) on the following demographic variables: ethnicity (p=0.42, n=815); age group (p=0.42, n=815); having husband/partner (p=0.38, n=812); parity (p=0.53, n=744); and eligibility for free maternity services (p=0.39, n=744). However, these two groups differed on maternal education (p<0.001, n=793) whereby the proportion of women with a tertiary education was greater in the group with data on gestation at booking compared to the group missing this data (48% vs. 29%). Given the results from this study show that women without tertiary education are more likely book late for antenatal care, the magnitude of this association has likely been underestimated.

Discussion

Findings from this study show that women with limited resources, with no tertiary education, or not living with a husband/partner are at a greater disadvantage when it comes to timely booking for antenatal care. Māori and Pacific women are also much more likely to book late for antenatal care than women of European and other ethnicities. This suggests that late booking for antenatal care in CMDHB is likely due to sociodemographic factors, social deprivation, and inadequate social support. Our findings are consistent with research undertaken to assess factors related to untimely initiation of prenatal care among women in high-income countries who reside in disadvantaged areas. This research has identified some comparable barriers including, inadequate social support,[15-18] lower maternal educational level,[15,18-20] economic hardships,[15,17,20] and transportation and access difficulties.[19,21]

The main strength of this study is its large multi-ethnic sample size, which adds to a small body of existing literature regarding antenatal care in this NZ population. It also provides additional insight and information to guide local system design and policy. However, it must also be recognised that the characteristics of the CMDHB resident population are different to other parts of NZ, which would limit generalisability of findings to the rest of country. Nonetheless, our findings would be applicable to women in high-income countries who reside in disadvantaged areas. There is no current NZ

guideline on when antenatal care should commence and hence, a cut-off was chosen in line with other literature that used 18 weeks as a definition of very late booking.[22]

A study limitation is the unavailability of a response rate due to lack of information on the number of women approached for recruitment and who declined participation. Our study relied on participant recall of gestation at pregnancy diagnosis and booking, which may be subject to misclassification bias that we expect occurred indiscriminately. Because of the large number of participants, a quantitative design was chosen which may mean that some novel barriers were not identified. A validated, standardized and widely used questionnaire was not available limiting the extent to which this study's findings could be compared to previous research.

Given the barriers to timely initiation to antenatal care identified in this study, maternity care providers may consider more flexible models of care and ways of delivering care within the community. This could be done via home visits, after hour's clinics, and having midwifery clinics within GP practices in the local community. Location of hospitals and clinics should be considered when planning public transport routes or vice versa. In order to provide the best care to a multi-ethnic population, it is vital to continue to actively recruit and train multi-ethnic medical and midwifery staff, ensure interpreters are available, and provide written information in a range of languages.

Interventions are needed to improve the early diagnosis of pregnancy which could lead to more timely initiation of antenatal care. This may include emphasis on the importance of school health programs that educate girls about normal menstruation and seeking medical attention for missed or abnormal periods, as well as consideration of ways to extend this knowledge to adult women. Options should be explored for making pregnancy tests more freely available.

Currently, women have free visits to their GP if the pregnancy test is positive, but have to pay for the consultation if the test is negative. Public health interventions are needed to improve specific knowledge on the importance of seeking care early and how to go about getting care. The general practitioner is an important facilitator of maternity care in our study population, being the first point of contact for many women. By using pre-existing networks, consultation regarding current unmet needs can be undertaken, and strategies to facilitate early risk assessment and support timely access to maternity services can be disseminated.

There is a need for robust pregnancy data collection and management in order to be able to accurately assess the proportion of women booking late for antenatal care, which would enhance the success of any future interventions. Currently, it is not possible to use existing data collection processes to accurately identify the number and characteristics of the women who book late for pregnancy care. With an improvement in the maternity data collection systems, further research could address whether the rates of late booking seen in Pacific and Māori women are accounted for primarily by higher levels of socioeconomic deprivation, or if there are also elements within the current system that are not culturally appropriate. Research among women who have a late diagnosis of pregnancy and factors associated with this would help inform public health strategies to reduce this problem.

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VIEWPOINT

The importance of measuring unmet healthcare needs

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Abstract

Major restructuring of the health sector has been undertaken in many countries, including New Zealand and England, yet objective assessment of the outcomes has rarely been recorded. In the absence of comprehensive objective data, the success or otherwise of health reforms has been inferred from narrowly-focussed data or anecdotal accounts. A recent example relates to a buoyant King's Fund report on the quest for integrated health and social care in Canterbury, New Zealand which prompted an equally supportive editorial article in the *British Medical Journal* (*BMJ*) suggesting it may contain lessons for England's National Health Service. At the same time, a report published in the *New Zealand Medical Journal* expressed concerns at the level of unmet healthcare needs in Canterbury. Neither report provided objective information about changes over time in the level of unmet healthcare needs in Canterbury.

We propose that the performance of healthcare systems should be measured regularly, objectively and comprehensively through documentation of unmet healthcare needs as perceived by representative segments of the population at formal interview. Thereby the success or otherwise of organisational changes to a health system and its adequacy as demographics of the population evolve, even in the absence of major restructuring of the health sector, can be better documented.

The problem

In 1938 the Social Security Act for health care was passed in New Zealand with the aim of creating universal access to a comprehensive national health service in which barriers to accessing required healthcare, including financial, would be removed. Ten years later the National Health Service (NHS) with similar aims was enabled in the United Kingdom.[1]

Major restructuring of the health sector has occurred, sometimes at frequent intervals, in these and many other developed countries, yet documentation of the overall success (or otherwise) of these changes has often been ignored even though they can produce unintended consequences. For example, 4 years after initiation of radical healthcare restructuring in New Zealand in 1993 there had been no formal, comprehensive review of achievements and outcomes.[2] However, predicted outcomes of the market oriented alternative to state control in New Zealand, such as hospital profits and provider competition, failed to appear. Meanwhile, positives, such as better organisation of general practice, improvements in Māori health organisation, and creation of the national pharmaceutical purchasing agency (PHARMAC), which did eventuate were unforeseen.[3]

The 1990s "big bang" approach to structural change, utilised under New Zealand's unicameral political system, seems more likely to produce results that are unpredictable than an incremental approach to change which is more typically undertaken in countries with a bicameral political system.[3] In England, reorganisation (or breakup) of the NHS is underway with fears that, despite its bicameral political system, privatisation will play a prominent role.[4]

In the absence of broad-based objective data collected routinely on an ongoing basis, ratings of the outcome of such policy changes or a health system *per se* can be readily reported as anywhere from superlative (usually by political leaders and public officials) to a dismal failure—often via anecdotal patient or health professional experience.

In this brief article, we contend that in predominantly tax-funded systems with goals such as those of New Zealand and England, unmet healthcare need should be defined and included in any performance assessment.

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This should apply across restructuring of the health sector, following the implementation of new models of care whatever their objective, and even in the absence of modifications in the health system when changes in population demographics can alter health requirements substantially. We note the potential for unbalanced reporting in its absence, and describe some ways in which unmet need could be measured.

A recent example of the problem

Inadequacies in assessing the performance of a healthcare system were brought home to us recently. On the one hand, a King's Fund investigation reported in 2013 that over some 5 years the District Health Board in Canterbury, New Zealand "*..has moved towards (a more integrated system of healthcare) that manages demand more effectively in primary care and allows the hospitals to run more efficiently, thus concentrating more of their care on those who actually need to be in hospital*".[5] This report formed the basis for an editorial article in the British Medical Journal (BMJ) which suggested that the Canterbury experience offers several insights for the National Health Service (NHS) in England.[6]

On the other hand a perceived serious and possibly increasing level of unmet healthcare need in the same Canterbury region has seen the establishment of the Canterbury Charity Hospital. A recent three year (2010–2012) review of this places on record the services, mostly surgical, provided to patients unable to access treatment in the public system and who could not afford private care.[7] This review noted that, beyond the hundreds of patients treated, many appointment requests to the Charity Hospital were rejected because volunteer services in some specialties were not available. The experience of the Charity Hospital led to the conclusion that there are "… *substantial, undocumented unmet healthcare needs in the region*."[7]

The former report by the King's Fund[5] and the BMJ editorial[6] suggest that substantial improvements in healthcare in Canterbury have occurred whilst the latter article on the Charity Hospital suggests that, across the same time period, unmet healthcare needs in the region are "*alarmingly high*".[7] Neither report is particularly helpful in assessing the overall effectiveness or otherwise of changes to the organisation of healthcare services in Canterbury.

We agree with the key comment in the King's Fund report that "*Canterbury is far from alone in facing the challenge of measuring the impact of more integrated care*".[5] In our view the moral (and fiscal) imperative dictates that no major reform of a healthcare system should be considered, let alone implemented, in the absence of measuring its impact on a broad canvas of healthcare needs, including unmet need, in the target population.

We also assert that unmet healthcare needs should be a core component of any health system assessment, even in the absence of major restructuring or the implementation of new models. This is for the simple reason that failure to meet such needs, particularly for medical and surgical services, is in breach of a basic human right to good health and healthcare.

The way forward

We concur with the growing body of research indicating that the performance of a healthcare system should be measured regularly, objectively and comprehensively by a body at arm's length from, and preferably independent of, the healthcare system.[8,9] This, however, is easily stated but less easily implemented with a wide range of possibilities and different combinations when it comes to approach and indicators that could be used.[10,11]

Generally speaking, there are three different sources of information: routine data relating to service coverage, scope and costs, and the incidence of disease; reports from healthcare professionals; and reports from patients. Often these are considered together, as in measurement of hospital performance, but none is ideal and frequently there is an absence of one of the three aforementioned perspectives on performance.

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For example, some indices built from routine data (longevity, perinatal mortality rate, the number of emergency medical admissions, readmission rates and childhood inoculation rates, for example) are important and readily quantified—but provide a narrow perspective of overall health delivery in a community.

When it comes to health professional reported data, estimating patient access to services is problematic,[12] can be readily manipulated, and cannot alone be relied upon to provide robust data.[13] It may be possible for medical professionals to provide accurate information regarding the status of their patients across periods of reform or collectively raise concerns when standards of care are unacceptable. However, the inadequate performance of health professionals in the Mid Staffordshire events highlights the problems associated with such reporting.[14,15]

As is now well known, conditions of appalling healthcare flourished in the main hospital of the Mid Staffordshire NHS Foundation Trust between 2005 and 2008, amid cost cutting and a drive to meet government targets, yet the response of health professionals was inadequate. It would be naïve to consider that the situation in Mid Staffordshire was and is unique. As working relationships (including employment links) between medical staff in primary and secondary care in particular change over time, so perceptions by medical staff of patient needs will inevitably alter with time.

Accordingly, data, provided by medical and other healthcare staff, can be insightful but, if not standardised and collected in accordance with carefully defined criteria, need to be viewed with a degree of caution.

From a patient's perspective there are possibly three core elements to a health care system which should be measured; accessibility, timeliness and quality of care. The first and second incorporate unmet need whilst the third, quality of care, is readily quantified by, for example, readmission rates and other quantitative indicators, and is also amenable to process and experience measurement.

In our view, the centre point to assessing the performance of a healthcare system should utilise documentation of unmet healthcare needs as perceived by representative segments of the population at formal interview. At present, various agencies and research groups have attempted this, some in a robust and objective manner[16,17] and some with sometimes questionable methods, for example, a tele-marketing approach of phoning individuals until a quota is reached.[18] While providing a reasonable snap-shot of unmet need in different countries, such studies can easily be disregarded by policy-makers.

A representative study of unmet need should involve selection of a random sample identified using robust statistical sampling procedures rather than accessible and potentially biased samples of convenience which characterise many of the 'patient exit' and other surveys conducted by healthcare providers.

Representative interviews, we suggest, should be repeated regularly and cover all aspects of unmet healthcare needs including dental, psychiatric, birth control and disability, as well as unmet general medical and surgical needs. The interview protocol should, ideally, be identical across many countries to enable time-matched comparisons between different healthcare systems and longitudinal assessments of the effects of organisational changes within any one country, as advocated by agencies such as the OECD but not yet achieved.[19]

With this approach healthcare sector performance with regard to unmet need could be assessed, first, by documenting changes within the country over time and across any restructuring period and, second, by comparing changes in unmet need between countries some of which did not undergo restructuring.

As a starting point we suggest that population based sampling methods such as those used by The New Zealand Health Survey and others could be the basis for such surveys.[16 17 20] Currently the New Zealand example of a national Health Survey captures data on, amongst other things, health utilisation and management of diagnosed medical conditions, but does not attempt to measure the core elements

of unmet need: undiagnosed conditions or conditions for which health care has been sought but has not been provided.

Questions about avoiding health care due to financial barriers were asked in a related New Zealand government-sponsored Survey of Family, Income and Employment but did not assess the specific conditions for which healthcare needs were not met and was, in any case, discontinued in 2010.[21] Surveys of this kind, coupled with information from healthcare providers, especially general practitioners, could provide robust estimates of unmet need and potentially identify specific problematic conditions, as well as identify demographic features of those most likely to be affected. In this way, there would be capacity to bring together a range of measures from the three different information vantage-points cited above in developing new methods for assessing unmet need, which also meet with suggested benchmarks for this.[22]

It is important that the range of measures used be standardised to avoid the possibility of a positive, but limited, finding as indicating general good health of a healthcare system. Of course, it is possible that variables from Statistics New Zealand's Integrated Data Infrastructure could also be drawn upon.

While for a different population and component of its healthcare system, the United States Centers for Medicare and Medicaid Services (CMS) has demonstrated that it is possible to implement a nation-wide standard survey of a random sample of public and private hospital patients (the Hospital Consumer Assessment of Healthcare Providers and Systems—or HCAHPS).[23] The government of Thailand has similarly commissioned a random household survey focused specifically on unmet need for healthcare services.[17]

It is time now for policymakers in New Zealand, England and elsewhere to follow suit in further developing such techniques and extending them beyond only patients who have been able to access hospital care.[22] In this way, they may be able to respond to the need to better understand and comprehensively measure the important and unexplored issue of unmet need for healthcare in our communities. Without this, goals of delivering on fundamental human rights to good health, as well as robust health system performance measurement, cannot be delivered.

The result will be the continued delivery of reports such as the King's Fund's[5,6] that provide what is perhaps an important story, but present only one facet of the reality.

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VIEWPOINT

Pathways to health and wellbeing for Pacific children—how are we tracking?

Fa'asisila Savila, Elaine Rush

Abstract

The government's 5-year strategy for improving Pacific people's health and wellbeing, *'Ala Mo'ui Pathways to Pacific Health and Wellbeing 2010–2014*, emphasised disease prevention and improvements in health systems as priority outcomes. Actions that would contribute to disease prevention included reducing barriers to health in structural mechanisms (such as better access to healthy housing) and improving health service systems. However, after 4 years since its release, not only have important structural barriers remained but so have the poor health outcomes of Pacific peoples in New Zealand.

Government commitment to Pacific health

The document *'Ala Mo'ui Pathways to Pacific Health and Wellbeing 2010–2014* set out the government's priority outcomes and actions that would contribute towards achieving better health outcomes for Pacific people.[1]

Recognition of the importance of prevention was mentioned, "[w]e know that for many of the health issues of greatest concern, downstream treatment costs can be reduced through effective prevention and protection" (p11); and it was promising to see children and families as being critical components of the equation.

Urgent themes for achieving better health outcomes for Pacific peoples were both explicit (e.g. improving nutrition and increasing physical activity) and implied (e.g. reducing risk factors such as obesity). However the salient issue of maternal health was completely missing, despite the authors citing relevant literature.[2] An omission of the importance of the health of mothers reveals a potentially crucial disconnect between the Pacific health strategy and its aims of supporting healthier children resulting in a healthier population overall.[3]

The document states that elimination of poverty is desired for the Pacific region by way of international aid and this is admirable. For New Zealand, however, the message is less clear as the intentions are focussed on improving broader structural issues such as education, employment, income and housing. This is an ambitious approach, as it requires significant collaboration between government ministries. But is this level of collaboration achievable and realistic?

Additionally, *'Ala Mo'ui* speaks very generally of intentions to improve health services and systems, but specifically how this is meant to be achieved is also unclear.

Structural mechanisms and health for Pacific peoples

Given the commitments of *'Ala Mo'ui* and that we are drawing close to the end of the strategy's timeline, what are the structural circumstances and how has the Pacific community fared over this time?

Perhaps the most critical issue is the level of poverty experienced among the nation's children which is unacceptably high at around 21%, or over a-quarter of a million (approximately 270,000).[4] About half (47%) of these children were either Māori or Pacific, equivalent to 34% of all Māori and Pacific children living in poverty by 2011.[4]

The Salvation Army report on the state of Pasifika people in New Zealand also provides some insight into how conditions have tracked over time.[5] (The terms Pasifika and Pacific are used interchangeably in the report).

Evidence of escalating inequity is in the more than five-fold increase in Pasifika families approaching the Salvation Army for food parcels in 2012 compared to 2007 (p27). Participation in social food programmes is an indication of the high rate (70%) of food insecurity in Pacific homes,[6] and both of these are indicators of relative poverty and financial hardship.[7]

Citing *Household Labour Force Survey* data, the Salvation Army report highlights that, in spite of the country's relatively stable unemployment rate from December 2009 to December 2012 (from 6.5% to 6.9%), Pasifika unemployment remained consistently high, going from 14% to 16% in the same period. In terms of age, the highest rates of unemployment were seen in the youngest working age group 15-24 years with Pacific (29%) and Māori (28%) double that of European (14%).[8]

Increasing income inequality for those in employment was evident in the growth of the income gap between Pacific and non-Pacific. For the average weekly income between the two groups in 2007, Pacific were already receiving $190 less than non-Pacific ($477 cf. $667 respectively). This income difference increased to $240 by 2012 ($479 cf. $721 respectively). The non-Pacific average weekly income increased by $54 whereas Pacific incomes increased by only $2.

Lower incomes and poverty have been attributed to increased stress, poorer food (nutrition) availability,[9] and obesity in women and children.[10] This is in the context of nutrient-rich foods being more expensive than the nutrient-poor, energy-dense and more filling food options.[10]

Lower incomes also have a negative effect on housing affordability, quality and home ownership, exacerbated by an ongoing decline in social housing.[12] Current real estate data show that in South Auckland, where most Pacific people live, house prices have increased rapidly by around 30% since 2011.[13]

Hargreaves cites a recent OECD report which found that of the 34 countries in the OECD, New Zealand was the second most expensive country to buy a home and the least affordable place to live in terms of price to income.[14,15] Evidence of this is borne out in the 2013 Census where individual home ownership in the total population had fallen to just below half (49.9%), from 54.5% in 2006.[16,17]

Pacific individuals were less likely to own a home with less than one-fifth (18.5%) reporting ownership, compared with over one-quarter for Māori (28.2%), over one-third for Asian (34.8%) and more than half of all Europeans (56.8%).[18]

The outcome

The culmination is that after four of the 5 years of *'Ala Mo'ui*'s strategy period, the structural mechanisms that would help contribute to better health outcomes for Pacific people remain, in general, worse than that of non-Pacific.[19,20]

Positive signs could be the recently reported achievements in the National Standards' assessments for mathematics, reading and writing among young Pasifika children.[21] However, there are some apparent setbacks to the positive data. First, as children age, educational performance is declining.[21,22] This means that the curriculum or the National Standards assessments are not preparing Pasifika children for secondary school and that modifications need to be made to meet the educational needs of children and families. Second, education leaders say the data are unreliable because of the potential for measures to be assessed subjectively by individual schools,[23,24] calling into question the overall integrity of the data. Thirdly, and more pertinently, the education achievement disparities between Māori/Pacific and non-Māori/Pacific students remain high.

For Pacific an approximately 20 percentage-point lower achievement difference existed for all three National Standards' subjects, reading (64.1% vs. 84.1%), mathematics (60.8% vs. 79.8%) and writing (57.6% vs. 76.3%) when compared with Pakeha/European school children (years 1 to 8).[21]

Finally, there is a lack of evidence of better health and wellbeing outcomes as envisioned by *'Ala Mo'ui*. Current prevalence of type-2 diabetes mellitus among Pacific people is high compared to other ethnic groups and incidence in younger Pacific will continue to increase largely due to high rates of obesity.[6] Our recent publication reported a 70% prevalence of overweight (including 50% obesity) at age 11 years in a birth cohort (n>1000) of Pacific children from South Auckland in 2009/2010, demonstrating rapid physical growth in this population.[25]

Compared to European, Pacific babies have higher birth-weights which are directly related to maternal body weight.[26] Given that the propensity for rapid weight gain is intergenerational, where a genetic predisposition is amplified in the prenatal period, early intervention is critical.

We urge the government to act with haste to provide more supportive environments for Pacific mothers and children, improve housing and food security, and address widespread poverty. Preventing the upstream causes is the pathway to health and wellbeing for Pacific children in New Zealand.

Competing interests: Nil.

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MEDICAL IMAGE

A rare and unexpected cause for bronchiectasis

Thomas C Reid, Vinu M Abraham

A 44-year-old woman with longstanding asthma was referred for worsening cough over a 2-year period. She reported frequent exacerbations, with purulent sputum and occasional small volume haemoptysis. Smoking history was minimal (1.5 pack years). She had a prolonged history of sinus infections and documented prior pneumonia, pertussis infection, but no known TB exposure.

Sputum grew *Haemophilus influenzae* but was negative for atypical organisms including mycobacteria. Radiology showed severe cystic bronchiectasis within the left lower lobe (Figure 1). PET CT imaging showed the lesion to be non-FDG avid, with no significant lymphadenopathy. Bronchoscopy revealed an obstructing polypoid lesion at the orifice of the left lower lobe (Figure 2). Multiple biopsies and brushings demonstrated only normal bronchial mucosa.

Following discussion at the lung cancer multidisciplinary meeting the patient underwent left lower lobe lobectomy.

Figure 1. CT chest showing collapse and cystic bronchiectasis of left lower lobe

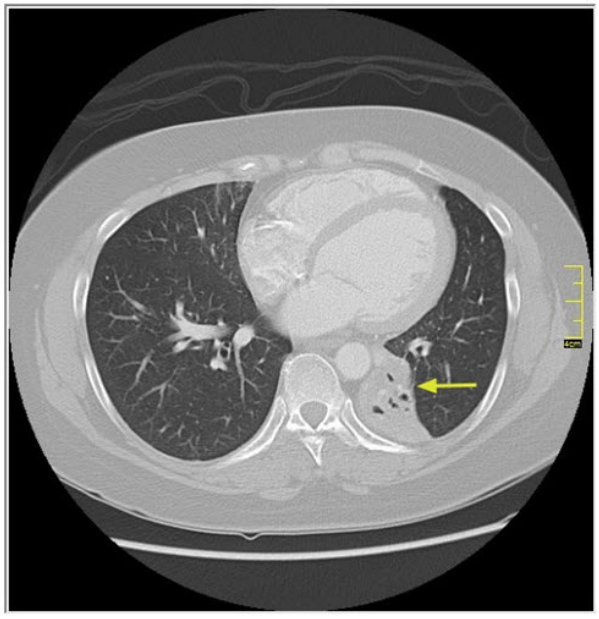
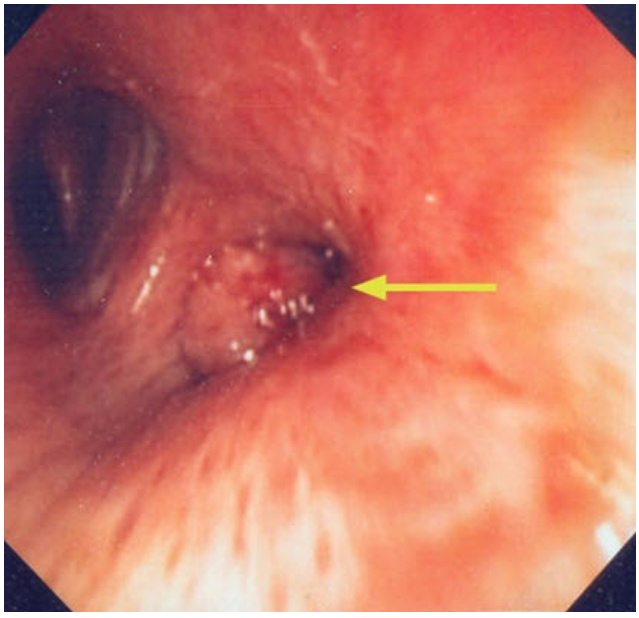


Figure 2. Bronchoscopic view from left main bronchus showing polypoid lesion in left lower lobe orifice



What is the diagnosis?

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-17-oct-2014/6334

Answer and Discussion

Histology demonstrated chronically inflamed but normal mucosa overlying the lesion. The core of the lesion was hyalinised, cytologically bland fibrous tissue demonstrating features of a *pulmonary fibroma*.

Benign endobronchial neoplasms are extremely rare, comprising less than 10% of bronchial tumours.[1] Most malignant lesions of the tracheobronchial tree originate from the mucosa, whereas benign neoplasms usually stem from mesenchymal structures.[2]

Prognostic information is limited due to the rarity of these lesions, however, similar case reports have demonstrated no recurrence at 12 months and almost 4 years respectively.[3,4]

Learning points

- This case highlights the importance of bronchoscopic evaluation in the presence of lobar collapse, especially in a young patient.
- There is a definite role for surgery in bronchiectasis when associated with endobronchial neoplasms, or when disease is severe and localised to a single lobe.

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LETTER

Ethnicity of psoriasis patients: an Auckland perspective

Martin Lee, Steven Lamb

Psoriasis is a common skin condition[1] with both genetic and environmental influences. Much is still not known about the epidemiology of psoriasis, especially in New Zealand, as most of the epidemiological studies thus far have been from overseas.

In 2005, a New England Journal of Medicine review article on psoriasis suggested that psoriasis has a lower prevalence in indigenous populations, and of particular mention was that there were no cases in the Samoan population. It has also recently been reported that there is a statistically significant difference in psoriasis prevalence between the various ethnic groups in the United States.[3]

We sought to look at rates of psoriasis in a New Zealand context with particular attention to the ethnicity of patients seen in our department. An audit was undertaken looking at the ethnicities of the psoriasis patients that were treated in Auckland District Health Board (ADHB) over the last 5 years (2009–2014).

We included psoriasis patients who had severe psoriasis requiring our service as data on these patients was more readily available. Patients who were admitted as inpatients to Auckland City Hospital, or underwent a course of phototherapy at the Greenlane Clinical Centre, from 2009 to 2014 were identified. Their notes were consulted and the ethnicity of each patient was recorded. This audit involved non-identifiable data and therefore ethics approval was not required.

Ethnicity	Number of patients	Percentage of patients
New Zealand European	273	53.42%
Maori	52	10.17%
Samoan	29	5.68%
Tongan	22	4.31%
Nieuan	4	0.78%
Cook Island Maori	20	3.91%
Fijian	8	1.57%
Asian	93	18.20%
Other	10	1.96%
TOTAL	511	100.00%

In total, 511 psoriasis patients were identified from the ADHB area. Out of these the biggest group were NZ Europeans (53.42%). A substantial minority of patients were Maori and Pacific Islanders (26.42%). As a comparison, the general ADHB population is comprised of 19.1% Maori and Pacific Islanders and 52% NZ Europeans.[4] Of note, Samoans represented 5.68% of the total number of psoriasis patients in this audit. So while rates may be lower compared to NZ Europeans, this skin disease is still seen in this ethnic minority.

Although we were unable to capture all the psoriasis patients in the ADHB area due to our current data collection system, the audit that we have done suggests that the New Zealand indigenous population of Maori and Pacific Islanders do indeed make up a substantial minority of patients with psoriasis. Further population based studies looking at the true national prevalence of psoriasis patients and their ethnicity in all New Zealand is warranted.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-17-oct-2014/6335

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100 YEARS AGO

Correspondence. Request for tubercular pathological material from children 16 years of age and under

Letter to the Editor published in NZMJ July 1914;13(53):268.

Sir,—I shall be indebted if you will kindly bring the above request under the notice of the profession. There appears to be comparatively little juvenile tuberculosis in New Zealand, and consequently there is considerable difficulty in getting pathological material for investigation.

I shall be grateful for specimens such as sputum, pus, cerebrospinal fluid, glands, portions of bones or joints, which any of your readers may obtain from operation or post mortem cases.

I am, etc.,

Otago University, June 23rd, 1914.

SYDNEY T. CHAMPTALOUP.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-day-month-year/6339

METHUSELAH

Needle-free jet injection for administration of influenza vaccine

Since 2010, the US Centers for Disease Control and Prevention has recommended annual influenza vaccination for all people in the USA aged 6 months or older who do not have contraindications. However, coverage falls far short of this goal, particularly in young adults. Needle phobia and the risk of needle-stick injury may be relevant.

This non-inferiority trial aimed to assess the immunogenicity and safety of trivalent influenza vaccine given by needle-free jet injector compared with needle and syringe. The jet injectors use a high-pressure narrow jet of liquid drug to penetrate and deliver the drug to the desired depth. 1250 participants were randomised to receive vaccination by the jet injector or needle and syringe.

The researchers report that "the immune response to influenza vaccine given with the jet injector was non-inferior to the immune response to influenza vaccine given with needle and syringe. The device had a clinically acceptable safety profile, but was associated with a higher frequency of local injection site reactions than was the use of needle and syringe."

Lancet 2014;384:674–81.

Safety of pertussis vaccine in pregnant women in UK

A sharp increase in confirmed cases of pertussis observed in the UK during 2011–12 led to the introduction of a pertussis vaccination programme targeting pregnant women in their third trimester aimed at reducing infant morbidity and mortality. This observational study was designed to evaluate the safety of pertussis-containing vaccines in pregnant women in the UK.

Over 20,000 pregnant women with a record of vaccination containing pertussis were identified. They were compared with a matched historical unvaccinated cohort. The conclusion reached was that there was no evidence of an increased risk of stillbirth or any of a range of predefined adverse events related to pregnancy after vaccination with a vaccine containing pertussis.

An editorial commentator commends the study. He notes that the vaccine used included low-dose diphtheria toxoid and inactivated polio vaccines as well as acellular pertussis vaccine. He speculates that if pertussis vaccine was available without the other components it might encourage more frequent booster doses in the general community.

BMJ 2014;349:g4219 & g4518.

Self-monitoring and medication self-titration in hypertensive patients at high risk of cardiovascular disease

Self-monitoring of blood pressure with self-titration of antihypertensives (self-management) results in lower blood pressure in patients with hypertension, but there are no data about patients in high-risk groups. This paper reports on a randomised trial comparing these management techniques in patients with a history of stroke, coronary heart disease, diabetes or chronic kidney disease.

The primary outcome was the difference in systolic blood pressure between intervention and control groups at the 12-month office visit. After 12 months, the mean blood pressure had decreased to 128.2/73.8 mmHg in the intervention group and to 137.8/76.3 mmHg in the control group, a difference of 9.2 mmHg in systolic and 3.4 mmHg in diastolic blood pressure.

So self-management appears to be appropriate for hypertensive patients in the high-risk category.

JAMA 2014;312(8):799–808.

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1404-day-month-year/6336

PROCEEDINGS

Proceedings of the 225th Scientific Meeting of the Otago Medical School Research Society, Wednesday 24 September 2014

Periventricular nucleus kisspeptin neurons project to the perinuclear zone of the supraoptic nucleus. A Seymour, R Campbell, C Brown. Centre for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

Oxytocin is a hormone synthesised in supraoptic nucleus (SON) neurons and is important for parturition. However, the mechanisms that regulate oxytocin neuronal firing during parturition are poorly understood. We have shown that intracerebroventricular kisspeptin increases oxytocin neuron firing rate in late pregnant rats, but not virgin rats *in vivo*. Furthermore, there is an increase in kisspeptin fibre density in the perinuclear zone (PNZ), immediately dorsal to the SON. We aim to investigate a potential role for kisspeptin to regulate oxytocin release in late pregnancy to prepare for parturition.

Here we have used retrograde tracing and immunohistochemistry to study the origin of PNZ kisspeptin fibres in virgin and late pregnant (day 21) rats. Under isofluorane anaesthesia, green fluorescent microspheres were stereotaxically injected into the PNZ. Following 4 -7 days recovery, rats were anaesthetised with 60 mg/kg pentobarbitone and perfused. Brains were sliced and labelled for kisspeptin. The average numbers of cells per section expressing kisspeptin, tracer or both were counted and compared between groups.

Only kisspeptin-positive cells in the periventricular nucleus (PeN) co-expressed tracer. There was a significant increase in the number of cells expressing kisspeptin in late pregnant rats (7.7 ± 1.7 mean ± SEM, n = 4) compared to virgin rats (2.1 ± 0.6, n = 6, $P = 0.007$, student's t test). There was also a significant increase in the number of cells co-expressing kisspeptin and tracer in late pregnant rats (1.4 ± 0.26,) compared to virgin rats (0.43 ± 0.27, $P = 0.034$). However, the number of tracer-positive cells was similar in virgin (18.4 ± 3.9) and late pregnant rats (16.6 ± 2.6, $P = 0.74$).

These results show that PeN kisspeptin neurons project to the PNZ. Hence, these neurons might act as a positive regulator for oxytocin release at parturition to aid delivery of the offspring.

Enhanced sympathetic activity contributing to seizure-induced cardiomyopathy: Therapeutic option? M Read, D McCann, R Millen, J Harrison, S Kerr, I Sammut. Department of Pharmacology and Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin.

Seizures are associated with enhanced sympathetic activity resulting in cardiac dysfunction and structural damage. The current study examined ictal electrocardiographic (ECG) activity up to 7 days following seizure induction. It was hypothesised that intervention with atenolol, a peripheral β_1 antagonist, could attenuate this pathology.

Male Sprague-Dawley rats (320-350g) were implanted with ECG electrodes to allow telemetric recordings during seizures. Baseline 30 min recordings were taken prior to seizure-induction by intrahippocampal kainic acid (2 nmol, 1 µl/min). Animals were treated with saline or atenolol (5 mg/kg) 60 min post-seizure induction (n = 12/group) and for the remainder of the study (up to 14 days). Control animals were administered intrahippocampal saline and subcutaneous saline at 60 min. Data was analysed using a 2-way repeated measures ANOVA.

Seizures were associated with a significant increases in heart rate (HR, 36 ± 2.7%) and blood pressure (20 ± 6.5%) above baseline ($P < 0.05$) suggesting elevated sympathetic activity. Troponin I levels were elevated 24 hours (0.61 ± 0.03 ng/ml) following seizure induction (0.15 ± 0.02 ng/ml at baseline, $P < 0.05$), demonstrating acute myocardial damage. Echocardiography at 7 and 14 days revealed deterioration in cardiac function as determined by decreased ejection fractional (80 ± 5% and 75 ± 1%, respectively). Histological examination in the saline animals indicated the presence of reversible ischaemic damage, fibrosis and inflammatory cell filtration, contributing to increased susceptibility to aconitine-induced arrhythmias. Atenolol intervention was effective at reducing the HR, QTc interval and systolic blood pressure back to baseline. Furthermore, atenolol treatment preserved cardiac function and prevented structural damage at 7 and 14 days, reducing the risk of arrhythmia.

These results show that seizures are associated with enhanced sympathetic modulation resulting in altered ECG activity and cardiac pathology. Atenolol intervention provides a promising therapeutic approach to seizure-induced cardiomyopathy.

Colorectal tumour associated macrophages are more pro-inflammatory than adjacent control bowel tissue macrophage populations. S Norton1, E Taylor1, E Dunn1, F Munro2, M Black3, J McCall2, R Kemp1. 1Department of Microbiology and Immunology, Otago School of Medical Sciences, 2Department of Surgical Sciences, Dunedin School of Medicine, 3Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin.

A high infiltration of macrophages in colorectal cancer is associated with improved prognosis for patients, the opposite to what is observed in many other cancers. The objective of this project was to characterise colorectal tumour macrophages to help explain this association.

Human macrophage functional phenotypes were defined in vitro using multicolour flow cytometry, ELISA and qPCR. Corresponding populations were subsequently detected, using flow cytometry, in both tumour tissue and non-transformed bowel tissue from colorectal cancer patients.

A significant greater frequency of inflammatory macrophages (CD45+CD33-CD14lo/-CD11b+CD64+CD206int) (tumour = 0.99 ± 0.26, control bowel = 0.27 ± 0.11, mean % total live immune cells ± SEM, Wilcoxon matched-pairs signed rank test, P = 0.02, n = 7) was observed in the tumour tissue of each patient. Analysis of patient samples revealed other myeloid derived immune cells. The frequency of myeloid derived suppressor cells (CD45+CD33+CD11b+CD64-CD14-) was significantly increased (tumour = 0.64 ± 0.22, control bowel = 0.26 ± 0.07, P = 0.03, n = 7) in tumour tissue compared to control bowel. A large population of gut resident macrophages was observed in both tumour and control bowel tissue. These macrophages are highly phagocytic and unresponsive to cytokines – a phenotype that could be beneficial in restricting tumour growth. Here, this population could be subdivided into gut resident (CD45+CD33+CD14-CD11b-CD64-) and inflammatory gut resident (CD45+CD33+CD14+CD11b+CD64+) macrophages. Macrophages (CD45+CD64+CD11b+), sorted from both tumour and control bowel tissue, were cultured with T cells (CD3+) sorted from patient blood. Tumour macrophages increased T cell IFN-γ and IL-17 production, as measured by flow cytometry, compared to T cell cultured alone, whereas control bowel macrophages did not.

This study highlights the complexity of macrophages and provides methods to examine them ex vivo from human tissue. Data gained from this study could be used for future investigation of macrophages as both prognostic and therapeutic targets.

Optogenetic activation of gonadotropin-releasing hormone neurons reveals minimal requirements for pulsatile luteinising hormone secretion. P Campos, A Herbison, B Hyland. Centre for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

The reproductive system is critically dependent upon patterned pulsatile hormone release that is driven by the gonadotropin-releasing hormone (GnRH) neurons. The patterns of neuronal activity responsible for generating the pulsatile release of GnRH are unknown. We developed a methodology in mice for remotely controlling the activity of the GnRH neurons *in vivo* to establish the parameters of activation required to evoke a pulse of luteinising hormone (LH) secretion from the pituitary.

Injections of Cre-dependent channelrhodopsin (ChR2)-bearing adeno-associated virus into the median eminence of GnRH-Cre mice resulted in the selective expression of ChR2 in GnRH neurons (93 ± 8 % double-labeled neurons, mean ± sem, n = 6, in the rostral preoptic area (rPOA)). Acute brain slice experiments demonstrated that ChR2-expressing GnRH neurons could be driven to fire with high spike fidelity with blue light stimulation frequencies up to 40 Hz. *In vivo*, optical fibers were implanted in the vicinity of GnRH neurons within the rPOA of anesthetised, ovariectomised mice. Optogenetic activation of GnRH neurons for 30 s to five min time periods over a range of different frequencies revealed that 10 Hz stimulation for two minutes was the minimum required to generate a pulse-like increment of LH (1.49 ± 0.08 fold increase, n = 8) which was significantly different ($P <$ 0.001, one-way ANOVA) from control animals. Under these conditions, the dynamics of optogenetically-evoked LH secretion are very similar to that of endogenous LH pulses with the rise time and increment in LH being identical. This suggests that the minimal parameters of GnRH neuron activation reported here are likely to be that occurring *in vivo* for pulsatile LH secretion.

This study provides the first major insight into the nature of GnRH neuron activation required to generate pulsatile LH secretion and provides the foundations for understanding pulsatility within the reproductive axis.

Triazole drug target structures in a resistant yeast strain. A Sagatova[1], M Keniya[1], F Huschmann[1,2], S Willbanks[3], R Cannon[1], J Tyndall[2], B Monk[1]. [1]Sir John Walsh Research Institute and Department of Oral Sciences, Faculty of Dentistry, [2]School of Pharmacy, [3]Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin.

Fungal pathogens are estimated to be responsible for ~1.5 million deaths annually. Triazole drugs provide some of the most widely used treatments of fungal infections. They target the membrane protein lanosterol 14α-demethylase (Erg11p) which catalyses the rate limiting step of ergosterol biosynthesis. Inhibition of Erg11p depletes cell membranes of ergosterol and inhibits fungal growth. Resistance to triazoles can arise due to mutations in Erg11p that reduce binding affinity of the drug. An increasing incidence of resistance in fungal pathogens such as *Candida* species is of major concern. This project aims to understand how a mutation in Erg11p differentially affects the binding of triazoles.

Wild type hexahistidine-tagged *ERG11* or a mutant allele that translates to a single amino acid change found in clinical isolates of pathogenic fungi was cloned in a *Saccharomyces cerevisiae* membrane protein overexpression system. Endogenous *ERG11* was deleted. Recombinant ScErg11p6×His was solubilised with N-decyl-β-D-maltoside and purified by Ni-NTA affinity chromatography and size exclusion chromatography. Purified enzyme was used for ligand binding assays and crystallographic studies. X-ray crystal structures of the ScErg11p Y140F mutant in complex with itraconazole (ITC)

and fluconazole (FLC) were determined at a resolution of 2 Å from crystallographic data collected at the Australian Synchrotron.

The *Candida albicans* Erg11p Y132F mutation gives resistance to FLC in clinical isolates. The equivalent Y140F mutation in ScErg11p conferred resistance to FLC but not ITC. The ScErg11p Y140F structure with the long-tailed triazole ITC revealed binding matching that of the wild-type, with an additional water molecule between a heme carboxyl and the aromatic side chain of F140. Comparison of wild type ScErg11p structure to the Y140F mutant in complex with FLC revealed a disruption of well-ordered hydrogen bonding interactions between the enzyme and the drug. Disruption of this hydrogen bonding network helps to explain FLC resistance of the mutant enzyme.

Modulation of heart rate by specific β_1- and β_2-adrenoceptor stimulation in conscious Zucker type II Diabetic Fatty rats. R Cook, C Bussey, P Cragg, R Lamberts. Department of Physiology and HeartOtago, Otago School of Medical Sciences, University of Otago, Dunedin.

Resting heart rate (HR) is the strongest predictor of mortality in patients with cardiac disease. The β-adrenoceptor (β-AR) functional responsiveness and β_1-AR expression, key components of sinoatrial rate regulation, are reduced in many cardiomyopathies. An *in vitro* model suggests co-localisation of 'funny'-channels and β_2-ARs via lipid-rich caveolae is the mechanism through which HR is modulated. β_2-AR redistribution in the failing heart compensates for the decreased β_1-AR function. Whether similar β_2-AR subtype changes contribute to HR dysfunction in diabetes is unknown. We aimed to determine the effects of specific β_1- and β_2-AR stimulation on HR in type II diabetes *in vivo*.

Male Zucker Diabetic Fatty (ZDF) rats and lean littermates (20-week old, $n = 8$) were implanted with a radiotelemeter to measure arterial blood pressure and derive HR and a vascular access port to inject drugs intravenously. Cumulative doses of isoproterenol (non-selective β_1- and β_2-AR agonist, 0.001 – 3 $\mu g.kg^{-1}$) or fenoterol (non-selective β_2-AR agonist, 0.001 – 3 $\mu g.kg^{-1}$) in the presence or absence of atenolol (selective β_1-AR antagonist, 2000 $\mu g.kg^{-1}$) were injected.

Increases in HR due to non-selective β-AR stimulation were not significantly different between groups across doses (at 0.1 $\mu g.kg^{-1}$: 106 ± 10 vs. 109 ± 13 bpm). However the HR response to specific β_2-AR stimulation was significantly reduced in ZDF rats (25 ± 4 vs. 2 ± 4 bpm and 47 ± 7 vs. 20 ± 2 bpm; $P < 0.002$ at 0.03 and 0.1 $\mu g.kg^{-1}$, respectively). HR responses adjusted to the baseline were modulated by β_2-AR in controls although in ZDF rats HR regulation involved both β_1- and β_2-ARs.

Thus, in conscious ZDF rats β-AR responsiveness was not affected, whereas the role of β_1-ARs was increased. Therefore, HR regulation by β_1- and β_2-AR is altered in diabetes, and β_1-AR signaling might play a compensatory role in maintaining β-AR reactivity.

Polymerase-1 and transcript release factor and caveolae in prostate cancer; which is more important? J-Y Low, H Nicholson. Department of Anatomy, Otago School of Medical Sciences, University of Otago, Dunedin.

Prostate cancer poses a significant health threat to men world-wide. Caveolae are "cave-like" invaginations that are found in the plasma membrane. Polymerase-1 and transcript release factor (*PTRF*) is reported to be involved in the formation of caveolae. Expression of *PTRF* and caveolae are lost in prostate cancer cell lines and tissues while restoration of *PTRF* expression leads to formation of caveolae and reduced aggressive phenotypes *in vitro* and *in vivo*. However it is unclear whether the effect seen is due to *PTRF* itself or the restoration of caveolae. This study examines whether *PTRF* or caveolae are involved in prostate cancer progression.

Using normal prostate epithelial cells, RWPE-1, *PTRF* was knocked down with 120 nM siRNA, with scrambled siRNA used as control, and caveolae were disrupted with 10 mM of methyl-β-cyclodextrin (MBCD). Transmission electron microscopy was performed to determine the number of caveolae.

Cell proliferation was measured with CellTiter 96 aqueous non-radioactive cell proliferation kit. Migration and invasion assays were performed with Transwell migration and Matrigel invasion inserts respectively. Changes in cellular signalling were examined with Pathscan intracellular signalling array. Statistical analyses were computed with Student's unpaired *t*-test.

Knock down *PTRF,* or MBCD treatment, reduced caveolae numbers in RWPE-1 cells ($P < 0.05$ siRNA; $P < 0.01$ MBCD, n = 50 cells). Following both treatments increased proliferation ($P < 0.05$, n = 6), migration ($P < 0.05$, n = 3) and invasion ($P < 0.001$ siRNA; $P < 0.01$ MBCD, n = 3) was observed. However, cell-signalling arrays showed a different pattern of signaling molecules activation. Two fold increase in p-STAT3 ($P < 0.05$, n = 4) was seen after knocking down *PTRF*, while disrupting caveolae resulted in two fold increase of p-ERK1/2 ($P < 0.01$, n = 4).

Both *PTRF* and caveolae may be involved in prostate cancer progression, however these elements may drive prostate cancer progression through different signaling pathways.

Enhancement of a robust arcuate GABAergic input to gonadotropin-releasing hormone neurons in a model of polycystic ovarian syndrome. A Moore, M Prescott, R Campbell. Department of Physiology and Centre for Neuroendocrinology, Otago School of Medical Sciences, University of Otago, Dunedin.

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility among women of reproductive age. An increase in luteinising hormone (LH) pulse frequency associated with PCOS is suggestive of changes in gonadotropin-releasing hormone (GnRH) neuron regulation. We hypothesise that altered neuronal regulation of GnRH neurons is due to changes in their afferent synaptic input.

PCOS was modeled in mice by prenatal androgen (PNA) exposure. GnRH-green fluorescent protein (GFP) mice were used to assess synaptic input to GnRH neurons in control and PNA-treated mice (n = 8 / group). Immunohistochemical labeling of brain sections revealed a significant increase in the density of vesicular GABA transporter (vGaT) appositions with GnRH neurons in PNA-treated mice (0.8 ± 0.08 appositions/µm) compared to controls (0.4 ± 0.02 appositions/µm, $P < 0.05$, two-tailed t-test). As GABA signaling to GnRH neurons can be excitatory, increased GABAergic input may elevate GnRH neuron activity. However, the identity of GABAergic neuronal populations regulating GnRH neuron activity remains largely unknown.

To address whether increased GABA innervation of GnRH neurons originates in the arcuate nucleus (ARN), a Cre-dependent adenoviral vector expressing farnesylated enhanced GFP (EGFPf) was injected into the ARN of vGaT-Cre mice. Immunofluorescent labeling revealed that EGFPf-positive ARN GABAergic projections heavily contacted and even bundled with GnRH neuron dendrites. In control and PNA-treated mice, 61 ± 6.1 % and 60 ± 10.5 % of GnRH neurons closely apposed projections from ARN GABAergic neurons, respectively (n = 6 / group). Furthermore, the density of fibres apposing the GnRH neuron dendrite was even greater in PNA-treated mice (0.09 ± 0.02 apposing fibres/µm) compared to controls (0.04 ± 0.006 apposing fibres/µm, $P < 0.05$).

These data describe a novel, robust GABAergic circuit originating in the ARN that is enhanced in a model of PCOS and may underpin the neuroendocrine pathophysiology of the syndrome.

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PROCEEDINGS

Proceedings of the Waikato Clinical School Research Seminar, Wednesday 17 September 2014

General Anaesthetic Modulation of Memory-Related Gene Expression in the Cerebral Cortex

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General anaesthetics have been in clinical use since the mid 19th century, having remained one of the most important drugs in medicine by enabling major surgical procedures to be carried out. One of the fundamental outcomes of anaesthesia is amnesia, as this prevents patient recall of events surrounding surgery. However, very little is known about how anaesthetics alter memory function to cause amnesia. The hippocampal region of the brain has been widely investigated for its role in memory formation but the cerebral cortex also has newly recognized importance in memory consolidation and storage processes. Therefore, our research focuses on molecular changes in the cerebral cortex with respect to altered expression patterns of the *Arc, Bdnf, CamKIIα, Grin1* and *Gjd2* genes. These genes all encode proteins with documented roles in various aspects of memory consolidation and may represent molecular targets for general anaesthetic action. The aim of this research was to investigate the gene expression patterns of *Arc, Bdnf, CamKII2α, Grin1* and *Gjd2* during periods of anaesthesia induced by sevoflurane, isoflurane and propofol. Real-time quantitative PCR (qPCR) was used to analyse expression of mRNA extracted from the cerebral cortex of mouse brain tissue. As brain activity is reduced during periods of anaesthesia, we expected to see down-regulation of the activity-dependent genes selected for this study. Different age groups of mice were also used for a comparative age-related analysis of anaesthetic effects in the brain. Preliminary results indicate that sevoflurane treatment does not alter expression of the *Gjd2* gene but may down-regulate the *Grin1* gene. More results are required for statistically significant evaluations to be made about all five genes of interest.

Evaluation of the influence of ethnicity and deprivation on the Hyperthyroid Symptom Scale score in euthyroid patients.

Tamatea JAU, Campbell M, Hodgson F, Elston M, Conaglen JV

Introduction: Thyrotoxicosis is a common endocrine disorder with an incidence of 0.2%,[1] and when untreated, leads to congestive heart failure, arrhythmias and premature death.[2] To measure and compare clinical severity of thyrotoxicosis Klein et al[3] developed the "Hyperthyroid Severity Scale" (HSS). This is a 10 item questionnaire that uses a 0-4 point scale, measuring common hyperthyroid symptoms. The HSS has been used in a number of different population groups with thyrotoxicosis (US, [3,4,5] UK,[6] Netherlands,[7] Bangladesh,[8] Brazil,[9] Turkey,[10, 11] and Italy[12]), although this clinical scoring system has not previously been used to compare severity between ethnic groups. As the scale reviews general symptoms, there is also the potential for co-morbidities to confound results. Given health disparities seen in Aotearoa/New Zealand for Māori and those with socioeconomic deprivation there is potential for ethnicity and deprivation to affect their HSS score. Locally there has been the suggestion of the possibility of ethnic difference in symptom reporting. While validated for use within hyperthyroid patients the HSS has not been applied to euthyroid patients to ensure accuracy for

hyperthyroidism alone, neither has the role of ethnicity or socioeconomic deprivation on the HSS been investigated.

Methods: Convenience sampling within local general practices recruited 60 Māori and 60 non-Māori participants of which 100 participants (47 Māori and 53 non-Māori) were confirmed to be biochemically euthyroid. Each participant completed HSS questionnaires demographic questions regards to ethnicity[13], and the eight NZiDep[14] questions for socioeconomic status. Two additional items to the HSS score were assessed which were; tremor and hyperdynamic praecordium. The same information were collected on 64 consecutive hyperthyroid participants presenting to an endocrinologist in the Waikato region.

Results: Within the euthyroid group Māori were younger (30years vs 52 years, p<0.0001) and had a different age distribution (p<0.0001) than non-Māori similar to that seen in the general population. The median HSS scores were similar (6 (0-16) vs 4 (0-23), p=0.2) between groups and age-stratification showed no difference (p=0.12) in HSS score between Māori and non-Māori.

The NZiDep 8 point score was divided into those without deprivation (score 0-1, n=112) and those with deprivation (score 2-8, n=50). Within the euthyroid group, those with deprivation were younger (47 years vs 39 years (p=0.021), more likely to be Māori (40% vs 65%, p=0.034) with no gender bias (38% vs 24%; p=0.14). There was a difference in HSS scores between those without deprivation and those with deprivation (median HSS score 3 (0-16) vs 4 (0-27); p= 0.044) but once age-stratified no difference in HSS scores existed between the groups (p=0.15)

When hyperthyroid patients were compared to all euthyroid patients there was no difference in median age (45 years (16-93), 47 years (15-67); p=0.92) or gender (24% male, 33% male; p=0.21). There was a large difference between mean HSS scores (19 (2-47), 5 (0-34); p<0.005). Age-stratification showed a large difference remained within all age groups (p<0.005).

Conclusion: Despite a wide variation in HSS scores in all individuals, the results were able to accurate reflect symptoms consistent with hyperthyroidism when compared to euythroid individuals. Within euthyroid individuals there appears to be no difference between Māori and non-Māori or between high and low NZiDep score individuals.

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Breast cancer survival inequity in New Zealand: How much of it is due to demographics, screening, tumour biology, comorbidities and treatment?

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Abstract:

Introduction: Ethnic disparities in cancer survivals are well known among many populations for a variety of cancers. Underlying reasons for these disparities are complex and poorly understood, but include patient, tumour and healthcare system factors. We investigated on the breast cancer survival disparity between Indigenous Māori and European women in New Zealand and quantified the relative contributions of patient, tumour and healthcare system factors towards this survival disparity.

Methods: All women with newly diagnosed breast cancer in the Waikato, New Zealand between 1999 and 2012 were identified from the Waikato Breast Cancer Register. Cancer specific survival between Māori and NZ European women was compared using Kaplan-Meier survival curves while contributions of different factors towards the survival disparity were quantified with Cox proportional hazard modelling.

Results: Of the total of 2791 women included in this study, 2260 (80.1%) were NZ European and 419 (15%) were Māori. Compared with NZ European women, Māori had a significantly higher age adjusted cancer specific mortality (hazard ratio [HR] =2.02, 95% confidence interval [CI], 1.59-2.58) with significantly lower 5-year (76.1% vs. 86.8%, $p<0.001$) and 10-year (66.9% vs. 79.9%, $p<0.001$%) crude cancer-specific survival rates. Stage at diagnosis explained approximately 40% of the survival disparity, while screening, treatment and patient factors (i.e. comorbidity, obesity and smoking) contributed by approximately 15% each. The final model accounted for almost all of the cancer survival disparity between Māori and NZ European women (HR=1.07, 95% CI, 0.80-1.44).

Conclusions: Māori women experience an age-adjusted risk of death from breast cancer, which is more than twice that for NZ European women. Lower screening coverage, delay in diagnosis, inferior quality of treatment and greater patient comorbidity appear to be important factors contributing to survival disparity between Māori and NZ European women.

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The use of Not for Resuscitation (NFR) orders on an acute psychogeriatric inpatient unit

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Aim: Resuscitation decisions are an important consideration in any inpatient setting, including psychiatric units but become more complex when the patient is unable to participate in the process or make informed decisions. Due to dementia or acute mental illness, the decision making capacity of many patients on admission to the psychogeriatric inpatient unit is compromised. The aim of this study is to determine the proportion and characteristics of patients who received a resuscitation order during their admission to the acute psychogeriatric inpatient unit.

Method: We retrospectively reviewed all admissions of >24hours to the Waikato Hospital acute psychogeriatric inpatient unit between January and December 2012 to determine the prevalence of NFR orders and the factors associated with their completion.

Results: 12% of patients had an NFR order, completed on average 11 days after admission. Having an NFR order was associated with the presence of an EPOA (p=.013), use of the MHA during admission (p=.025), being admitted from residential care (p=.039), and level of impairment on admission as measured by the HoNOS impairment subscale (p<.001), behaviour subscale (p=.019) and total HoNOS score (p=.001). The presence of an NFR order was not associated with age (p=.556), gender(p=.056), ethnicity (p=.596), marital status (p=.062), duration of admission (p=.947) or diagnosis of cognitive impairment (p=.056).

Conclusion: Having an EPOA and level of impairment on admission were the factors most associated with the presence of an NFR. Further studies are needed to determine potential psychiatrist and system factors that may be influencing resuscitation decisions.

Two year outcomes of children treated with dextrose gel for neonatal hypoglycaemia: Follow up of the Sugar Babies Study.

DL Harris[1, 2], J Ansell[2], TY Yu[3], B Thompson[3], T Wouldes[4], JE Harding[2] on behalf of the CHYLD study team.

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Background: Neonatal hypoglycaemia is associated with poor neurodevelopmental outcome. Dextrose gel is an effective treatment for hypoglycaemia, but its long term effects are unknown[1].

Aim: To determine two year outcomes of children randomised to dextrose or placebo gel for treatment of neonatal hypoglycaemia.

Methods: At risk babies who became hypoglycaemic (<2.6 mM) were randomised to 40% dextrose or placebo gel. Children were assessed at two years' corrected age for neurological function and general health (paediatrician assessed); cognitive, language, behaviour and motor skills (Bayley III); executive function; and vision (clinical examination and global motion perception). Primary outcomes were neurosensory disability (cognitive, language or motor score below -1 SD or cerebral palsy or blind or deaf) and processing problem (executive function or global motion perception worse than 1.5 SD from the mean). Data are mean (SD), n (%), or relative risk (RR), 95% confidence interval.

Results: 184 children were assessed; 90/118 (76%) randomised to dextrose and 94/119 (79%) to placebo gel. Mean birth weight was 3093 (803) g and gestation 37.7 (1.6) weeks. 66 children (36%) had neurosensory disability (1 severe, 6 moderate, 59 mild) with similar rates in both groups (dextrose 34 (38%) vs placebo 32 (34%), RR 1.11, 0.75-1.63). Processing difficulty was also similar in both groups (dextrose 8 (10%) vs placebo 16 (18%), RR 0.52, 0.23-1.15).

Discussion: Treatment with dextrose gel appears safe. Neurosensory impairment is common amongst children treated for neonatal hypoglycaemia.

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SDH deficient phaeochromocytomas and paragangliomas demonstrate increased SSTR2A and SSTR3 expression

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Context: Many neuroendocrine tumours, including phaeochromocytomas (PCs) and paragangliomas (PGLs), express one or more somatostatin receptors (SSTR) 1-5. A number of studies have reported SSTR expression in PCs and PGLs. However, receptor expression patterns have been conflicting and until recently specific monoclonal antibodies were not available against SSTR1-5.

Objectives: The aim of this study was to compare SSTR1-5 expression in succinate dehydrogenase (SDH) deficient PCs and PGLs (defined as having absent SDHB immunostaining) to those tumours with normal SDHB staining.

Design: Immunohistochemistry for SDHB and SSTRs 1-5 was performed using specific monoclonal antibodies on archived formalin-fixed paraffin-embedded tissue.

Results: 182 PC/PGLs were included (129 adrenal, 44 extra-adrenal, 9 metastases); 32 tumours were SDH-deficient whereas 150 tumours had positive SDHB staining. SDH-deficient tumours were more likely to demonstrate moderate or strong staining for SSTR2A and SSTR3 when compared to SDH-sufficient tumours (91% vs 49%, $p<0.0001$ and 50% vs 21%, $p=0.0008$, respectively). Immunostaining for the other SSTRs was not different between SDH-deficient and tumours with preserved SDHB staining.

Conclusions: SSTR2A and SSTR3 are more likely to be expressed in SDH-deficient PC/PGLs as compared with tumours demonstrating normal SDHB staining pattern. These findings suggest that the role of somatostatin analogue therapy (unlabeled or radiolabeled) should be re-examined in the context of the underlying SDHB immunohistochemistry pattern.

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In vitro effects of selenium on DNA damage in BRCA1 cell lines

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Breast cancer is the most common cancer affecting women worldwide and they have an 11% lifetime risk of developing breast cancer. Selenium (Se) is an essential trace mineral that plays critical roles in maintaining health in humans. The aim of this research was to investigate Se dosage effects on *in vitro* human breast cancer cells in order to examine cell survival and the level of DNA damage. Two forms of Se compounds were investigated; sodium selenite (inorganic) and methylseleninic acid (MSA, organic). To test this, SUM149PT cells that harbour a 2288delT mutation in *BRCA1* were cultured and examined for evidence of toxicity using a colorimetric MTT assay and the single cell gel electrophoresis Comet assay.

The MTT assay demonstrated that this particular BRCA1-mutated cell line is very sensitive to Se (both organic and inorganic forms). The IC_{50} of sodium selenite and MSA against these cells was 0.09 µM, and 0.045 µM respectively, whereas the IC_{50} against various other published cancer cell types was in the range of 2.5-50 µM. Preliminary results from the Comet assay show that there is increasing DNA damage when cells are treated with increasing concentrations of sodium selenite (0.025 µM and 0.05 µM).

This particular BRCA1-mutated cell line appears to be extraordinarily sensitive to both Se species. The next step in this research is to investigate other BRCA1-mutated and non-mutated breast cancer cell lines to determine if this sensitivity is specifically linked to *BRCA1* mutations. This data has potential clinical implications in the therapy of patients with BRCA1-mutated cancers.

Withdrawal…… from Opioid Prescribing

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Introduction

Morphine is the orally administered opioid of choice for severe pain, although other strong opioids such as oxycodone and methadone are also used (1). Oxycodone use in New Zealand has dramatically increased since it became fully subsidised, with most prescribing occurring in hospitals (2, 3, 4).

A previous audit at Waikato Hospital showed oxycodone was not always prescribed according to best practice. This may also apply to prescribing of other strong opioids. A linked programme of audit, intervention and re-audit was therefore conducted to highlight areas for improvement.

Aims

- Conduct a baseline audit to assess prescribing of orally administered strong opioids.
- Design and deliver an intervention to improve opioid prescribing.
- Conduct a final audit to evaluate the effectiveness of the intervention.

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Method

Baseline and Final Audit

- Data collected retrospectively from medication charts of patients discharged from two orthopaedic wards
- Data collected over ten consecutive weekdays
- Included prescribing of strong oral opioids only (oxycodone, methadone and morphine)
- Data collected included patient demographics, names of strong oral opioids prescribed, doses and administration frequency. Review dates and maximum doses charted for PRN medicines, and medicines on admission and discharge were also collected
- Exclusion criteria: any patient discharged to convalescent care, other wards or other hospitals

Intervention

- Twenty minute education session delivered to orthopaedic nursing and medical staff on separate occasions. Key points covered included:
- Current situation of increasing oxycodone use worldwide
- Results of baseline audit at Waikato Hospital
- Best practice guidelines recommend morphine first-line for severe pain (1, 5)
- Differences between oxycodone and morphine e.g. oral oxycodone has approximately twice the potency of morphine (oxycodone 5mg = morphine 10mg)
- For acute pain in opioid naïve patients recommend use of immediate release (IR) formulations
- For PRN opioids chart a maximum daily dose
- Regularly review the patient and have a tapering plan
- Opioids on discharge:
    a. Communicate with GP and patient
    b. Include plan and duration of treatment in discharge summary

Results and Discussion

Patient demographics were similar in both audits. Only 63% of patients were prescribed a strong oral opioid in the final audit, compared with 88% in the baseline audit. This was largely due to a decrease in the proportion of patients prescribed oxycodone (25% versus 39% in the baseline audit), while the proportion prescribed morphine was virtually unchanged.

The proportion of patients on morphine who were prescribed a sustained release formulation decreased from 31% to 13%, and similarly from 26% to 10% for patients on oxycodone. There was very little change in the proportion of patients charted a maximum daily dose for PRN strong opioids or those who had a review date present

There was a modest reduction in the proportion of patients discharged on strong oral opioids. These were almost always included in the discharge summary.

Conclusion

This audit shows medical and nursing staff education can improve prescribing of orally administered strong opioids. Further work is needed to determine if such improvements can be sustained over a longer period, and if the intervention can be extended to other areas.

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Systematic Review of Minimally Invasive Follicular Thyroid Carcinomas

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Introduction: Minimally Invasive Follicular Thyroid Cancer is an early form of follicular thyroid cancer with an excellent prognosis. It is often detected after diagnostic thyroid lobectomy or as an incidental finding following thyroidectomy for other pathology. Currently there are is a lack of clear guidelines and variable practice for the management of MIFTC.

Aims: We sought to identify risk factors that may affect prognosis and thus influence management of MIFTC. The risk factors reviewed include age of patient, tumour size, and metastases at presentation.

Methods: We performed a literature search looking at studies involving MIFTC patients with prognostic data such as cause specific survival, mortality and metastatic rates. PubMed was used as the search engine with exclusion of studies that had patients with previous history of thyroid cancers, or previous history of thyroid operations, or previous non-thyroid malignancy or previous radioactive iodine.

Following this a qualitative review of the eligible studies was performed by two authors a quantitative analysis was not possible.

Results: Nine case series were isolated after review of 153 abstracts. The data found was heterogenous and there was variable reporting of definitions of MIFTC, treatment strategies and outcomes. Meta-analysis was not possible. Patients with MIFTC tended to be younger with a mean age of 44. The tumour size mean was 3.1 cm. Lymph node metastases rate was 0-3 % and distant metastases on presentation was 0 -9.4%. 10 year cause specific survival ranged from 95.2 – 100%. Age appears to the single most significant factor affecting prognosis.

Conclusion: We suggest that patients less than 45 years old with MIFTC less than 4 cm be treated with lobectomy alone provided no other risk factors such as margin involvement or regional or distant metastases. Patients less than 45 years old with MIFTC more than 4 cm should have a total thyroidectomy. Older patients or patients with other risk factors should be discussed in an MDM setting for adjuvant therapies like RAIA.

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