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This Issue in the Journal

Seasonal variation in vitamin D levels in the Canterbury, New Zealand population in relation to available UV radiation

John Livesey, Peter Elder, M Jane Ellis, Richard McKenzie, Ben Liley, Chris Florkowski

We measured blood vitamin D levels in volunteers and patients in Canterbury (119 females, 82 males; median age 45 years, range 18 to 83) and found that most people are vitamin D deficient most of the time when compared to the latest international recommendations, particularly in late winter and early spring. We then used mathematical modelling to predict the daily amount of vitamin D supplementation required to correct this deficiency and found that about 2600 international units per day is needed. This is well above current New Zealand guidelines of 1600 international units per day and suggests that the widespread consumption of relatively high prescription strength doses of vitamin D is likely to be needed to ensure the optimal health of the Canterbury population by reducing the incidence of chronic diseases such as fractures in older people, cancer, and muscle weakness.

Vitamin D and muscle strength in patients with previous fractures

Charles A Inderjeeth, Denise Glennon, Anthony Petta, Jessamine Soderstrom, Irene Boyatzis, Jeffrey Tapper

Vitamin D deficiency is a common and important problem in older people and it is an important factor in osteoporosis. Vitamin D deficiency may also be an important cause of poor muscle strength and falls, especially in the elderly. Our study at a hospital in Western Australia studied vitamin D levels and leg muscle strength in 99 women aged over 60 and found that low vitamin D levels were associated with poor leg muscle strength. Correcting Vitamin D deficiency may be important in reducing fracture through both reducing osteoporosis and reducing falls through improved muscle strength.

The failure to diagnose inborn errors of metabolism in New Zealand: the case for expanded newborn screening

Callum Wilson, Nicola J Kerruish, Bridget Wilcken, Esko Wiltshire, Dianne Webster

Inborn errors of metabolism refer to a group of rare genetic chemical disorders. Children with these conditions often present with serious symptoms such as coma. However because these symptoms are usually due to other more common conditions clinicians may not investigate the patient for an underlying metabolic disorder. This is unfortunate as treatment (if commenced very early) dramatically improves the outcome. This paper reports the findings of a nationwide 3-year surveillance study that shows that these disorders have been under diagnosed in recent years in New Zealand. A small number of children are likely to have died yearly as a result.

The recent introduction of expanded newborn screening, a process whereby key chemicals are measured in the neonatal Guthrie card blood test prior to the child becoming sick, will hopefully improve this situation. The paper further discusses this new form of screening, its advantages and limitations.

Phenylketonuria—the lived experience

Nicole Frank, Ruth Fitzgerald, Michael Legge

This research is based on interviews with eight people who live with phenylketonuria (PKU) in New Zealand. PKU is a severe genetic disorder affecting the body's ability to produce certain proteins which help to break down food into its constituent components. It is treated by following a very strict diet which must begin at birth and be followed for life. People who live with the disease describe the effect of it as turning them into expert negotiators in the medical, social, and personal spheres of their lives. They recount the consistent juggling of the risk of their unknown futures with the conflicting demands for expressing affection and pleasure through shared eating with family and friends versus the need to adhere very strictly to their diets to try to retain their health and mental facilities.

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

Doron Hickey, Grace Joshy, Peter Dunn, David Simmons, Ross Lawrenson

Type 1 diabetes is categorised as either being positive or negative for various auto-antibodies related to pancreatic function. It has not been established whether the actual titres of anti-GAD or anti-IA2 antibodies at diagnosis have prognostic implications, although the presence of anti-GAD is believed to be indicative of beta-cell destruction. Our study did not show any statistically significant associations between antibody status and subsequent hospital admission for diabetic ketoacidosis. But a positive anti-IA2 status was associated with better glycaemic control (HbA1c<10%). If there is evidence of antibodies to IA2 present then this is a predictor of better glycaemic control and it may be that these patients will have less complications than those who are anti-IA2 negative. We believe this is the first time this finding has been reported.



Vitamin D—how do we define deficiency and what can we do about it in New Zealand?

Robert Scragg, Jim Bartley

Although we live in a sunny clime, and the sun is the main source of our vitamin D, for some reason New Zealanders have lower vitamin D levels in their bodies than people in other comparable countries at similar latitudes.

Vitamin D status is determined by blood levels of 25-hydroxyvitamin D (25OHD). Recent findings from the 1997 adult nutrition survey show a mean 25OHD level of 50 nmol/L in New Zealanders aged ≥ 15 years, considerably lower than mean values above 70 nmol/L seen in the adult US population which lives at similar latitudes as the New Zealand population, and similar to the mean level of 50 nmol/L in the UK adult population which lives at higher latitudes (i.e. further from the equator than New Zealand).¹

Mean vitamin D levels are lower still among Māori (42 nmol/L) and Pacific people (37 nmol/L).¹ Furthermore, South Asian people are likely to have low vitamin D levels because of their darker skins, and veiling with traditional dress by many Muslim immigrants also places them at increased risk of developing vitamin D deficiency.³ Moreover, osteomalacia and rickets are conditions that have re-emerged in clinical practice.^{2,3}

Given our lower than expected vitamin D status, the two articles on vitamin D in this issue of the *Journal*, one from Christchurch which confirms the low vitamin D levels described above⁴ and one from Perth (Western Australia) which reports a significant positive association between serum 25OHD levels and leg muscle strength,³ are timely since they contain conclusions that are relevant to both clinicians and policymakers.

Although the article by Inderjeeth and colleagues reports results from a sample of women aged >60 years living in Perth,⁵ their findings most likely apply to older New Zealand women since the mean 25OHD of 52 nmol/L in the Perth sample was higher than the value of 43 nmol/L in New Zealand women aged ≥ 65 years in the 1997 nutrition survey;¹ and probably also applicable to New Zealand men aged ≥ 65 years who had a mean 25OHD level of 52 nmol/L.¹

The Perth study is consistent with a recent meta-analysis which found that vitamin D supplementation reduced the relative risk of falling by 22%, with an absolute risk reduction of 7%, so that the number needed to treat (NNT) to prevent one fall was 15, although the time period required for treatment is unclear as this was not provided by the authors of the meta-analysis.⁶

There is a well-described mechanism for this effect since vitamin D receptors have been identified in skeletal muscle, and vitamin D supplementation increases muscle strength by increasing the size and number of type II muscle fibres, so that gait and balance are improved. Thus, vitamin D, in combination with calcium, protects against hip fracture by increasing bone density and muscle strength.⁷

There is a further finding from the Perth study and this directly addresses the question of how we define vitamin D deficiency. Previous research has determined that vitamin D deficiency is defined by a serum 25OHD below 50 nmol/L.⁸ Yet, this conclusion is challenged by the observation in the Perth study showing that the association between serum 25OHD and muscle strength was strongest in women with 25OHD levels above 50 nmol/L.

This result is consistent with emerging research, from both physiology and epidemiology, that optimum vitamin D status occurs at serum 25OHD levels above 80 nmol/L. Indeed, metabolic studies have shown that the proportion of dietary calcium absorbed from the gut maximises (at just over 30%) when serum 25OHD levels are above 80 nmol/L.⁹

However, the strongest evidence comes from epidemiological studies which have shown that the risk of a range of medical conditions—including bone density, periodontal disease, colon cancer, hypertension, and lung function—is lowest in people with serum 25OHD levels above 80 nmol/L.^{10–12}

Some of this evidence comes from New Zealand studies. A large workforce diabetes survey carried out in Auckland and Tokoroa found that the risk of undiagnosed diabetes and impaired glucose tolerance was lowest at a serum 25OHD level above 83 nmol/L.¹³ An Auckland-based case control study of myocardial infarction (which reported 25OHD levels as nmol/L instead of the correct units of ng/mL) found that the lowest risk of myocardial infarction occurred at a 25OHD level above 43 ng/mL (or 107 nmol/L).¹⁴

It is still unclear whether there is a threshold at a 25OHD level of about 80 nmol/L for maximal health gains associated with increased vitamin D, or whether the relationship between 25OHD and health status continues to improve above this value; further research is being carried out to clarify this.

But either way, defining vitamin D deficiency as a 25OHD level below 50 nmol/L is clearly not supported by the current evidence; optimum health occurs at much higher levels than this. Most hospital laboratories currently define vitamin D deficiency as a serum 25OHD <50 nmol/L, and clinicians need to reinterpret this value for their patients in light of the above evidence.

Clinicians, and policymakers, will also find relevant information in the Christchurch study by Livesey and colleagues.⁴ Besides confirming the results of previous research showing low vitamin D levels in New Zealanders, this study has estimated both the amount of vitamin D synthesised from sun exposure in both summer and winter, and also the amount of oral vitamin D required to increase winter serum 25OHD levels up to optimal levels.

Their estimate—1450 IU or 2600 IU of vitamin D₃ each day is required to increase serum 25OHD to 75 nmol/L or 100 nmol/L, respectively—is way above the current recommended level of 400 IU per day for people aged 51–70 years and 600 IU for people aged >70 years, but in line with current international opinion (see reference 1 of their paper).

Given that mean serum 25OHD levels of New Zealanders average 50 nmol/L for both children and adults, the evidence that health status improves at 25OHD levels above

50 nmol/L indicates that vitamin D needs to be promoted higher up the public health agenda, since 84% of the adult population have 25OHD levels below 80 nmol/L.¹

At the moment, non-government organisations, such as the Cancer Society of New Zealand and the Health Sponsorship Council, are driving the development of policy on sun exposure, vitamin D, and health, but with the focus firmly on (avoiding) sun exposure.

As Livesey and colleagues discuss, a second strategy—increasing vitamin D supplementation—needs to be considered in New Zealand since vitamin D synthesis from the sun during winter for people in Christchurch is estimated to be only 60 IU per day.⁴

However, a third strategy also needs to be thrown into the mix—mandatory vitamin D fortification (currently it is optional) of certain foods such as margarine and milk products, which already happens in several countries, including the US, UK, and Australia.

As research continues to emerge, the Ministry of Health soon will need to engage on the broad issue of vitamin D and health, and take ownership of it.

Competing interests: None.

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Seasonal variation in vitamin D levels in the Canterbury, New Zealand population in relation to available UV radiation

John Livesey, Peter Elder, M Jane Ellis, Richard McKenzie, Ben Liley, Chris Florowski

Abstract

Aim The optimal plasma 25-hydroxyvitamin D (25(OH)D) concentration is probably >75 nmol/L but in temperate regions lower levels are common. Few studies report the intensity of solar ultraviolet (UV) radiation when 25(OH)D is measured. We measured plasma 25(OH)D and incident solar UVB radiation in Christchurch and modelled the relationship between them.

Methods 25(OH)D, total calcium (Ca_T), ionised calcium (Ca_I) and parathyroid hormone (PTH) were measured in healthy volunteers (119 female, 82 male; median age 45 years, range 18 to 83) between February and July 2004. Vitamin D-weighted UV energy measurements (dUV) for Christchurch were from the National Institute of Water and Atmospheric Research (NIWA) UV Atlas.

Results In February 2004, 88% of 25(OH)D levels were below 75 nmol/L, increasing to 100% in June and July. Severe deficiency (<12.5 nmol/L) was found in 1.5% of subjects. From February to July, 25(OH)D and Ca_I fell and Ca_T rose ($p < 0.001$, < 0.01 , and < 0.001). There was a hyperbolic relationship between PTH and 25(OH)D while Ca_T and Ca_I correlated negatively with PTH ($r = -0.30$ and -0.33 ; both $p < 0.001$). Monthly mean dUV intensity ranged from $10 \text{ kJ} \cdot \text{m}^{-2} \cdot \text{day}^{-1}$ in Dec 2003 to $0.5 \text{ kJ} \cdot \text{m}^{-2} \cdot \text{day}^{-1}$ in June 2004. Compartmental modelling estimated that a Christchurch person made 1200 IU/day of vitamin D in mid-summer but only 60 IU/day in midwinter. Daily supplements of 1450 or 2600 IU vitamin D₃ are predicted to raise the annual minimum mean plasma 25(OH)D to 75 or 100 nmol/L respectively.

Conclusions Most Christchurch people are vitamin D deficient most of the time and a daily supplement of 2600 IU vitamin D₃ would correct this.

It is recommended by some authorities that the plasma concentration of 25-hydroxyvitamin D₃ [25(OH)D] should be at least 75 nmol/L.¹⁻³ This figure is based both on observational evidence relating 25(OH)D levels to the risks of fracture, periodontal disease, colorectal cancer, and lower-extremity muscle weakness, and on the 25(OH)D levels found in those, such as farmers and lifeguards, with sun exposure typical of conditions in which modern skin tones evolved.

Further, a randomised controlled 4-year study of cholecalciferol plus calcium supplementation in postmenopausal women, which raised plasma 25(OH)D from 72 to 96 nmol/L, reduced by 77% the likelihood of being diagnosed with cancer between 1 and 4 years after the initiation of the trial.⁴

In contrast, surveys, especially of older people, even in apparently sunny countries such as Spain, Italy and Greece,⁵ Brazil,⁶ and Australia,⁷ show high proportions of people with 25(OH)D levels less than 75 nmol/L, particularly during winter months.

Within New Zealand, a survey of the Auckland workforce found that a large proportion of the workers, if not the majority, had serum 25(OH)D concentrations below 75 nmol/L,⁸ as did Auckland elderly,⁹ pregnant women in Wellington,¹⁰ Dunedin elderly,¹¹ and New Zealand children throughout the country.¹²

In a survey of New Zealanders aged 15 years and older, 3% were considered to have frank deficiency (<18 nmol/L) and 48% insufficiency, based on a cut-off of 50 nmol/L,¹³ and with differences apparent due to age, gender, latitude, and season.

Only a few studies at a limited number of latitudes (23°S,⁶ 37°S,⁹ and 68°N¹⁴) have measured the intensity of ultraviolet radiation (UV) at ground level at the same time as the 25(OH)D measurements were made. The studies at 23°S and 37°S were limited to older subjects (>40 years and >65 years respectively) and the study at 68°N had only 15 participants and covered a time period of only 60 days.

We now report the relationship between plasma 25(OH)D levels and solar UV in the general adult population in a southerly New Zealand location. We also develop a model of vitamin D metabolism to assist in the effective remediation of poor vitamin D status.

Methods

Subjects

Volunteer group—The subjects were residents of Christchurch, New Zealand (44°S), who volunteered to participate in a study to establish reference intervals for endocrine and metabolic test methods. The study was approved by the Upper South B Regional Ethics Committee. Recruitment was performed by contacting individuals selected randomly from Christchurch electoral rolls (241 responses, a 14% response rate) or by advertising (76 responses).

Volunteers completed a health questionnaire and were accepted if aged 18 or over, considered themselves healthy, and did not meet exclusion criteria that included diabetes and endocrine conditions, relevant cancers, steroid medication and recent hospitalisation. Of the initial volunteers, 33% were excluded either to meet study criteria or to avoid a more severe gender imbalance.

A single morning blood sample was collected within the period of February to August 2004 from 209 individuals of whom 105 were fasting. After further excluding those who were taking vitamin D supplements or cod-liver oil, 25(OH)D measurements were available for 201 volunteers (119 females, 82 males).

The mean (\pm SD) age was 46 \pm 14 years with a median of 45 years (range 18 to 83) and the mean (\pm SD) body mass index was 26.3 \pm 4.7.

Patient group—This group consisted of patients within the Christchurch region from whom samples were submitted to Canterbury Health Laboratories for measurement of plasma 25(OH)D between 1 July 2003 and 31 December 2004.

3702 samples were from females and 1138 from males, with a mean (\pm SD) age of the whole group of 59 \pm 23 years and a median age of 63 years (range 0.1 to 101). Samples were submitted from hospital wards, outpatient clinics and private practices. It is not known how many patients were taking vitamin D supplements.

Biochemical analyses

25(OH)D was measured using the DiaSorin radioimmunoassay kit (Stillwater, MN, USA). The antibody cross-reacts with vitamin D₂ and D₃ equally and results are the mean of duplicate determinations with internal and external QC samples in each batch. The low, medium, and high QC

values with coefficients of variation are 16.5 (16.2%), 35.9 (7.8%), and 132 (7.8%) nmol/L respectively. The laboratory is a participant in the DEQUAS (Charing Cross Hospital, London, UK) vitamin D external quality control programme.

Plasma calcium was measured on the Abbott Aeroset analyser (Abbott Laboratories, Abbott park, IL, USA) by colorimetry using the Arsenazo-III dye method with correction for albumin (+ 0.02*[40 – albumin(g/L)]). The intra-assay CV was 0.8% at 3 mmol/L.

Serum ionised calcium was measured on the Corning C865 blood gas analyser (Ciba Corning Diagnostic; Medfield, MA, USA) by calcium ion-selective electrode (between-batch CV 1% at 1.22 mmol/L). Assay stability was assured, as a matter of routine, by collation of daily patient means for all major analytes on the Abbott Aeroset analyser and by collation of monthly means and SDs for all internal QC samples. No significant assay drift was evident for either calcium or albumin over the time period of the study.

Parathyroid hormone (PTH) and C-telopeptide (CTX) were measured using the Roche Elecsys 2010 system. The low, medium, and high QC values with coefficients of variation are 2.2 (6.9%), 8.2 (5.3%), and 31.5 (4.7%) pmol/L for PTH—and 0.46 (7.5%), 0.59 (10.4%), and 1.64 (5.2%) µg/L for CTX.

Bone-specific alkaline phosphatase (BALP) was measured using the Beckman ACCESS system and the low and high QC values with coefficients of variation are 10.9 (7.5%) and 64.2 (6.8%) µg/L.

UV radiation

Daily UV irradiances (W/m^2) at 1-hour intervals were taken from the National Institute of Water and Atmospheric Research (NIWA) UV Atlas software package (<http://www.niwascience.co.nz/services/uvozone/atlas>).

The irradiances for Christchurch were summed to give the mean for each month of total erythemally-weighted UV (eUV) and vitamin D-weighted UV (dUV) per day. For erythema, the weighting is according to McKinlay and Diffey.¹⁵ For vitamin D, the weighting is from Maclaughlin Anderson and Holick,¹⁶ normalised to unity at 315 nm and truncated at 315 nm as suggested by MF Holick (personal communication, 2006).

The data product is derived from a combination of short-wave pyranometer data to estimate cloud effects, satellite-derived estimates of ozone, and a radiative transfer model.¹⁷ The pyranometer data are from LICOR LI-200 sensors. The accuracy is approximately $\pm 10\%$.

The UV data in the current study is the environmentally available UV. This study did not attempt to measure or estimate personal UV exposure, which depends on an individual's lifestyle, and may be only 3% or less of that available.¹⁸

Statistical analysis

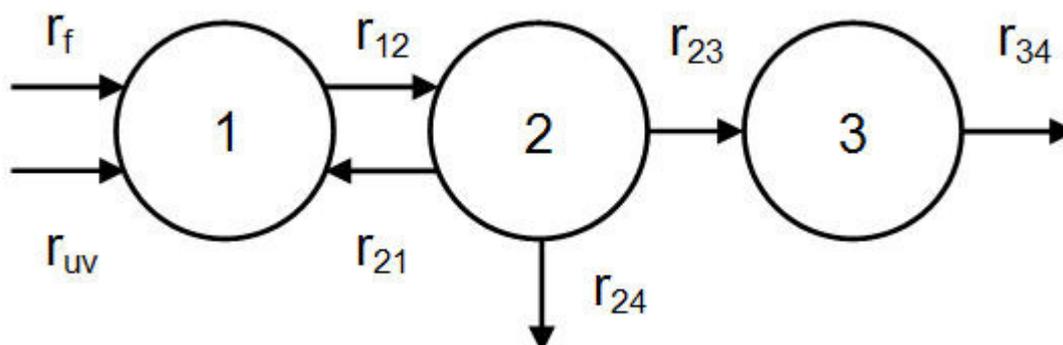
The NCSS statistical package (Kaysville, Utah, USA) was used for analyses. Confidence intervals (CI) for estimates are 95% intervals. Correlations were calculated by the non-parametric Spearman procedure and a significance level of 0.01 was used in view of the number of correlations examined.

Modelling

We used the three-compartment model of vitamin D metabolism shown in Figure 1 to represent the production and losses of vitamin D₃ and 25(OH)D in humans.

Compartments 1 and 2 are, respectively, faster and slower turnover vitamin D₃ compartments while compartment 3 contains 25(OH)D. Parameter v_3 , the volume of the 25(OH)D compartment, was taken to be 8 litres,¹⁹ and the half-life of 25(OH)D was taken to be about 10 days,²⁰ giving a value for k_{34} of 0.5. The other parameters in the model are: v_1 , v_2 , the volumes of compartments 1 and 2; r_f , the dietary intake of vitamin D; k_{uv} , the rate constant for cutaneous vitamin D production by solar dUV; rate constants k_{12} and k_{21} representing the interchange of vitamin D between compartments 1 and 2; k_{23} , the rate of conversion of vitamin D to 25(OH)D; k_{24} , the rate of metabolism of vitamin D by other pathways; and k_{34} , the rate of conversion of 25(OH)D to other metabolites. The parameters α and β define the non-linear feedback control of k_{23} by the concentration of 25(OH)D.

Figure 1. Model of vitamin D metabolism



Compartments 1 and 2 contain vitamin D₃ and compartment 3 contains 25(OH)D; 4 denotes further (undefined) metabolites. Rates (nmol/day) are denoted r and rate constants k . Parameters α and β define the feedback of 25(OH)D on its production rate. r_f =dietary vitamin D₃, $r_{uv}=k_{uv}E_{uv}$, E_{uv} =dUV energy, $r_{12}=k_{12}c_1$, $r_{21}=k_{21}c_2$, $r_{24}=k_{24}c_2$, $r_{23}=k_{23}c_2=c_2\alpha/(1+\beta c_3)$, $r_{34}=k_{34}c_3$.

To obtain values for the parameters in the model, the best-fit values for v_1 , v_2 , k_{12} , k_{21} , α , β , k_{24} , and k_{34} were estimated from the data taken from the literature given in Table 1 using the downhill simplex optimisation procedure.²¹ Then, to estimate the quantitative relationship between UVB radiation in Christchurch and the plasma 25(OH)D levels in the volunteer group, best-fit estimates of r_f and k_{uv} were obtained by fitting the model to the mean monthly 25(OH)D values in the volunteer group and the daily dUV energy intensity measurements during 2003 and 2004. The goodness-of-fit criterion was the minimum absolute deviation.

Table 1. Data from the literature used to estimate the parameters of the model in Figure 1

Dosage	Reference	Datum	Units	Observed value	Predicted value
300000 IU D ₃ oral bolus	Wu et al ²²	25(OH)D, maximum	day	17	22
		Δ 25(OH)D, maximum	nmol/L	65	77
		Δ 25(OH)D, 100 days	nmol/L	38	37
50000 IU D ₃ oral bolus	Armas et al ²³	Δ D3, 1 day	nmol/L	30	31
		Δ D3, 3 days	nmol/L	12	12
		25(OH)D, maximum	day	15	23
		Δ 25(OH)D, maximum	nmol/L	17	18
10000 IU D ₃ daily	Heaney et al ²⁴	Δ 25(OH)D, 21 days	nmol/L	63	44
		Δ 25(OH)D, 130 days	nmol/L	152	148

Values predicted by best-fit model parameter values also shown.

Results

The results for plasma 25(OH)D are summarised in the upper two panels of Figure 2. Plasma 25(OH)D tended to rise as UVB energy rose in spring and to fall as UVB energy fell in autumn. For the individual values in the volunteer group, the amplitude of a sine function fitted to 25(OH)D was 17.3 nmol/L (CI=12.1 to 22.6, n=201), and for the monthly mean 25(OH)D in the patient group was 8.4 nmol/L (CI=4.5–12.2, n=17).

The 25(OH)D levels tended to lag behind UVB and for both subject groups the Spearman correlation between dUV and 25(OH)D was at a maximum when the lag was 2 months, being 0.89 (n=6, p=0.02) for the volunteer group and 0.79 (n=16, p<0.001) for the patient group.

There was no significant difference in the monthly mean 25(OH)D levels between females and males in the volunteer group (mean difference=0.5 nmol/L, CI =-4.4–5.3 nmol/L, n=6)—but in the patient group, monthly mean 25(OH)D levels were higher for females (mean difference=2.9 nmol/L, CI=0.5–5.3 nmol/L, n=18).

Table 2 gives the proportions of subjects in the volunteer group with 25(OH)D levels below commonly used^{9,10} cut-off levels. The large majority had below optimal levels (<75 nmol/L) regardless of the time of year and the majority showed insufficiency (<50 nmol/L) in June, July, and August.

Deficiency (<25 nmol/L) was evident in at least a few individuals in each month studied and rose to 35% of the volunteer group in July–August. Only 1.5% of the volunteers had 25(OH)D below 12.5nmol/L (1 person in May and 2 in July).

Table 2. Monthly proportions of the volunteer subject group with plasma 25(OH)D concentrations below specified levels

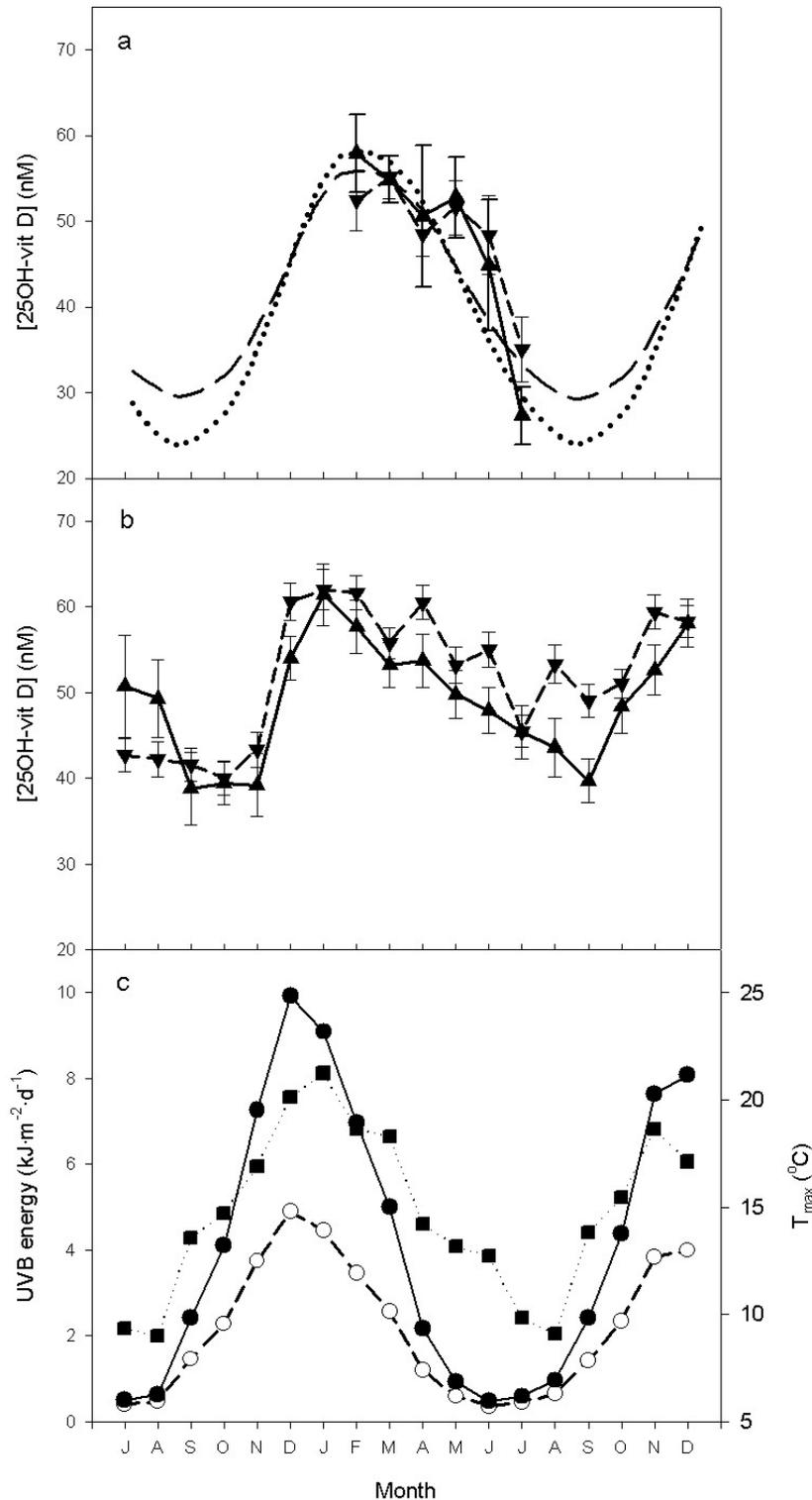
Month	Number of subjects	<25 nM (%)	<50 nM (%)	<75 nM (%)
February	40	3	40	88
March	63	2	40	91
April	28	7	39	93
May	35	3	46	91
June	11	9	64	100
July–August	26	35	89	100

The correlations between the time of year and the measured analytes, and between the analytes, are given in Table 3 for the volunteer group. As the year progressed 25(OH)D levels fell (p<0.001), total calcium (Ca_{tot}) rose (p<0.001), and ionised calcium (Ca⁺⁺) fell (p<0.01). PTH levels were neither significantly correlated with time of year nor with 25(OH)D levels but for the non-linear regression function, PTH=a + b/25(OH)D, the estimates of a and b (with CI) were 2.83 (2.51–3.15) and 24.4 (12.7–36.1).

The mean±SEM February (n=40) and July/August (n=25) values for total calcium were 2.20±0.02 and 2.28±0.02 mmol/L respectively. The corresponding values for ionised calcium were 1.19±0.01 mmol/L and 1.14±0.01 mmol/L.

The monthly ratios of mean daily dUV and eUV energies in Christchurch are shown in Figure 3.

Figure 2. Monthly plasma 25-hydroxy vitamin D concentrations in male and female Christchurch residents (mean±SEM) for (a) the volunteer group and (b) the patient group; (c) represents the corresponding monthly means of the UVB energy received daily at ground level and the maximum daily temperature. The first month is July 2003 and the last month is December 2004.



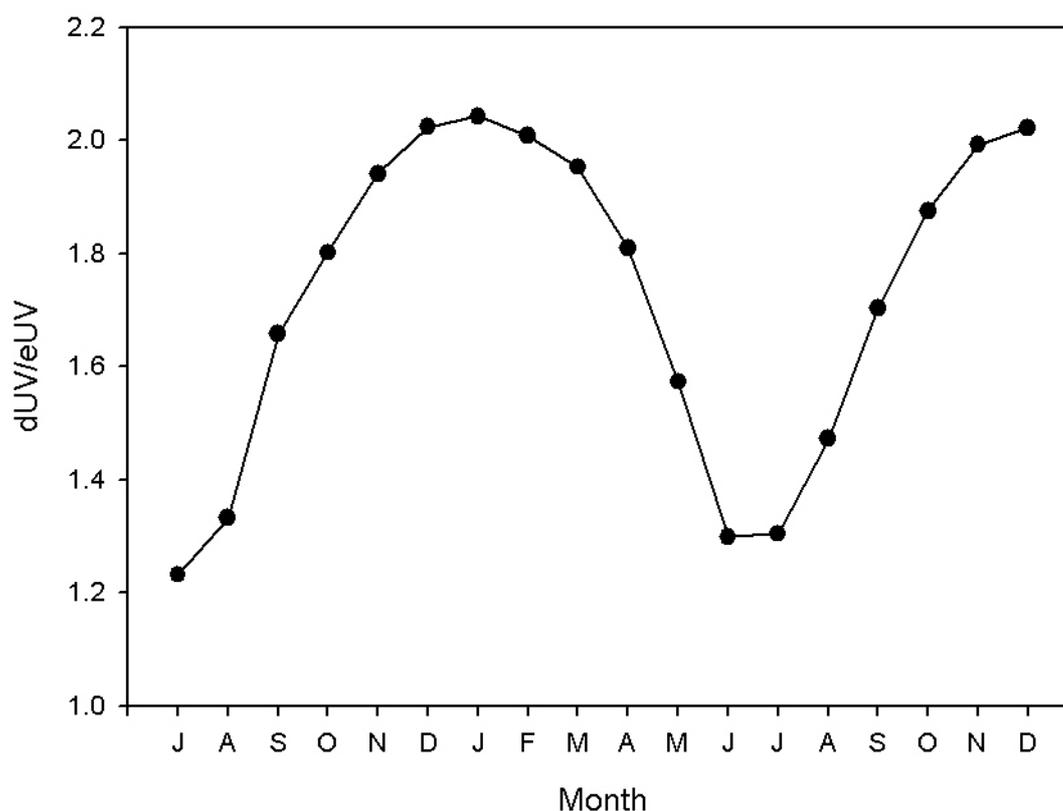
In (a) and (b), ▲—▲ male, ▼—▼ female. The smooth dashed line in (a) is the prediction of the best-fit model (dietary vitamin D 350 IU/d), and the dotted line shows the best fit if dietary vitamin D is assumed to be 200 IU/d. In (c), ●—● dUV, ○ - - - ○ eUV, ■ ··· ■ maximum temperature. The one volunteer studied in August (with a 25(OH)D value of 22 nmol/L) is not included.

Table 3. Correlations within the volunteer group

Variables	Time	25(OH)D	PTH	BALP	CTX
25(OH)D	-0.30**	1			
PTH	-0.16	-0.10	1		
BALP	-0.01	-0.21*	0.20*	1	
CTX	-0.10	-0.13	0.33**	0.45**	1
Ca _{tot}	0.37**	-0.08	-0.30**	0.03	-0.07
Ca ⁺⁺	-0.19*	0.21*	-0.33**	-0.02	0.00

* p<0.01, **p<0.001; PTH=Parathyroid hormone; BALP=bone-specific alkaline phosphatase; CTX=C-telopeptide.

Figure 3. Ratio of mean daily vitamin D-weighted UV energy (dUV) to mean daily erythemally-weighted UV energy (eUV) in Christchurch monthly from July 2003 to December 2004



The best-fit values of the parameters for the model of vitamin D metabolism are given in Table 4. The estimated dietary intake of vitamin D (r_f) is 23 nmoles/day (9 µg/day)

or 350 IU/day) and k_{uv} is estimated to be $8 \text{ nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$. The predicted values for the literature-derived data using the best-fit parameters are given in Table 1.

The plasma 25(OH)D concentrations predicted for the volunteer group throughout 2004 are shown in Figure 2a, both for the best-fit dietary vitamin D intake of 350 IU/d, and for an assumed dietary intake of 200 IU/d, in which case the best-fit value of k_{uv} is $10 \text{ nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$.

Table 4. Best-fit estimates of the parameters of the model of vitamin D metabolism

Parameter	Value	Units
v_1	53	litre
v_2	60	litre
v_3	8^\dagger	litre
r_f	23	$\text{nmol}\cdot\text{day}^{-1}$
k_{uv}	8.0	$\text{nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$
k_{12}	39	$\text{litre}\cdot\text{day}^{-1}$
k_{21}	6.9	$\text{litre}\cdot\text{day}^{-1}$
k_{24}	0.81	$\text{litre}\cdot\text{day}^{-1}$
k_{34}	0.5^\dagger	$\text{litre}\cdot\text{day}^{-1}$
α	1.33	$\text{nmol}\cdot\text{day}^{-1}$
β	0.039	$\text{litre}\cdot\text{nmol}^{-1}$

† Values obtained directly from literature.

The quantity of supplemental vitamin D needed to raise the modelled annual minimum mean plasma 25(OH)D in the volunteer group to 75 nmol/L is predicted to be 1450 IU/d ($36\mu\text{g}/\text{d}$), or to raise the annual minimum mean to 100 nmol/L, 2600 IU/d ($64\mu\text{g}/\text{d}$). In the latter case, the annual maximum mean plasma 25(OH)D is predicted to be 114 nmol/L. For both simulated supplement doses the annual maximum mean plasma 25(OH)D occurred in mid February and the annual minimum mean in early September.

In the absence of sunlight, the corresponding supplementation required is predicted to be 1600 IU/d ($41\mu\text{g}/\text{d}$) and 2700 IU/d ($68\mu\text{g}/\text{d}$). On the other hand, if year-round sunlight exposure were to be doubled, in the absence of supplementation, the annual maximum plasma 25(OH)D is predicted to rise from 56 nmol/L to 80 nmol/L and the annual minimum to rise from 29 nmol/L to 37 nmol/L.

Discussion

The two principal findings of this study are firstly that most, if not all, of the apparently healthy general population in Christchurch do have not adequate circulating levels of 25(OH)D at some time during the year, and secondly that relatively high levels of supplementation with vitamin D would be required to achieve healthy concentrations of 25(OH)D year round.

Considering first the high prevalence of vitamin D deficiency, Table 2 shows that even in summer, in February, only 12% of the volunteer group had optimal (>75 nmol/L) plasma 25(OH)D levels. This percentage fell during the autumn and winter until in June, July, and August, no one achieved this level.

Of even greater concern is that in every month studied, at least some of these self-declared “healthy” people were vitamin D deficient (<25 nmol/L). By July-August this proportion reached 35%.

The situation appears to be little better in the patient group where the average monthly levels of plasma 25(OH)D ranged from 40–62 nmol/L. This is despite it being likely that many of this group were on vitamin D supplementation and were having their 25(OH)D measured to check the dose level (Simon Wynn-Thomas, personal communication, 2007). Evidently few of this group would have maintained a level of 25(OH)D of at least 75 nmol/L year round.

These findings raise the question of what could be done about the near universal state of vitamin D deficiency in Christchurch, particularly in winter. Supplementation with vitamin D₃ is probably the most practical possible remedy on account of its ease of administration, safety,²⁵ and cost effectiveness. The novel modelling done in this paper is designed to give a guide to the necessary dosage levels and is the first description of a model of vitamin D metabolism that includes solar radiation.

The model suggests that taking 1450 IU of vitamin D₃ per day, in addition to normal sun exposure and dietary intake, would maintain the average 25(OH)D levels in healthy Christchurch people at 75 nmol/L or above all year. However many would still fall below 75 nmol/L at some time, so an annual minimum average of 100 nmol/L is probably more desirable and this is predicted to require a supplement of 2600 IU per day.

In New Zealand, prescription vitamin D₃ is only available as 50000 IU (1.25 mg) tablets (Cal.D.Forte[®]), hence 2600 IU/d is approximately equivalent to 1 tablet every 19 days, or approximately 2 per month. This is considerably greater than the dose rate recommended in the Medsafe datasheet (<http://www.medsafe.govt.nz/Profs/Datasheet/c/CalDFortetab.htm>) of 1600 IU/d (1 tablet per month), but well below the 10000 IU per day which has recently been suggested as no-observed-adverse-effect level.²⁵ However safety data from large studies and beyond 5 years is lacking.

Our finding that supplemental vitamin D₃ of about 1450 IU/d would be required to raise minimum average levels of 25(OH)D to 75 nmol/L is comparable to the 1700 IU/d that Vieth and coworkers¹ estimate to be required to raise levels from 50 nmol/L to 80 nmol/L, and so suggests our model is plausible.

Another strategy for raising 25(OH)D levels might be greater personal exposure to solar dUV, although this is not without risk as excessive UVB exposure can result in skin and eye damage.

Could the risk be minimised by choosing conditions where the ratio of vitamin D production to erythema is maximal? As can be seen from Figure 3, the vitamin D produced from a given erythemal exposure is greater in summer than at other times of year. This is because the sun is higher in the sky and hence the shorter wavelength dUV is less attenuated by the atmosphere compared to the attenuation of the longer wavelength eUV. Similarly, sun exposure at midday is preferable to exposure earlier or later in the day if the aim is to maximise vitamin D production while minimising burning.

However, we would not recommend a vitamin maintenance strategy based on midday summer sun for three reasons. Firstly, in summer it can take as little as 15 minutes to cause sunburn in sensitive individuals. Secondly, low levels of 25(OH)D are primarily a wintertime problem—but, as vitamin D in the body has a relatively short half-life of about 90 days,²² summer production would be of limited effectiveness by late winter. Thirdly, because the skin has some ability to repair UV damage, the same total dose received over a longer period, say weeks, results in less (or no) burning, compared to the same dose received in a shorter period, say 30 minutes.

Our estimate of $8 \text{ nmol}\cdot\text{m}^2\cdot\text{kJ}^{-1}$ for the rate constant for production of vitamin D by dUV (k_{uv} , Table 4) for a presumably typical person in Christchurch, allows the estimate that on an average day in midsummer when dUV energy is say 10 kJ/m^2 , that person gains 1200 IU/d of vitamin D from their solar exposure. In contrast, in midwinter, when average daily dUV is probably about 0.5 kJ/m^2 , only about 60 IU would be made.

Since the amount of solar exposure our subjects had was not measured, we cannot estimate the absolute amount of additional solar exposure that would be needed to raise 25(OH)D levels to at least 75 nmol/L year round. However our modelling prediction that doubling average solar exposure year-round would only raise the average minimum 25(OH)D by 8 nmol/L suggests that it would probably be impossible to raise the annual minimum to 75 nmol/L by increasing sun exposure in Christchurch.

Hence this leaves vitamin D supplementation as the only practical measure for usefully raising the annual minimum plasma 25(OH)D level. Note that doubling solar exposure does not double 25(OH)D levels, and the non-linearity between dUV exposure and plasma 25(OH)D is also evident between summer and winter when dUV varies by about ten-fold but 25(OH)D by about two-fold.

A similar study to the present one was conducted in Auckland, New Zealand, at about the same time (January 2004 to May 2005).⁹ There, the monthly mean plasma 25(OH)D levels in women were a little higher (maximum 63 nmol/L in March, minimum 40 nmol/L in August) than in Christchurch, but the mean levels found in men were markedly higher (maximum 102 nmol/L in March and minimum 59 nmol/L in September).

The generally higher 25(OH)D levels in Auckland no doubt reflect its lower latitude (37°) but it is not clear why the men were found to have much higher levels than the women, particularly as we did not find a significant gender difference in Christchurch in the volunteer group and, if anything, a reverse gender difference in the patient group (Figure 2).

Our observation of no significant negative correlation between PTH levels and 25(OH)D may be because very few (1.5%) of the volunteer group had severe vitamin D deficiency ($25(\text{OH})\text{D} < 12.5 \text{ nmol/L}$). However when parametric statistics rather than non-parametric were used, a non-linear hyperbolic relationship was evident.

Our three compartment model of vitamin D metabolism (Figure 1) is based on the two compartment model proposed and used by Heaney and coworkers,²⁴ but with two additions. One addition is a rapid turnover vitamin D compartment (compartment 1) in order to account for plasma measurements of vitamin D_3 ,²³ and the other addition is

that the rate of conversion of vitamin D to 25(OH)D, r_{23} , is under feedback control by 25(OH)D. This is to account for observations suggesting that the increase in plasma 25(OH)D is not linear with increasing dose of vitamin D, but tends to lessen with larger doses.²⁶

The assumption that this non-linearity is due to feedback by 25(OH)D is largely speculative, since another possibility is that the 25-hydroxylase enzymes in the liver tend to become saturated by larger quantities of vitamin D. However preliminary manipulation of our model suggested that the former assumption provided a better fit to the data in Table 1 than did the latter possibility (data not shown). Note that our model is a pragmatic mathematical construct designed to describe the plasma measurements in a way that allows predictions to be made; it is not intended that the compartments correspond to definite physiological or anatomical entities.

There is no straightforward way to estimate the uncertainties in the parameter estimates for the model (Table 4) because different assays for 25(OH)D can give differing values, the uncertainty of some of the data in Table 1 is unknown, and the parameter optimisation algorithm does not lend itself to error estimation. In addition, different experimenters can obtain quite different estimates for ostensibly the same parameter, for example the slope of the relationship between vitamin D₃ dose and plasma 25(OH)D increment.²⁶

The limited number of months for which we measured 25(OH)D levels in the volunteer group limits the precision of the estimates of the values of the model parameters k_{uv} and r_f . As the estimate of 350 IU/d for vitamin D intake from food (and from visits to sunnier places), r_f , might be considered high, k_{uv} was also estimated on the assumption that r_f was 200 IU/d. This gave a value of k_{uv} that was only 25% higher, suggesting that the best-fit estimate of k_{uv} is reasonably robust. However, we have not been able to allow for the probably greater exposure of skin to the sun in the warmer months.

Studies are underway to improve the seasonal range of measurements, to directly measure personal exposure to solar UV and to quantify the relationship between personal UV exposure and vitamin D status. The measurement of actual personal exposure to UV is critical and will be novel and challenging.

It should be noted that our model, and its predictions regarding dosages to raise 25(OH)D levels, apply only to vitamin D₃ since Heaney's group²³ have shown that vitamin D₂ is metabolised much more rapidly and does not raise or maintain plasma 25(OH)D levels as effectively.

In summary, our study finds firstly, as many others¹ have, that residents in temperate regions have unhealthily poor vitamin D status, and secondly, that modelling suggests that vitamin D supplementation in greater than the usually recommended dosage is required to address the problem.

Competing interests: Drs Florkowski and Elder are employees of Canterbury Health Laboratories, which might benefit commercially if there is an increased interest in testing vitamin D levels in patients upon this paper's publication (although this paper does not explicitly advocate testing vitamin D status).

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Vitamin D and muscle strength in patients with previous fractures

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Abstract

Aim To assess the vitamin D status and its association with objective left leg muscle strength measurements in patients with long-bone fracture discharged from a tertiary hospital in Western Australia. The secondary objective was to determine whether tests of balance and functional status are valid predictors of muscle strength and if they correlate with serum 25 hydroxyvitamin D (25OHD) levels.

Methods This was a cross sectional study. Patients who had been discharged from a tertiary hospital following a low impact fracture over a 12-month period were invited to participate. Invitation was through a postal survey audit of osteoporosis risk and treatment and requesting participation in the study. Females over the age of 60 were included. Patients agreeing to participate were invited to attend a research clinic. Patients had demographic data, muscle strength, functional assessments, and biochemical parameters including serum 25OHD assessed.

Results Of the 99 subjects who completed the study, the mean 25OHD level was 52.0 nmol/L. The main univariate associations with 25OHD were cognitive function, functional indices, sun exposure, albumin, and parathyroid hormone (PTH). In a multivariate model, the strongest and most significant association was between muscle strength and 25OHD levels ($r=0.489$, $p<0.001$). Muscle strength was most strongly associated with 25OHD levels >50 nmol/L ($r=0.51$, $p<0.001$).

Conclusion This study demonstrates a significant association between 25OHD levels and left leg muscle strength. This independent association supports the hypothesis that 25OHD deficiency may be responsible for poor muscle strength.

Low trauma fracture is a major health problem for postmenopausal women and to a lesser extent older men. The two major causes of fracture in these groups are osteoporosis and falls. There are established pharmacological treatments for osteoporosis,^{3,4} however treatment of falls is much more difficult.⁵

In the setting of osteoporosis, higher body sway, quadriceps weakness, and conditions linked with increased risk of falling are associated with a significantly increased risk of fractures.^{6,7} Studies have also suggested an association between bone mineral density and muscle strength.⁸

Muscle strength has been shown to decline with age⁹ and has been shown to be associated with the functional status of older people.¹⁰ Frail older people¹¹ and patients with hip fracture¹² are reported to have a high prevalence of vitamin D deficiency due to reduced sunlight exposure, reduced synthesis of vitamin D, low vitamin D dietary intake, poor absorption, and hepato-renal disease.^{11,12}

Receptors for vitamin D metabolites that are functionally responsive to vitamin D have been identified in human skeletal muscle.^{13,14} Vitamin D deficiency and osteomalacia have been shown to be associated with myopathy,^{15,16} and have in some studies^{17,18} been shown to be reversible with vitamin D treatment.

However, other studies looking at vitamin D supplementation in unselected or vitamin D replete patients have shown no benefit with vitamin D supplementation¹⁹ or no association between serum vitamin D level and muscle strength.¹⁶

Fractures caused by falls occur in about 5% of older persons each year.^{1,20} It has been suggested that vitamin D deficient patients are at higher risk of falls due to increased postural sway.^{21,22} In at least one study, supplementation with vitamin D and calcium reduced the risk of falls in recurrent fallers.²⁰ However, evidence for the association between vitamin D levels and muscle strength on objective testing has not been conclusively proven.¹⁶

A possible reason for the inability to show a direct association between vitamin D levels and muscle strength, and the failure to show any improvement with vitamin D supplementation,¹⁹ may be due to poor patient selection. It is postulated that vitamin D replete patients will not benefit from further supplementation.

Hence in this study we looked at a frail, at risk population of patients who had previously been treated for hip or other long-bone fractures following a fall. We assessed muscle strength as the primary measure rather than using an indirect measure like falls.

The main aims of the study were to assess the vitamin D status of this group of patients and to assess whether there is an association between their serum 25 hydroxyvitamin D level and objective muscle strength measurements. The secondary aim was to determine whether tests of balance and functional status are valid predictors of muscle strength and whether they correlate with serum 25 hydroxyvitamin D levels.

Methods

Subjects—Patients were selected from a tertiary hospital database in Western Australia with a primary admission diagnosis of a long-bone fracture as described previously by Inderjeeth et al in *Internal Medicine Journal* (2006).²³

Only subjects who were identified from the case notes as suffering a low impact fracture of the hip, humerus or forearm were invited to participate. Subjects had to be female, aged >60 years, at least 6 months post fracture and be able to walk independently with or without walking aids and participate in muscle strength measurements. 365 patients were identified as suitable from case records over a 12-month period and invited to participate in the study. Patients were mailed an osteoporosis questionnaire and invited to attend a Fracture, Falls and Balance Clinic for assessment of their osteoporosis and offered participation in this study.

Exclusion criteria were male gender, poor cognition (defined as mini mental state examination <20), significant systemic disease limiting their ability to participate, hypercalcaemia, primary hyperparathyroidism, or a long-bone fracture within 6 months to allow for fracture healing and muscle recovery. Patients on vitamin D supplements were allowed in the study. Enrolment occurred throughout the year and was not seasonally based. The protocol was approved by the Sir Charles Gairdner Hospital Ethics Committee. All subjects gave informed consent.

Study design—All patients had demographic data collected and a research nurse and doctor collected information using validated instruments. Instruments selected include the Berg Balance Scale (BBS),²⁴ which was used to determine the subject's balance in a variety of spheres. The subject's daily functional status was assessed using the Frenchay Activity Index (FAI).²⁵

The Modified Bartel Index (MBI)²⁶ was used to assess functional independence in relation to personal care and mobility. The Falls Efficacy Scale (FES)²⁷ was used to assess patient's confidence and fear of falling in carrying out routine tasks. RPH (Royal Perth Hospital) outdoor score^{11,12} was used to measure sunlight exposure [range 0(no exposure) to 7(regular adequate exposure)].

Timed "Up & Go" (TUAG)²⁸ was used as a measure of functional mobility. Cognitive function was assessed using the mini mental state examination (MMSE)²⁹ and mood was assessed using the brief assessment of depression (BASDEC).³⁰

Muscle strength was measured in the left leg using a Keylink Kinitech Dynamometer.³¹ Left leg power and torque were measured in flexion and extension. Left leg flexion and extension was measured in a standard seating position as recommended by the manufacturer of the Keylink Kinitech Dynamometer.

Seating position was adjusted for height and the angle of the hip and knee were standardised. The highest reading of three measures for each were taken. Left Leg Extensor maximum power (LLExtmp) and Left Leg Extension peak Torque (LLExtpt) and Left Leg Flexor maximum power (LLFxmpt) and Left Leg Flexor peak torque (LLFlxpt) were measured.

Blood samples were collected to measure serum calcium, phosphate, creatinine, albumin, alkaline phosphatase, intact parathyroid hormone (PTH), and 25 hydroxyvitamin D (25OHD). The blood samples were taken in standardised tubes as recommended by the local pathology centre and the reference limits were as standardised for the local population.

Blood samples were collected in the morning on the day of the muscle strength assessment. All blood tests were performed at the one pathology centre. 25OHD was determined by radioimmunoassay using the Diasorin kit. The confidence values at 37 and 135 nmol/L were 10.8% and 8.1% respectively.

Statistical analyses—The data were entered into an SPSS software database and analysed by a biostatistician. Descriptive statistics were performed including mean, standard deviation (SD), and range. Univariate correlations (Pearson's) for normally distributed variables and Spearman's for non normally distributed variables were performed looking for association between 25OHD, functional and biochemical parameters, and between muscle strength, functional and biochemical parameters.

Stepwise multivariate analysis was performed looking for significant associations between muscle strength and age, biochemical, and functional parameters. The t-test and one-way ANOVA were used to assess differences between groups. A p value of <0.05 is considered significant.

Results

Of the 365 patients mailed questionnaires, 105 subjects agreed to participate in this cross sectional study and were enrolled. A total of 99 subjects adequately completed all assessments and were included in the muscle strength analysis. Of the 6 excluded subjects, 3 had primary hyperparathyroidism, 2 had no serum 25OHD measurement, and 1 had difficulty completing the muscle strength assessment.

All subjects were female with a mean age of 79.5 with a standard deviation of 7.9 and a range of 61 to 95 years. All patients enrolled had sustained a previous long-bone fracture. Thirty-four percent had sustained a lower limb fracture (hip) only, and 53% an upper limb fracture (wrist or humerus) only. Thirteen percent of subjects had sustained both upper and lower limb fractures.

The mean 25OHD level of the cohort was 52.0 nmol/L (SD 22.3) with a range of 16–159 (reference limits >50 nmol/L). Only 10% were taking vitamin D either as simple vitamin D or as multivitamin supplements. The values of the functional and biochemical parameters assessed are reported in Table 1.

Table 2 describes the univariate associations between 25OHD and age, functional, and biochemical assessments. All functional assessments were significantly associated with measured serum 25OHD apart from the patients' age, Berg Balance Scale, and the depression scale.

Table 1. Mean (SD), minimum, and maximum values for age, functional, and biochemical measures of patients

Measure (reference range)	Number	Mean	SD	Minimum	Maximum
Age (years)	105	79.5	7.9	61	95
MMSE (0–30)	97	28.5	1.7	23	30
FAI (0–45)	91	29.4	8.6	0	45
BASDEC (0–20)	85	3	3	0	16
RPH (outdoor score) (0–7)	94	4.8	1.5	0	7
FES (0–10)	94	8	1.8	3	10
TUAG (normal <12 sec)	93	16.9	7.7	7	49
BBS (0–56)	95	57.4	9.9	29	74
Calcium (2.15–2.55 mmol/L)	99	2.4	0.1	2.15	2.83
Phosphate (0.8–1.4 mmol/L)	96	1.1	0.2	.51	1.69
Creatinine (50–95 umol/L)	101	79.2	22.6	46	148
Albumin (35–50 g/L)	102	40.8	2.5	33	47
ALP (30–135 U/L)	94	85.9	29.4	19	206
PTH (0.9–9 pmol/L)	100	5.6	5.2	.9	43.0
25OHD (50–160 nmol/L)	103	51.9	22.3	16	159

SD: Standard Deviation; **MMSE:** Mini Mental State Examination; **FAI:** Frenchay Activities Index; **BASDEC:** Brief Assessment Schedule Depression Cards **FES:** Falls Efficacy Scale; **RPH:** Royal Perth Hospital; **TUAG:** Timed “Up & Go” Score; **BBS:** Berg Balance Scale; **ALP:** Alkaline Phosphatase; **PTH:** Parathyroid Hormone; **25OHD:** 25 hydroxyvitamin D; **g/L:** grams per litre; **mmol/L:** Millimole per litre; **umol/L:** Micromole per litre; **pmol/L:** Picomole per litre **U/L:** Units per litre.

Table 2. Association between 25 hydroxyvitamin D and age, functional, and biochemical measures

Measure	Number	Correlation (r)	p value
Age	103	-0.05	0.63
MMSE	95	0.22*	0.03
BASDEC	84	-0.13	0.25
FAI	90	0.23*	0.03
RPH (outdoor score)	93	0.30**	0.002
FES	93	0.25*	0.01
TUAG	91	0.19	0.06
BBS	94	0.15	0.14
Calcium	98	-0.05	0.62
Phosphate	95	-0.12	0.27
Creatinine	100	0.05	0.59
Albumin	101	0.32**	0.001
PTH	100	-0.22*	0.03

MMSE: Mini Mental State Examination; **BASDEC:** Brief Assessment Schedule Depression Cards **FAI:** Frenchay Activities Index; **RPH:** Royal Perth Hospital; **FES:** Falls Efficacy Scale; **TUAG:** Timed “Up & Go” Score; **BBS:** Berg Balance Scale; **PTH:** Parathyroid Hormone; *p<0.05; **p<0.01.

Albumin and PTH were the only biochemical assessments associated with measured serum 25OHD. There was a positive association with albumin and a negative association with PTH. The two factors most strongly associated with 25OHD were serum albumin (r=0.32, p=0.001) and the RPH outdoor score (r=0.30, p=0.002).

Table 3 describes the significant univariate associations between muscle strength and age, functional and biochemical assessments. Although most of the functional

assessments were associated with muscle strength, serum 25OHD level was the only biochemical assessment associated with muscle strength.

Table 3. Association between muscle strength and age, biochemical, and functional measures

Measure	Muscle strength							
	LLExtpt		LLExtmp		LLFlxpt		LLFlxmp	
	r value	p value	r value	p value	r value	p value	r value	p value
Age	-0.304**	0.002	-0.295**	0.003	-0.248**	0.004	-0.248*	0.014
MMSE	0.329**	0.001	0.246*	0.019	0.330**	0.001	0.147	0.163
BASDEC	-0.140	0.215	-0.157	0.164	-0.233*	0.037	-0.215	0.055
FAI	0.147**	<0.001	0.377**	<0.001	0.419**	<0.001	0.310**	0.004
RPH (outdoor score)	0.309**	0.003	0.298**	0.005	0.309**	0.003	0.258*	0.015
FES	0.368**	<0.001	0.307**	0.003	0.325**	0.002	0.212*	0.046
TUAG	-0.447**	<0.001	-0.408**	<0.001	-0.464**	<0.001	0.361**	0.001
BBS	0.407**	<0.001	0.383**	<0.001	0.375**	<0.001	0.279**	0.007
25OHD	0.424**	<0.001	0.427**	<0.001	0.315**	0.002	0.252*	0.012

LLExtpt: Left Leg Extensor Peak Torque; **LLExtmp:** Left Leg Extensor Max Power; **LLFlxpt:** Left Leg Flexor Peak Torque; **LLFlxmp:** Left Leg Flexor Max Power; **MMSE:** Mini Mental State Examination; **BASDEC:** Brief Assessment Schedule Depression Cards **FAI:** Frenchay Activities Index; **RPH:** Royal Perth Hospital; **FES:** Falls Efficacy Scale; **TUAG:** Timed “Up & Go” Score; **BBS:** Berg Balance Scale; **25OHD:** 25 hydroxyvitamin D; *p<0.05; **p<0.01.

Table 4. Multivariable associations between muscle strength and age, biochemical, and functional measures

Measure	Muscle strength							
	LLExtpt		LLExtmp		LLFlxpt		LLFlxmp	
	r value	p value	r value	p value	r value	p value	r value	p value
25OHD	0.489**	<0.001	0.476**	0.001	0.367*	0.019	0.259	0.055
BBS	0.310*	0.020	0.272*	0.043	0.198	0.148	0.206	0.125
TUAG	-0.161	0.241	-0.125	0.362	-0.303*	0.023	-0.238	0.075

Model includes age and all biochemical and functional measures. Only those measures with significant associations are shown. **LLExtpt:** Left Leg Extensor Peak Torque; **LLExtmp:** Left Leg Extensor Max Power; **LLFlxpt:** Left Leg Flexor Peak Torque; **LLFlxmp:** Left Leg Flexor Max Power; **25OHD:** 25 hydroxyvitamin D; **BBS:** Berg Balance Scale; **TUAG:** Timed “Up & Go” Score; *p<0.05; **p<0.01.

Table 4 describes the significant multivariate associations between muscle strength and all other parameters measured (age, biochemical, and functional). In the multiple regression model, 25OHD was significantly associated with both extensor assessments (LL Extpt r=0.489, p<0.001 and LL Extmp r=0.476, p=0.001) as well as the flexor PT (r=0.367; p=0.019) assessment, and showed a strong trend to an association with flexor MP (r=0.259, p=0.055).

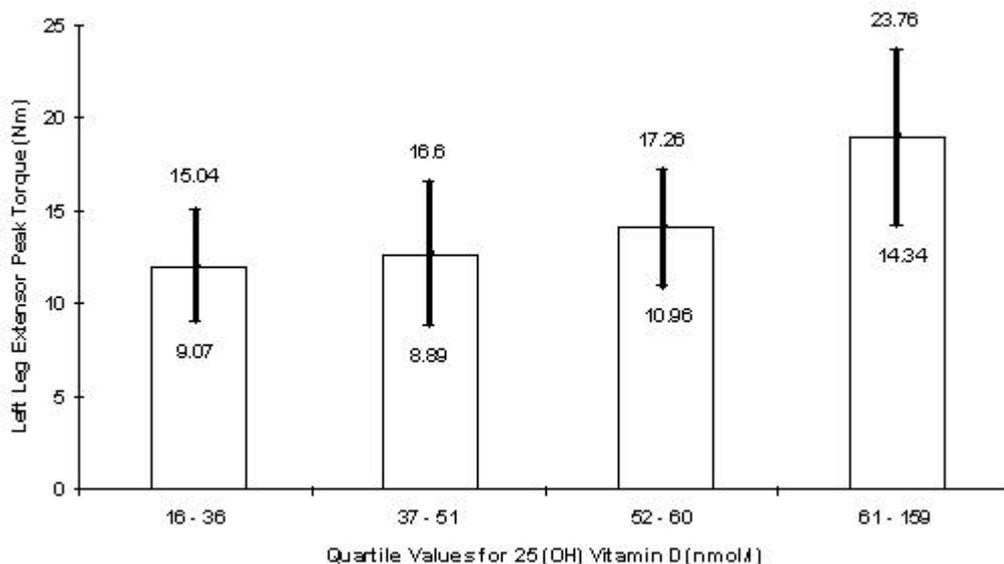
Only two other factors (both functional) showed any association with muscle strength in the multiple regression model. Berg Balance was associated with extensor strength while TUAG was inversely associated with left leg flexor PT only. Site (upper or lower limb) and side of fracture (left or right) did not change the association between muscle strength and 25OHD and were non significant associations in the multiple regression model.

The functional assessments with no significant association in the regression model included MMSE, BASDEC, FAI, RPH outdoor score, and FES. The biochemical assessments with no significant association in the regression model included calcium, phosphate, albumin, alkaline phosphatase, and parathyroid hormone.

Forty-seven patients had a 25OHD level <50 nmol/L and 14 patients had a 25OHD <30 nmol/L. The association between muscle strength and 25OHD was strongest in the sub-group with 25OHD levels >50 nmol/L ($p < 0.01$ for all four muscle strength assessments with the r value ranging between 0.46 and 0.51).

The association between muscle strength and 25OHD levels was not significant in subjects with 25OHD levels <50 nmol/L ($p > 0.05$). Using one-way ANOVA, the quartile with the highest 25OHD level (>60 nmol/L) demonstrated the highest mean muscle strength (Figure 1). However, this association was only significant for LL Extpt ($p = 0.035$) but not LL Extmp ($p = 0.065$), LL Flxpt ($p = 0.11$), or LL Flxmp ($p = 0.25$).

Figure 1. Mean and 95% confidence intervals of muscle strength (left leg extensor peak torque) for quartiles of 25 hydroxyvitamin D



Subgroup analysis was undertaken to compare muscle strength and 25OHD between the group with left versus right-hip fracture and those with upper-limb and lower-limb fractures. There was no significant difference in left-leg muscle strength based on side of hip fracture ($p > 0.05$). However, those with upper-limb fracture only had higher left-leg muscle strength than those with lower-limb fracture ($p < 0.05$). There was no significant difference in 25OHD levels in these subgroups ($p > 0.05$).

Discussion

Vitamin D deficiency is being increasingly identified as a significant problem in older patients.^{11,12,32} Its impact on bone has been extensively investigated. However, its impact on muscle strength and falls is less well understood.

Given the high incidence of falls, osteoporosis, and vitamin D deficiency in older individuals, establishing an association and correcting vitamin D deficiency may be potentially beneficial in improving muscle strength, reducing falls, and hence reducing fractures.

This cross sectional study looked at the potential association between muscle strength and 25OHD deficiency in patients previously admitted with fracture, including 46% with a previous hip fracture.

We found a moderate and significant positive correlation between muscle strength and 25OHD. Although a number of factors appear to be associated with muscle strength on univariate analysis, the only factors independently associated after correction for other factors in a multiple stepwise regression analysis were 25OHD, the Berg Balance Scale, and the Timed "Up & Go" score.

The 25OHD level appears to be the only consistent significant association with left-leg muscle strength with a moderate positive correlation. The association with Berg Balance and Timed "Up & Go" is weaker and only associated with some parameters of muscle strength. Although side of fracture does not appear to influence muscle strength, the presence of lower limb fracture does appear to result in worse muscle strength.

The main limitation of this study is the relatively low response rate. In addition, as with other similar studies, frailer subjects and those with cognitive impairment were excluded on the basis that they could not perform the muscle strength assessment.

These are both groups that are more likely to have been vitamin D deficient. The relatively high mean 25OHD level of 52 nmol/L reflects this and unfortunately the relatively small sample size does not allow for adequate subgroup analysis.

The stronger association between 25OHD level and muscle strength parameters in the sub-group with levels >50 nmol/L is unexpected, as we would have predicted a stronger association in the group deemed to be vitamin D deficient i.e. <50 nmol/L. This may reflect a threshold level of 25OHD which must be reached before vitamin D starts to affect muscle strength in patients.

It would also strongly support the argument that 25OHD levels need to be maintained well above 50 nmol/L for adequate replacement and benefit in terms of muscle strength. This is an area that certainly requires further study especially with regards to the impact of replacement of vitamin D in subjects with levels below 50 nmol/L and the most appropriate level desirable for greatest benefit in terms of muscle strength.

Higher levels may be the goal rather than aiming for low normal levels for greater benefit in terms of muscle strength and possibly bone.

The strength of this study is that it looked at a high-risk group who are more susceptible to vitamin D deficiency due to reasons of relative frailty, previous falls,

and fractures. This is the population that would need to be targeted as a priority in terms of vitamin D replacement.¹²

In patients with osteoporosis, the goal should be to reduce fracture risk. To achieve this we need to look beyond the improvement of bone strength and quality. Falls prevention is another obvious objective.

As muscle weakness is a major cause of falls, improving muscle strength is an important component of this strategy. Hence identifying and treating conditions likely to be associated with reduced muscle strength (such as vitamin D deficiency) is an area that warrants further investigation. And to confirm the causal association between vitamin D and muscle strength, a large randomised controlled intervention trial is needed.

Competing interests: None.

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The failure to diagnose inborn errors of metabolism in New Zealand: the case for expanded newborn screening

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Abstract

Aims Expanded newborn screening uses a new technology, tandem mass spectrometry, to diagnose an additional 20 plus rare treatable inborn errors of metabolism based on the further analysis of the current newborn Guthrie card blood sample. The purpose of this study was to investigate the incidence of these disorders in New Zealand, based on clinical diagnosis rates, and compare these to the incidence, based on the established expanded newborn screening programme, in New South Wales, Australia.

Methods Over a 3-year period, the cases of inborn errors of metabolism notified to the New Zealand Paediatric Surveillance Unit and/or identified by the relevant metabolic laboratories were recorded and compared to the incidence rates during the same period in New South Wales.

Results There were 175,000 and 270,000 births in New Zealand and New South Wales respectively during the study period. Eight cases of treatable inborn errors (potentially diagnosable by newborn screening) were diagnosed in New Zealand compared to 41 (including two prior to screening) in New South Wales. The disorder medium chain acyl Co-A dehydrogenase deficiency was diagnosed twice in New Zealand and in 24 newborn infants in New South Wales.

Conclusions Without expanded newborn screening, inborn errors of metabolism are under-diagnosed in New Zealand. This study supports the recent establishment of screening in New Zealand.

Inborn errors of metabolism are genetic defects of biochemistry that may result in clinical illness. Individually they are rare conditions, but collectively they are not uncommon with an overall prevalence approaching 1:1000.^{1,2}

A group of conditions—disorders of intermediary metabolism—involve the catabolism of fats and protein. These are the fatty acid oxidation disorders and the amino and organic acidopathies. The former involve defects in the mitochondrial oxidation of fatty acids and present (classically) with hypoglycaemia, inappropriately low ketones, and subsequent encephalopathy often following a period of fasting and/or intercurrent illness in a child. The latter result in massive accumulation of specific amino and organic acids, sometimes with associated hyperammonaemia, and clinically often present with neonatal encephalopathy or alternatively with varied presentations later in life.

Because the diseases are rare, and the clinical phenotypes encountered are much more frequently seen in conditions such as sepsis, the correct underlying diagnosis is frequently missed. This leads to catastrophic outcomes, as death is likely if an accurate diagnosis is not made. In fact even when a correct diagnosis is made during

the initial presentation the outcome can be poor as neurological damage has already occurred. Thus diagnosis and treatment prior to clinical illness is ideal.

Expanded newborn screening (ENBS), using tandem mass spectrometry, accurately detects marker compounds in the dried blood spot from the neonatal Guthrie card. The technique is highly sensitive and specific and, once initial setting up costs are met, is relatively cheap when added to an existing newborn screening service.³

ENBS allows for the identification of around 30 different disorders—provided the sample is taken at the correct time, transported quickly to the screening laboratory, and analysed appropriately, and treatment is started prior to the child becoming unwell.⁴ The newborn screening service in New South Wales, one of the pioneers of ENBS, has recently shown that this leads to significant improvements in diagnostic rates and outcome.^{5,6}

The purpose of this study was to evaluate the incidence rates of the disorders of intermediary metabolism in New Zealand (NZ), based on the numbers of clinical diagnosis, from January 2004 till the commencement of ENBS in December 2006 and to compare these to the incidence rates, obtained mostly via EBNS, in New South Wales (NSW).

Method

From January 2004, paediatricians in NZ were sent monthly questionnaires (via email or regular post) from the New Zealand Paediatric Surveillance Unit (NZPSU). It asked whether they had diagnosed an inborn error of metabolism over the previous month. If they had then they were sent a further questionnaire regarding the exact diagnosis along with aspects of the clinical presentation and immediate outcome.

This study was approved by the Lower South Regional Ethics Committee. In addition the Auckland, Wellington, and Christchurch laboratories (that either perform the relevant metabolic investigations or facilitate samples being sent to the appropriate tertiary laboratories in Australia) were contacted and asked to report cases.

The numbers of patients diagnosed with disorders of intermediary metabolism diagnosed clinically (thus excluding PKU which is diagnosed by already established screening methods) in NZ from 2004–2006 were compared to those obtained from childhood clinical presentations and the expanded newborn screening programme (see Table 1 for a list of diseases screened that can be diagnosed by ENBS) based at The Children's Hospital at Westmead in Sydney, New South Wales during the same period.

The latter facility screens all newborns in New South Wales and the Australian Capital Territory (these two areas will be referred to as 'NSW' in this document).

Results

From 2004–2006 inclusive there were approximately 175,000 births in NZ⁷ and 270,000 births in NSW.⁸

During the 3-year study period, 15 cases of disorders of intermediary metabolism were reported in NZ (Table 2). One of these (Maple Syrup Urine Disease, MSUD) was diagnosed by the newborn screening programme (NZ is somewhat unusual internationally in that it had an established screening programme specific for this disorder during the period 2004–6); one was diagnosed prenatally (ornithine transcarbamylase deficiency, OTC) following a sibling diagnosis; and in 13 cases the diagnosis was made following metabolic investigations performed during the clinical investigation of a symptomatic patient. Eight cases (including one adult) were

diagnosed with disorders on intermediary metabolism that could have been detected by ENBS.

Table 1. Inborn errors of metabolism that can be diagnosed by expanded newborn screening

Fatty acid oxidation disorders

Carnitine uptake defect
Carnitine palmitoyltransferase 1 deficiency (CPT1)
Carnitine palmitoyltransferase 2 deficiency (CPT2)
Carnitine-acylcarnitine translocase deficiency
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
Trifunctional protein deficiency
Multiple acyl-CoA dehydrogenase deficiency (MADD)

Aminoacidopathies

Phenylketonuria (PKU)
Homocystinuria (Hcy)
Maple syrup urine disease (MSUD)
Argininase deficiency
Argininosuccinic acidaemia
Citrullinaemia type 1 (CIT I)
Citrullinaemia type 2 (CIT II)
Tyrosinaemia type II (TYR)

Organic acidopathies

Glutaric acidaemia type 1 (GA1)
Beta ketothiolase deficiency
Isovaleric acidaemia
Methylmalonic acidaemia (Cobalamin disorders- CblC)
Methylmalonic acidaemia (mutase deficiency) (MMA)
Holocarboxylase synthetase deficiency (HCS)
Propionic acidaemia
HMG-CoA lyase deficiency
2 Methyl 3 hydroxybutyric acidaemia
3 Methyl glutaconic acidaemia
3 Methylcrotonyl carboxylase deficiency (3-MCC)

Other

Vitamin B-12 deficiency

Table 2. Disorders of intermediary metabolism diagnosed in New Zealand: 2004–06

Disease	Method of initial diagnosis	Age of diagnosis	Outcome	Ability to diagnose on expanded newborn screening	Early diagnosis likely to improve outcome
MCAD	Clinical	9 months	Good	Yes	Yes
MCAD	Clinical	34 months	Good	Yes	Yes
MSUD	NBS	1 week	Good	Yes	Yes
GA1	Clinical	5 months	Poor	Yes	Yes
Ketothiolase	Clinical	6 months	Good	Yes	Yes
HCS	Clinical	1 week	Poor	Yes	No
MADD	Clinical	1 month	Poor	Yes	No
VLCAD	Clinical	40 years	Good	Yes	Yes
NKH	Clinical	1 week	Poor	No	No
NKH	Clinical	2 months	Poor	No	No
NKH	Clinical	1 week	Poor	No	No
NKH	Clinical	1 week	Poor	No	No
OTC	Prenatal	Antenatal	Poor	No	No
OTC	Clinical	10 years	Good	No	Yes
OTC	Clinical	14 years	Good	No	Yes

MCAD=Medium chain acyl Co-A dehydrogenase deficiency; GA1=Glutaric acidemia type I; HCS=Holocarboxylase synthetase (deficiency); MADD=Multiple acyl Co-A dehydrogenase deficiency; VLCAD=Very long-chain acyl-CoA dehydrogenase deficiency; NKH=Non-ketotic hyperglycaemia; OTC=Ornithine transcarbamylase (deficiency).

Table 3. Disorders of intermediary metabolism diagnosed in New South Wales: cohort born 2004-06 (N=45)

Disease	Method of initial diagnosis	Number of children	Early diagnosis likely to improve outcome
MCAD	NBS	24	Yes
CblC	NBS	1	Yes
MMA	Clinical-pre NBS	1	Yes
MMA	Prenatal	1	Yes
MSUD	NBS	1	Yes
VLCAD	NBS	3	Yes
CIT I	NBS	1	Yes
CIT II	NBS	1	Yes
TYR	NBS	1	Yes
OTC	Clinical	1	Yes
OTC	Prenatal	1	Yes
Hcy	NBS	1	Yes
GA1	NBS	4	Yes
MADD	NBS	2	Sometimes
3-MCC	Maternal	3	No
NKH	Clinical	2	No
B-12 deficiency	NBS	2	Yes

CblC=Cobalamin C deficiency; MMA=Methylmalonic acidemia; CIT I=Citrullinaemia type I; CIT II=Citrullinaemia type II; TYR=Tyrosinaemia; Hcy=Homocystinuria; 3-MCC=3-Methylcrotonyl carboxylase deficiency.

During the same period, 45 children were diagnosed in NSW (Table 3). Thirty-nine cases were disorders of intermediary metabolism diagnosed via ENBS. An additional two cases, potentially diagnosable by ENBS, were diagnosed prior to screening; one prenatally and one symptomatically in the first few days of life. Of the other four cases, three were diagnosed clinically after screening (two of non-ketotic hyperglycaemia [NKH] and one of ornithine transcarbamylase [OTC] deficiency, and one prenatally [OTC]).

Three mothers were diagnosed, based on the results' of their children's newborn screening, with the probably benign condition 3-methylcrotonylcarboxylase (3-

MCC) deficiency. In addition, the ENBS programme diagnosed two neonates with vitamin B-12 deficiency.

Specifically looking at the disorder—medium chain acyl Co-A dehydrogenase deficiency (MCAD)—two cases were diagnosed in NZ (1 in 87,500) and 24 in NSW (1 in 11,250).

Discussion

The duration of this study and the numbers involved are not sufficient to prove or disprove the effectiveness of ENBS. However larger studies (many of them from the NSW screening programme) have addressed this issue.⁴⁻⁶ This study does, however, illustrate a number of important points pertaining to the recent introduction of ENBS in NZ.

MCAD is by far the most prevalent disorder of intermediary metabolism (excluding PKU which has been screened for separately in NZ since the late 1960s), and thus the most important condition clinically. Classically it presents with hypoketotic hypoglycaemia and encephalopathy, following a period of catabolic stress such as a viral gastroenteritis, during the early childhood years.

Without screening, approximately 25% of cases die from MCAD prior to or without a diagnosis.⁹⁻¹¹ A slightly smaller percentage have at least one admission with characteristic clinical features (hypoglycaemia, encephalopathy) prior to a correct diagnosis being made. This is unfortunate as treatment is simple and cheap, and once a diagnosis is made, the outcome is excellent with a very low mortality and morbidity.^{6, 10}

The key to treatment is patient/parent education. Parents are instructed to make sure the child has a regular oral energy intake, especially when they are unwell and prior to going to sleep at night. During times of intercurrent illness they should commence the emergency regimen (Table 4). While some of the other disorders of intermediary metabolism require somewhat more complicated diets and medications, the emergency regimen is an important aspect in the treatment of all.

Perhaps a third of children with MCAD do not present clinically. They are the subgroup that for whatever reason (most likely an avoidance of significant childhood illnesses) are never subjected to significant catabolic stress and thus avoid situations where they are fully reliant on their bodies' ability to metabolise fatty acids.

It could be argued that ENBS is in fact harmful to these patients as it potentially introduces psychological stress to a family that were never going to have problems. However the ability to prevent mortality in the symptomatic children outweighs this probably minor concern. Increasing evidence also shows that the initial presentation of MCAD is not confined to the childhood years—and events such as self-induced alcohol intoxication, prolonged labour with unexpected fasting, and unrelated medical illnesses can precipitate metabolic decompensation in adulthood.^{12, 13} There is also evidence that some patients with MCAD can have chronic problems with fatigue, muscle pain, and exercise intolerance.^{11, 14}

Table 4. The Emergency Regimen for the initial home treatment of suspected metabolic decompensation in disorders of intermediary metabolism

<p>Children who are unwell but are still alert, feeding well and are not having recurrent vomiting should be commenced on the following emergency regimen.</p> <p>Stop normal solid feeds. Continue on any special formulas. Continue to take usual medications.</p> <p>Commence glucose polymer drink (e.g. maltodextran, polycose or similar) as prescribed by doctor/dietician. Every two hours during the day and every 2–4 hours during the night</p>		
Age (years)	Glucose polymer concentration (g/100ml)	Total daily volume
0-1	10	120-200 ml/kg
1-2	15	95 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml
<p>Continue to assess the child every two-four hours. If they improve, slowly recommence the normal diet. If they are unwell but stable continue with the emergency regimen. Contact doctor and/or metabolic service if child remains on the emergency regimen for more than 36–48 hours</p> <p>If the child becomes significantly unwell, drowsy and/or is having recurrent vomiting then they should be seen at the nearest hospital immediately. Contact your doctor or the metabolic service if concerned.</p>		

Two cases of MCAD were diagnosed in NZ during the study period and thankfully both had a good outcome. However, presuming a similar incidence as NSW, it is likely that 16 children (95% confidence interval: 9–22) were born with the condition during the study period. Of these, 3–4 children would have died.^{9,10}

We are aware of two NZ children dying from confirmed MCAD over the last 6 years. Thus purely for this one condition it is possible to make a good case for ENBS in NZ. A cost-benefit analysis commissioned by the New Zealand National Testing Centre in 2002 found that (over a 7-year period) the cost per death avoided would be \$11,500 and the cost per life year gained \$590.¹⁵

Another problem that has emerged with the advent of MCAD screening is the realisation that the mutation profile of patients with MCAD deficiency diagnosed by ENBS is somewhat different from that of those diagnosed clinically, in that the proportion of alleles with the common MCAD mutation in children who are diagnosed symptomatically is greater than in those that are diagnosed via ENBS.^{16,17}

This suggests that there are a group of MCAD patients identified by screening who, while having the typical blood biochemical profile, are at a lesser risk than those with the ‘classical’ form of the condition. This is hardly surprising as several other metabolic diseases (for instance MSUD and PKU) are known to have milder or intermediate forms. This phenomenon is likely to be seen in other conditions and illustrates the evolving nature of ENBS knowledge.

Most of the other fatty acid oxidation disorders (FAODs) are also readily diagnosed by ENBS. They tend to present in a similar manner to MCAD. Some, such as LCHAD, have an even poorer prognosis without screening.¹⁸ Others such as late-onset VLCAD tend not to present with childhood hypoglycaemia—but (as seen with

the case diagnosed in NZ during the study period) with exercise induced rhabdomyolysis in adulthood. Thus, while still a useful disease to diagnose early (the patient in question had many years of exercise induced muscle problems that could have been prevented with a high calorie oral carbohydrate intake prior to and during activity), one may encounter a situation in which a disease that is not going to cause problems for many years is diagnosed soon after birth.

While the case for ENBS for the FAODs (in particular MCAD) is strong, the situation is less clear for some of the amino and organic acidopathies.¹⁹ These disorders of protein catabolism generally present with encephalopathy and the long-term outcome is often dependent on the degree of neurological damage suffered during the first presentation.

Some, such as glutaric aciduria type 1 (GA I) and beta ketothiolase deficiency, tend to present after the neonatal period, and as treatment is available and screening can easily be added (with minimal additional cost to the screening programme for the FAODs), a good case for screening can be made.

The known case of GA I that presented during the study period in NZ resulted in severe disability that could have been prevented with early detection. Based on the NSW figures, it is possible (even likely) that there were other similar cases in NZ—although they remain undiagnosed and thus remain unreported.

NSW reported 41 children (1 in 6585) with treatable inborn errors of metabolism that can be detected by ENBS; 2 of these were diagnosed prior to screening. In NZ we diagnosed 7 children (1 in 25,000) during the same period, 1 (MSUD) by established screening, and 1 clinically in the first few days of life.

Assuming a similar incidence in both populations, as well as the 14 ‘missed’ cases of MCAD described above, there may have been an additional 6 (95% confidence interval: 2–10) cases of other inborn errors that were not diagnosed correctly, or (less likely) have not yet presented clinically.

In some conditions, such as the classical severe forms of methylmalonic aciduria and MSUD, the children are likely to be becoming sick within the first few days of life. This is illustrated by the NZ patient with MSUD who was diagnosed by the existing screening programme on the day following the child’s admission to hospital with encephalopathy. While an even earlier diagnosis would have been optimal, the screening diagnosis allowed for a much earlier diagnosis than would have been obtained on clinical grounds and thus undoubtedly improved the child’s outcome.

Thus in order to optimise outcome and screening programme effectiveness it is critical that the Guthrie card is obtained early (as soon is practical after 48 hours of age) and just as importantly transported quickly to the screening laboratory.

There are some disorders that ENBS cannot reliably diagnose. This is because the key metabolites in affected patients are not in a range that is significantly different from the extremes of the normal population and thus NBS is not sufficiently specific.

OTC deficiency—the most common of the urea cycle disorders and thus a disease in which it would be beneficial to screen for—is probably the most important of these. Therefore it is vital that clinicians remain alert for the possibility of an inborn error of metabolism in sick children and do not assume that just because the child has had a normal newborn screen that they do not have a metabolic disorder.

Direct communication with the screening laboratory and/or the related clinical metabolic service can be very useful in these cases. Based on the numbers of metabolic investigations performed there appears to be lesser index of suspicion of metabolic disease in symptomatic individuals in NZ compared to Australian centres.

Some disorders cannot be diagnosed by ENBS and in addition there is no effective treatment. Classical NKH, a condition characterised by early neonatal seizures and encephalopathy, is the best example of this. This is particularly relevant in New Zealand where NKH appears to have a high incidence in the Māori population as illustrated by the four cases diagnosed during the study period.

Another condition with a high incidence in New Zealand is biotin-resistant holocarboxylase synthetase (HCS) deficiency.²⁰ Typically classical HCS presents in the first few months of life, is easily treated with oral biotin, and is thus a good candidate disease for NBS. However in the Samoan population, due to the presence of a particularly pathogenic common mutation, it presents (on day 1 of life) with severe lactic acidosis and encephalopathy and treatment with biotin is overall disappointing. (However, newborn screening may assist families, by ensuring that a diagnosis is made, if all children are tested.)

Additional early evidence shows that several other metabolic diseases occur with particularly high frequency in the Pacific communities, probably due to a gene founder effect.²¹ Similarly, ethnic groups where consanguinity is not uncommon also have a high incidence. Thus the unique ethnic demographics of the NZ population need to be considered when interpreting international recommendations regarding ENBS

Some metabolic diseases detectable by ENBS are probably benign conditions in most patients. 3-methylcrotonyl coxylase (3-MCC) and short chain acyl Co-A dehydrogenase deficiency are two such conditions. The NSW screening programme diagnosed three mothers with 3-MCC deficiency by detecting the relevant raised metabolites in the Guthrie card of the newborn infant. The child's metabolism had not yet had a chance to clear these maternal compounds that had accumulated *in utero*.

SCAD deficiency has now been removed from the list of screened conditions. Similarly, although more clinically significant, woman who are vitamin B-12 deficient can be detected by noting a raised propionyl carnitine levels in their child's Guthrie card sample. The children are also B-12 deficient and are at significant risk as they are likely to be exposed to a low B-12 diet during infancy.

There have been a small but regular number of infants suffering from catastrophic complications of B-12 deficiency in NZ in recent years and hopefully ENBS will help to address this problem.

A high degree of specificity is important in all screening programmes. ENBS measures a number of key metabolites (corresponding to one or more disease), each with cut-off limits, outside of which a second sample is requested. Thankfully the highly accurate nature of mass spectrometry means that despite screening for 20 plus diseases, the cumulative false positive rate is only around 0.2%. Thus in NZ we may expect to ask for second samples in around 120 patients annually. The second sample is nearly always normal and reflects the normalisation of the neonates biochemistry rather than an inaccurate first test.

Nevertheless false positives can lead to heightened parental anxiety,²² and improved communication and education of all parties involved in screening has been suggested as the optimal strategy in reducing this.²³

Expanded newborn screening using tandem mass spectrometry is an important recent development in screening and paediatrics. Unlike most screening programmes whereby a single test is used to screen for a single disease, ENBS uses a single sample to measure a large number of compounds to look for a range of diseases.

With some of these diseases there is good evidence that current clinical detection methods are inadequate and likely to be leading to unnecessary mortality and thus a strong case can be made for newborn screening.

With other conditions the supporting evidence for screening is not yet available, usually because of the rarity of the individual disease, although clinical experience suggests there are likely to be benefits provided unnecessary delay is avoided in the collection, transport, and processing of the samples.

The change from a 'one test-one disorder' to a 'one test-many disorders' paradigm has added complexity to decision making in newborn screening. The National Screening Unit of the Ministry of Health, who have governance over the Newborn Metabolic Screening Programme, was required to examine in detail the implications of ENBS. Securing the required capital to purchase the tandem mass spectrometer was problematic and required a generous contribution from the Starship Foundation.²⁴

For these reasons, and despite evidence supporting the benefits of ENBS accumulating since the mid-1990s,^{25,26} NZ was the last (commenced in December 2006) of the newborn screening programme countries in the Asia-Pacific region to introduce ENBS.

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Phenylketonuria—the lived experience

Nicole Frank, Ruth Fitzgerald, Michael Legge

Abstract

Aim This study explored the lived experience of phenylketonuria (PKU) for the New Zealand adult and its relevance for issues of treatment adherence.

Method In-depth qualitative interviews were conducted with eight New Zealand adults with early-treated PKU regarding their experiences of living with PKU. The interviews were transcribed, and then analysed using grounded theory. A review of relevant medical, scientific and social science literature placed this analysis in a broader context.

Results A number of consistent themes emerged as characteristic of the participants' life experiences, including a chronic uncertainty existing on several levels, the challenges posed by the maintenance of interpersonal relationships with respect to the PKU diet, and a basic incompatibility between the PKU diet and many lifestyle demands. Social science commentary on the topics of risk management, stigma, and other types of "dieting" experiences further elucidates these themes.

Conclusion Based on the findings of this research, medical practitioners may be able to better tailor their services for, and interactions with, the adult PKU community, for example, by facilitating self-management, conveying realistic expectations of metabolic control, and increasing the volume of information directed to PKU adults.

Inherited metabolic diseases are a clinically diverse group of medical conditions which require specialist diagnosis and care. Although individually they are rare, they have a collective incidence estimated to be 1 in 1500 persons, which would indicate that many general practitioners would encounter an inherited metabolic disease in their practice at some stage.^{1,2}

Despite the poor prognosis of many of these disorders—which may result in intellectual handicap, deformities, and premature death—some may be treated or have intervention therapy to circumvent the pathological sequelae of the disease. One such inherited metabolic disease is phenylketonuria (PKU) and related forms of hyperphenylalanaemia, an autosomal recessive disorder first described in 1934. This group of inherited disorders of phenylalanine metabolism is primarily due to either a deficiency of the enzyme phenylalanine hydrolase in the classical form, or mutations in the enzyme in the variant forms.

With an incidence of 1 in 15,000 births in New Zealand, it is likely that there will be approximately 4 infants per year born with this disease (based on 60,000 births per year). Screening for this and other metabolic disorders at birth, ensures early detection and intervention under the guidance of a metabolic physician.

For PKU, the intervention therapy appears comparatively simple (although, as the results of the research will demonstrate, in practice, the treatment can be quite complicated and demanding). A restrictive diet low in phenylalanine and routine

monitoring of blood phenylalanine levels ensures that the amino acid does not increase to the point of neurotoxicity causing intellectual handicap.

Maintenance of this diet up to adolescence has been a success story in preventing the complications of this disease, and until recently, it was thought that dietary treatment of PKU could be discontinued once the individual reached adolescence with no adverse consequences. However, that assumption has since come into question.

Recent research shows the possibility of “alarming problems in cognition and social functioning” for adults who discontinue the PKU diet.³ Although there is no international consensus on the issue, many medical practitioners today, including the specialised medical team providing tertiary care for the PKU population in New Zealand, recommend life-long adherence to the PKU diet to all PKU patients.

Despite this recommendation, studies almost unanimously report low rates of treatment adherence in both paediatric and adult PKU populations,⁴⁻⁸ and adherence appears to decrease with age.⁸⁻¹¹

In this research we investigate the social impact of the restrictive diets for people living with PKU and how people living with PKU assess the constraints and consequences of dietary adherence in their own private lives outside of the medical consultation. In conducting this research we explored the lived experience of PKU for the New Zealand adult and its relevance for issues of treatment adherence in the light of contemporary medical, scientific, and social science literature around the subject.

Method

The research was conducted in two parts. First, the PKU-related literature was investigated, with articles being located through the databases Medline, Science Direct, Proquest, Factiva, InfoTrack, Nutrition and Food Sciences, and the *JAMA* website. In addition, relevant social science literature was also reviewed, including literature on the social significance of food and eating, dieting, stigma, and risk, with the last category added to the review after having been raised repeatedly by the participants during interviews.

By combining the medical and scientific literature with the social science literature, a broader understanding of individuals' accounts of living with PKU could be constructed. This multidisciplinary approach is in line with the NHC (2005) proposal for improving clinical support for people with chronic illness.¹²

The second part of this research involved qualitative research using data from interviews with eight New Zealand adults living with PKU. The goal of the interviews was to elicit data about the psychosocial aspects of the decision-making relating to choosing to adhere to or avoid the PKU diet.

The open-ended interviews lasted between 50 and 90 minutes, and covered the following topics: participant understandings of PKU, impressions of normalcy and difference in regard to PKU, identity formation, challenges of PKU and treatment adherence, coping mechanisms, change of experience over time, relationships with medical personnel, familial and social impact of PKU, emotional aspects of the experience of living with PKU, risk perception and how that relates to treatment adherence, personal agency and control, and the sensual aspects of the PKU diet.

Participants were located through a national database available to the National Metabolic Services team in Auckland. All PKU adults listed in this database (n=46) were contacted by letter inviting them to join the research project, and eight responded (the low response rate being typical of third party recruitment). However, this was a sufficient number of participants for data analysis using grounded theory,¹³ which focused on the meanings and experiences of living with PKU.

Six of those who responded were female; two were male. The ages of the participants at the time of the interview ranged from 31 to 43 years. Although this group presented a high degree of variation in areas such as marital status, socioeconomic standing, and life experiences (e.g. occupation, travel, pregnancy, and child-rearing), it should be noted that their collective perspective could vary in important ways

from those adults with PKU who did not respond to the project invitation. For example, although the older range of New Zealand adults was well represented (including one individual who was reportedly diagnosed just before routine screening began in New Zealand), the views of younger adults (in their 20s) were not represented.

The interviews were conducted by the first author (NF), transcribed verbatim, returned to the participants for checking, and then analysed by the first author (NF), with a second researcher (RF) checking the transcripts and thematic analysis for consistency of interpretation. The biomedical science information in both the interview analysis and the literature review was verified by the third author (ML).

Qualitative software was not considered necessary for this project. Ethical approval was obtained from the New Zealand Multi-Region Ethics Committee.

Results

Overview—The themes which emerged from the interviews are set out in Table 1, and their detailed analysis forms the basis of a more extensive publication¹⁴ and an unpublished Master's thesis.¹⁵ However, a number of the open coded categories were particularly relevant to patient-practitioner interactions. These were collectively identified in the axial coding as “uncertainty”, “difference” and “incompatible lifestyle demands” (shown by asterisk), and can be identified at a higher level of abstraction as forming part of the Medical, Social, and Personal Spheres of life for the interviewees.

Although a number of other themes arose within each of these spheres, for the purpose of this article, we will focus on only one theme per sphere (i.e. the theme which impacts the medical consultation most explicitly). The selected theme from each sphere of living will be discussed in tandem with the results obtained from the literature survey.

Medical Sphere: evaluating uncertainty—All interviewees raised the topic of uncertainty (functioning at the level of both future and present) in various contexts, and found this to be anxiety-provoking. Awareness of an uncertain future pervades the experience of living with PKU for this project's interviewees. Participants stressed the newness of their situation, and the fact that they are the first generation of early-treated adults with PKU, frequently noting that no-one (including the medical community) “knows what the future holds” for people with PKU.

Uncertainty was expressed in relation to how long they would live and how long they would retain their mental faculties. Phrases such as “uncharted territory” and “no-man's-land” were used to describe their situation, conveying a deeply uncertain future. Present uncertainty that people with PKU must confront is connected to the lack of medical certitude concerning PKU, and stresses ambiguity pertaining to the optimal mode of treatment. For although the New Zealand medical community appears to be consistently recommending a life-long PKU diet, the impression remains among participants that the necessity or benefit of this is still ultimately uncertain.

Participants also expressed uncertainty around the value of the ideal blood phenylalanine level, raising concerns that they received conflicting information from year to year. An additional area of uncertainty was identified relating to how to achieve the desirable levels, and the lack of apparent correlation with self-perceived behaviour.

Table 1. Overview of grounded theory coding analysis

Open Coding	Axial Coding	Selective Coding	Core Category
Extent of medical attention/intervention Experimentation ("guinea pig") Appreciation of medical attention/intervention Dependence upon medical attention/intervention Medicalization/objectification Medical expectation (moral onus)	Medical Scrutiny	Medical Sphere Evaluation of medical information and expertise	NEGOTIATOR
Anxiety about future health and ability Inconsistent medical views on best treatment Uncertainty concerning current blood levels Unsure of present effects of condition Hypothetical present ("what if?") Risk	Uncertainty*		
Medical expertise Usefulness of internet Information from friends, family, society Self-expertise (embodied knowledge)	Multiple Sources of Information		
Distinct food behaviour Stigma Exclusion Accommodation by others (or lack thereof) Camaraderie between individuals with PKU Normality Prevalence of alternative diets in society Others' lack of understanding Pressure/temptation to conform Reactions of others Avoidance of potentially awkward situations	Difference*	Social Sphere Management of information, impressions and interpersonal relationships (to elicit positive social responses)	
Self-denial Limitation of culinary experience Restricted quantities of food Lack of choice, freedom, and spontaneity Inability to "treat" oneself Lack of variety Sensual aspects of food (unsatisfactory) Challenges to life pursuits (e.g. having children, travel)	Deprivation	Personal Sphere Strategic incorporation of the PKU diet into personal lives	
Labour-intensive diet Distaste for cooking PKU-related time investments Time limitations Importance of routine for dietary adherence Lack of routine in everyday life	Incompatible Lifestyle Demands*		

The asterisk indicates coded categories discussed in this article and movement from left to right across the table indicates increasingly abstracted levels of analysis. The core finding is that people living with PKU who were

interviewed for this project consider the primary effect of living with their condition to be that they become “expert negotiators” in the *medical, social, and personal* spheres of their lives.

Uncertainty cannot be acted upon until it has been evaluated, and risk assessment plays a large role in this process of evaluation. Many of the observations made in the social science literature regarding this stress that both the recognition of, and the value given to, risks are subjective and contextually dependent,¹⁶ leading to varying perspectives on risk. Often, the perspective of a medical professional differs from that of a lay-person.

Petersen and Lupton observe that “the medical practitioner will tend to interpret data on risk through her or his own emotionally charged experience in working with individuals, having responsibility for their care and treatment, and being in the position of seeing patients die or avert death.”¹⁷ For these reasons, Peterson and Lupton argue that doctors will tend to view risks as more severe or negative than will patients, and will expect a higher level of adherence to recommended treatment to avoid the risk.

Lay people, however, may draw from a number of sources in addition to medical opinion to formulate their evaluations of risk, including their own experiences, the experiences of friends, the familiarity or abstractness of a particular risk, or the perception of a particular risk relative to other perceived risks— leading to a discrepancy between the risk assessments of the two parties.

Two participants gave especially good examples of the assessment of risk based on the information at hand. Interestingly, both individuals were off-diet at the time of the interview. The first participant very clearly assessed risk associated with PKU in relative terms, comparing it with other forms of risk to which she perceived herself to be susceptible. Because she saw her weight and her family history of other illnesses as additional (possibly more pressing) health risks, future harm from being off-diet was for her, “just another possibility”.

She therefore concluded:

...particularly with my other bits and pieces that I've got thrown into the mix as well...I think...that controlling blood levels is not necessarily going to make a big difference (female, age 35)

The second example of risk assessment highlights the abstract nature of risk communication. This participant explained that after reviewing some recent research demonstrating the benefit of returning to the PKU diet (for those who have been off-diet)

...it seems so far away...Like if 1 of the 200 people [*with PKU*] in New Zealand would say to me, ‘Well, that happened to me,’ I would probably take it more seriously...It just seems like another world (female, age 38).

Social Sphere: managing social difference—Although “difference” was experienced by interviewees to varying degrees, it was reported by all project participants. The most evident outward expression of difference was considered to be in relation to their eating habits—either when they are unable to eat what those around them are consuming, or when they consume something (such as the protein substitute) unfamiliar to others. Both instances serve to create a distinction between the

individual with PKU and others. In many cases, this difference led to a lack of social acceptance, exclusion, and stigma (especially in childhood).

The interviewees in general held a deep appreciation for the social nature of food consumption, a topic that the social science literature elaborates upon in great detail. Indeed, sharing food can be a potent symbol of community and relationship, friendship, trust, and intimacy.

Alternatively, the refusal of food can send equally strong messages indicating the refusal of such intimacy—effectively communicating “enmity and hostility”.¹⁸ Individuals with PKU wishing to maintain dietary control must continually reject food that is not permitted in their strict dietary regimen, and participants experienced this to be a very awkward social situation—desiring to maintain their diet, yet not wishing to inadvertently offend. The expectations involved with the sharing of food (and the resulting temptation and persuasion initiated by others) was reportedly one of the primary difficulties encountered in dietary adherence, and one of the most common reasons for transgression of the PKU diet.

Goffman’s work on stigma provides some interesting insights into the social nature of difference and the corresponding management of interpersonal relationships. He speaks of both information management and impression management in this regard. Goffman uses the concept of controlling or managing information in the context of difference to refer to the questions of “to display or not to display; to tell or not to tell; to let on or not to let on; to lie or not to lie; and in each case, to whom, how, when, and where.”¹⁹ These questions are certainly a matter of consideration and sometimes concern for adults with PKU, as the interviews demonstrated. Of perhaps even greater concern for many participants is Goffman’s concept of impression management.

Many examples of “impression management” were provided by the interviews, such as one participant’s method of always explaining her condition in social circumstances so as to not appear “rude” by her lack of participation in food-related events, or another participant’s offhanded, trivializing attitude toward her condition, which she found caused others to likewise regard her condition as minor and unproblematic.

In listening to participants explain their methods of managing their interpersonal relationships in the face of social difference, it is notable that emphasis is routinely placed on the feelings of others rather than the individual with PKU (as is common with experiences of stigmatisation¹⁹). This has important implications for treatment adherence. Participants consistently explained that they were most likely to transgress their PKU diet when the comfort and feelings of other people were at stake.

For instance, when asked in which situations she would find herself most likely to abandon (or make exceptions to) the diet, one participant replied:

...if I’ve been invited to someone’s place and they’re maybe someone who doesn’t know me very well, or knows me but they’re really kind of uptight about being a really good hostess, or...they’re not going to cope with me saying, “Well I can eat this, but I can’t eat that and that,” and they’d feel really bad about it...It’s usually more about the other people than me (female, age 35)

This leads to an interesting finding. Whereas some medical literature stresses the importance of a strong network of social support in adherence to the PKU diet,^{3,5,20,21} and adjustment to chronic medical conditions in general,²² participants in this project

alternatively spoke of others primarily as a *challenge* to dietary adherence, and consistently reported a very high degree of self-motivation, self-discipline, and independence in their maintenance of the PKU diet.

Personal Sphere: negotiating incompatible lifestyle demands—In common with members of the general population, individuals with PKU have strong feelings concerning the lifestyles they desire and for which they feel suited.

For instance, the strong disinterest in cooking and baking expressed by interviewees represents one grave conflict between desired lifestyle and the substantial time required to prepare special PKU foods (such as baking with low-protein flour).

In addition, as society shifts towards increasing consumption of convenience foods, individuals with PKU often feel left behind, attempting to juggle the modern expectations of jobs and families, without the aid of quick meal-time options. Several other challenging lifestyle incompatibilities were also mentioned, including adherence to the PKU diet while travelling (especially for extended periods of time and in unfamiliar locations).

A review of the social science discourse around dieting reveals that this “unrealistic” nature of the strict PKU diet (in its ideal form) represents one of many similarities between people’s experiences of the PKU diet and people’s experiences on other types of diets.

Both the PKU diet and other types of diets (e.g. diets for weight-loss) are externally defined, and as such, may not take into considerations the demands of “real life”. Commenting on women’s attempts to loose weight through dieting (but equally applicable, it seems, to the situation of people on a PKU diet), Bordo argues that “...total control [*over food*] is ultimately unsustainable” and that “ ‘the diet’ is itself a precarious, unstable...state...”²³

Similarly, Orbach notes that the “ideal” presented to women on diets for the purposes of weight-loss produces “a picture that is far removed from the reality of women’s day-to-day lives”.²⁴ The parallels here are self-evident and indicative of further insight to be gained through such a comparison.

The participants in this project negotiate these competing lifestyle demands partly through strategic dietary flexibility, delineating between the “exceptions” that would cause guilt and those considered permissible. For instance, exceptions made for the benefit of others were often justified, as in the example provided in the previous section. Many also appeared to view the occasional exception as harmless, but a string of exceptions as ultimately poor adherence.

As one participant explained...

...it’s not too bad if I just do a bit here and there, but if [*one thing leads to another and*] it all ends up bad choices, then I feel really bad” (female, age 43).

Another participant mentioned that intentional indiscretion would not cause guilt...

...if I made a conscious thing that...I was going to eat something and was just going to enjoy it, then no way [*would I feel guilty*]” (female, age 35)

Additionally, many participants indicated that “special occasions” such as birthdays, special meals out, or weddings, may constitute a justification for making guiltless exceptions to the PKU diet.

Routine also proved to be a strategic element aiding in adherence to the PKU regimen for many. Due to the limitations that the diet imposes on the individual, once a particular system is found to suffice, participants often hold to that system with little alteration. It is when participants are caught up in a healthy routine that they find treatment adherence to be most feasible. This particular strategy, however, is limited in its usefulness by the unpredictability of life and the impossibility of maintaining a routine at all times.

Ultimately, every aspect of PKU treatment (from the timing of blood tests to the invention of palatable, convenient ways to prepare the medical foods) requires a great deal of organisation and planning.

Participants expressed that one of the most difficult consequences of PKU is the need to think constantly, and ceaselessly, about diet. This results in what one participant referred to as a considerable “mental burden”.

Discussion

The difficulty of managing the highly restrictive low phenylalanine diet for PKU has significant ongoing effects for the patients in all aspects of their lives and serves as a reminder that patients juggle more than their diagnosis in living with a chronic illness.

Medical consultations have become simply one more arena in which to form an independent opinion of the relevance or otherwise of the advice being offered. On the other hand, the clinician has the opportunity to offer significant support through the provision of compassionate guidance to these patients in negotiating a life in which the future is perceived to be so uncertain.

Expert clinical support is also eagerly sourced and highly valued by women with PKU during their pregnancies when the maintenance of recommended levels of phenylalanine is difficult to achieve. (The recommended PKU diet during pregnancy is stricter than at other times, permitting fewer daily exchanges of phenylalanine. Tight control of phenylalanine levels is vital during this time as high levels of phenylalanine can cause serious developmental problems in the foetus²⁰.)

Many of the suggestions made by the participants for improved care relate directly to the three aspects of living with PKU identified in this paper.

One frequent grievance raised by interviews concerned new developments in knowledge and treatment concerning PKU. This was perceived to be neither readily accessible nor conveniently distributed, and due to the overall uncertainty felt by PKU adults and their need to personally evaluate available sources of information in order to choose a course of action, this was problematic.

Healthcare professionals could reduce this uncertainty by increasing the volume of information directed to the adult PKU community, and ensuring that the means of delivery is more appropriate. (For instance, a number of participants mentioned that information online is either inconvenient if they do not have ready access to the internet, or untrustworthy, indicating that there is a need for alternative methods of information distribution.)

The independence of adults with PKU stemming from the nature of social interaction with non-PKU individuals also has interesting implications for healthcare professionals. The importance of teaching dietary independence from a young age—

including the cooking skills necessary for dietary adherence—was raised, as not all participants were given such instruction during childhood.

Additionally, because their treatment is largely self-governed, interviewees stressed that the accessibility of their healthcare workers was important and highly valued. The complexities of contemporary social life should also be addressed within the clinical consultation.

To advise PKU adults to “bake” in a world of fast food chains, double income families, and renegotiated gender roles runs the risk of rendering the medical consultation invalid through its lack of relevance to contemporary lifestyles.

As we gain better knowledge of the molecular and biochemical implications of inherited metabolic diseases and design intervention strategies based on biochemical interactions, it is important to retain the perspective that treatments should not be based solely on the long-term clinical outcome but also on the life experiences of the individuals living with the disease.

PKU represents a classical “treatable” inherited metabolic disorder with a good clinical outcome; however, this research has demonstrated through exploring the lived experience of PKU, how professional support could be altered to better meet the needs of those with PKU and their families.

Competing interests: None.

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

Doron Hickey, Grace Joshy, Peter Dunn, David Simmons, Ross Lawrenson

Abstract

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

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

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

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

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

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

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

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

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

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

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

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

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

Method

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

Table 2. Anti-GAD measurements by ethnic group

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

Table 3. Anti-IA2 measurements by ethnic group

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Competing interests: None.

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Persistent anaemia due to scurvy

Vincent Ho, Pieter Prinsloo, John Ombiga

We present a case of a 45-year-old man from Papua New Guinea who presented with anaemia. A bleeding duodenal ulcer was thought initially to be the sole cause of his anaemia but when his anaemia did not resolve despite haemostasis and blood transfusion another explanation had to be entertained.

Physical examination noted florid features of scurvy and a poor dietary history was elicited. Scurvy is a rare clinical condition in modern times and a high index of suspicion together with a good history and physical examination is required to make a prompt diagnosis.

Case report

A 45-year-old man from Papua New Guinea presented to the Cairns Base Hospital's Emergency Department after being referred for investigation and management of anaemia. He had complained of a painful swollen right knee with limp and lethargy for the past 6 months. His local medical officer had prescribed him diclofenac 50 mg three times daily for the past 2 weeks for analgesia. In the last few days prior to admission to hospital he described epigastric pain and melaena. His past medical history was significant only for depression. He denied frequent alcohol consumption.

Laboratory investigations noted normochromic normocytic anaemia with a haemoglobin of 59 g/L. His white cell count, platelet count, and coagulation profile were all normal. Iron studies revealed low serum iron levels with high ferritin levels. Vitamin B-12 and folate levels were in the normal range.

His anaemia was attributed to an upper gastrointestinal bleed on the background of non-steroidal anti-inflammatory use. He was transfused 4 units of packed cells, commenced on intravenous proton-pump inhibitor therapy, and admitted for urgent endoscopy.

At endoscopy, a large duodenal ulcer was visualised and the bleeding vessels at the base were clipped, providing haemostasis. His epigastric pain and melaena resolved. In spite of this, over the next 3 days his haemoglobin progressively dropped to 63 g/L. A repeat endoscopy did not show any signs of repeat bleeding from the ulcer. Another cause for his anaemia was sought.

Physical examination revealed that he had marked gingival swelling and bleeding (Figure 1). His skin follicles were noted to have increased pigmentation and this was later confirmed to be perifollicular hyperkeratosis (Figure 2). His right leg was as hard as wood and he had prominent ecchymosis of his thigh with a large right haemarthrosis.

Further enquiry regarding his diet revealed that he had a very poor oral intake for many months and virtually took no vegetables or fruit.

Scurvy was suspected as the clinical diagnosis.

His plasma ascorbic acid level recorded as 5 micromol/L (normal range 20–120 micromol/L) thus confirming vitamin C deficiency.

Figure 1. Gingival swelling and bleeding in our patient with scurvy



Figure 2. Prominent classical perifollicular hyperkeratosis seen in scurvy



He was commenced on vitamin C 250 mg three times daily and his dentition, ecchymosis, and haemarthrosis improved rapidly. His full blood count quickly normalised. He was discharged on an oral proton-pump inhibitor, given advice regarding a healthy diet, and follow-up with a dietician was arranged.

Discussion

Scurvy is traditionally found in impoverished populations, people on 'fad' diets, alcoholics, and those with psychiatric disturbances.¹ Centuries ago it was common in sailors on extended voyages due to the lack of fresh fruit and vegetables on board. Initial presenting symptoms are generally non-specific and include weakness, anorexia, depression, and lassitude.²

The diagnosis of scurvy is based on the finding of specific clinical features supported by a consistent dietary history. A plasma vitamin C level of below 11 micromol/L supports the diagnosis of scurvy, as it corresponds to a total body store of less than 300 mg.^{2,3}

As a result of defective collagen biosynthesis due to ascorbic acid deficiency, blood vessel fragility manifests as petechiae, purpura, and large ecchymoses.⁴ Haemarthroses of the knee have been described.^{5,6}

Bleeding gums and gingivitis are prominent in individuals with pre-existing periodontal disease. Dermatological features include broken and coiled hairs (due to abnormal collagen formation), and perifollicular haemorrhages and hyperkeratosis.⁷ Anaemia is seen in 75% of cases of scurvy, with iron and folate deficiencies as contributing factors.⁸

The institution of treatment for scurvy is simple. Oral vitamin C supplementation leads to dramatic and rapid improvement in symptoms, with clinical manifestations disappearing within weeks.

Our case illustrates that even if a case of anaemia appears obvious, for example a classic picture of a gastrointestinal bleed, it is imperative to search for other causes if the anaemia still persists despite correction.

Scurvy is a rare clinical condition which can account for persistent anaemia if untreated, and a high index of suspicion with a good history and examination is required to make a prompt diagnosis in order to not delay treatment.

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Modern milk alkali syndrome—a preventable serious condition

Binay K Shah, Sharath Gowda, Hejmadi Prabhu, Jeffrey Vieira, Harish C Mahaseth

In the post H₂-blocker era, milk alkali syndrome has become very rare. However, with growing use of over-the-counter (OTC) calcium preparations, a resurgence of this disorder has been noticed. We report a case of severe hypercalcaemia resulting from overuse of calcium preparations.

Case report

A 47-year-old female from an adult home (residential care home / rest home) was brought to the emergency room with history of abdominal pain, loss of appetite, lethargy, and constipation.

Her past medical history was significant for Down's syndrome and hypothyroidism. Her home medications were risperidol, levothyroxine, alendronate 70 mg once a week; two calcium preparations (one containing calcium carbonate 500 mg and vitamin D 200 IU, and the other containing calcium carbonate 500mg) each three times a day; and raloxifene 60 mg once a day. It was not clear from the adult home notes why the patient was taking two calcium preparations: raloxifene and alendronate.

ER vitals (vital signs) were normal and the physical examination was unremarkable. Her lab results at admission revealed sodium 148 mmol/L (normal range: 135–145 mmol/L), potassium 3.3 mmol/L (3.5–5.3 mmol/L), chloride 104 mmol/L (97–107 mmol/L), bicarbonate 33 mmol/L (22–33 mmol/L), blood urea nitrogen (BUN) 25 mg/dl (5–19 mg/dL), creatinine 4.1 mg/dL (0–1.1 mg/dL), glucose 79 mg/dL, calcium more than 16.5 mg/dL (8.5–10.3 mg/dL), and albumin 3.8 g/dL; liver function tests and thyroid-stimulating hormone (TSH) were normal.

Intact parathyroid hormone (PTH) was 8.9 pg/mL (10–69 pg/mL) and serum protein electrophoresis and urine protein electrophoresis were normal. Renal sonogram showed no abnormality.

The patient was treated with intravenous (IV) fluids and furosemide for hypercalcaemia secondary to milk alkali syndrome. Her serum calcium normalised in 2 days and renal function returned to normal.

Discussion

The commonest cause of hypercalcaemia is hyperparathyroidism in outpatient settings and malignancy in inpatient settings. Milk alkali syndrome was a common cause of hypercalcaemia when peptic ulcer disease was treated with Sippy regimen¹ consisting of hourly administration of milk and cream with a mixture of bicarbonate containing salts that included calcium carbonate.

Renal failure and alkalosis as toxicities of Sippy regimen was recognised by Hardt and Rivers in 1923.² The hypercalcaemia which is now known to be central to the milk alkali syndrome was first described by Cope in 1936.³ With the advent of H₂ antagonists and proton pump inhibitors, the use of antacids to treat peptic ulcer disease declined dramatically and the incidence of the syndrome fell to 2% of all patients admitted with hypercalcaemia during 1985 to 1989.⁴

Recently, there has been resurgence of the cases of milk alkali syndrome due to common use of calcium therapy for osteoporosis, readily-available OTC calcium carbonate preparations, and use of calcium carbonate to minimise secondary hyperparathyroidism in patients with chronic renal failure.

In a recent study during surveillance period from 1998 to 2003, milk alkali syndrome was the third most common cause of hypercalcaemia (8.8%) and the second most common cause of severe hypercalcaemia (>14 mg/dL).⁵ Therefore, with the increased use of calcium carbonate for treatment of osteoporosis, an increased awareness of the milk alkali syndrome is necessary.

There is no correlation between reported intakes and the severity of the hypercalcaemia or other manifestations of the disease.⁴ In susceptible patients, milk alkali syndrome begins with development of hypercalcaemia. High serum calcium produces a decrease in glomerular filtration rate and along with increased alkali intake, causes metabolic alkalosis and further decreases calcium excretion.⁶ Nausea and vomiting further dehydrates the patient thereby worsening the effects of hypercalcaemia, renal failure, and metabolic alkalosis. Our patient was taking calcium preparation 3 grams/day.

Symptomatic patients and patients with serum calcium levels above 13.5 mg/dL generally warrant aggressive intervention. Treatment initially consists of IV normal saline and a loop diuretic.⁷

This case highlights a serious complication of a nonprescription drug when used inadvertently. Milk alkali syndrome is likely to become more common with increased use of calcium preparations for osteoporosis. It can easily be recognised by taking a thorough medication history.

Similarly before prescribing “safe” medications such as calcium preparations, we should carefully assess other similar medications that the patient may be taking.

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Risky knowledges: the sociocultural impacts of personal genetics in a knowledge-driven economy

Michael Legge, Ruth Fitzgerald

Abstract

The rapid developments in modern genetics are changing the way disease and wellness may be considered. New concepts are emerging such as predictive genetic testing and forecasting future disease, as well as internet genetic analysis available to the public. In this short communication we consider some of the implications relating to predictive genetic testing in the public domain.

Twenty-five years ago, genetics had a small part to play in general medicine. Although it was known that genes held the 'recipe' for the human body, and could provide clues relating to why health was affected, the understanding of the information and its application was a distant goal. There was little that could be done to predict how an individual's genes may lead to an illness or how a disease may be prevented in which genes played a part.

The inheritance of single gene disorders such as cystic fibrosis was understood, but how the incorrect genetic information led to the disease was poorly understood. Such a poor understanding of the molecular basis of disease led to inadequately formulated intervention strategies based on symptoms alone.

As molecular and biotechnology knowledge progressed, the specific identity of genes associated with both health and disease has increased producing changes in the conventional perceptions of disease. Genes have been identified which make certain individuals susceptible to a disease rather than actually having the disease. Equally in families, various members can be identified as either having a mutated gene, thereby increasing the risk of a disease or not having the mutation and therefore having a 'genetic advantage' over parents, siblings, or other members of the extended family.

The impacts of such knowledge became increasingly apparent as the draft of the Human Genome programme began to unfold in 2001 identifying approximately 30,000 genes from which we have both normal and abnormal function. Information relating to human genetics and health now escalates weekly—demonstrating that not only are genes implicated in disease but also they influence or are influenced by environmental factors on our bodies, including nutrition and how we repair, age, and respond to treatment.

Contemporary health applications of genetic knowledge

Rapid development of genetic testing and information has led to very specific tests for certain single gene disorders and implicated many other genes in the disease process. Genetic diseases not yet manifest can now be identified which has led to the development of predictive genetic testing—i.e. testing for a genetic disease which could (e.g. Huntington's Disease) or may (e.g. inherited breast cancer) develop in the future. In effect, individuals are being identified as being genetically susceptible to

future disease, changing the concept of health being defined as the presence or absence of disease to the concept of increased or decreased statistical probability of future disease developing.

These biotechnological advances can also predict whether a pre-implantation embryo may be susceptible to a genetic disease which (if it developed) would appear many years after the infant was born. Such a predictive test cannot, however, specifically identify that the individual will develop the disease.

Future innovations in genetic testing

Based on the use of the new genetic technologies, several major pharmaceutical and biotechnology companies¹ are promoting the concept of 'predictive medicine' or 'predisposition profiling'. This is the use of genetic tests to predict the chances that an individual will develop a serious illness (e.g. cancer, mental illness, heart disease).

A positive aspect of using this information is offering advice on lifestyle changes which may offset the physiological impacts of the abnormal gene—i.e. shifting the emphasis of medicine² from 'diagnosis and treatment' to 'disease prediction and prevention'. However, concerns arise regarding the use of the information.

For example, pharmaceutical companies may not only sell the genetic testing kits but also manufacture the drugs for treating those at high risk, or supply special dietary supplements when testing for 'nutrition genes'.

Medication may be given to otherwise healthy people who may never develop the disease thereby changing the resourcing structure of the health system, and information may be given to people who will worry unnecessarily or seek treatment for a health problem which may never occur. It places very personalised information into the broader community-raising issues relating to genetic identity, employment, insurance³, paternity⁴, and forensic use.

Generally, the assumption has been that genetic testing would occur in a medical context. However, recent developments in the United Kingdom and the USA (where the availability of 'over-the-counter' genetic tests exist in an unregulated environment) have raised major issues relating to:

- Quality and reliability of information,
- Interpretation of information,
- Entitlement of 'not-to-know' in other family members,
- Unexpected information,
- Testing for genes with social implications,
- Security of individual DNA and intellectual property rights,
- Role of informed consent, and
- The perceptions of society at large on identifying individuals with potential genetic disease.

Horizon scanning for unregulated practice

Although this is a relatively new area of applied health biotechnology, the transition from the disease gene identification process and the marketing of a diagnostic test will be rapid.

There are at least 10 multinational companies planning to sell genetic testing kits, which include Abbott, Bayer, Johnson and Johnson, and Roche. All of these and their related companies have links or agreements with at least 17 gene discovery companies who are searching for patentable gene products or data from abnormal gene function (www.forbes.com).

Currently companies are selling personalised genetic testing over the Internet with services being offered for cancer susceptibility genes ('The best time to beat cancer is before you ever get it'—www.myriadtests.com); nutrition-related genes (www.scicona.com); paternity, maternity, immigration testing, and genealogy (www.genetrack.com); and home paternity testing (www.dna-worldwide.com).

More recently, a new DNA test has been offered in the UK and USA for fetal sex testing at 6 weeks gestation as well as gene profiling for diseases with Mendelian inheritance patterns in at-risk groups such as Ashkenazi Jews ("Ashkenazi kits"—www.elugicene.com).

Conclusion

Direct-to-consumer genetic testing⁵ is a new and rapidly emerging area both for health-related and non-health related applications, which moves the traditional concept of testing from health providers to the individual and a third party. This raises significant issues relating to accuracy and reliability of the testing services information, the competency of the genetic testing provider, the interpretation and reporting of the results to an individual or family (with little or no support or skills to interpret the information), and the loss of genetic privacy—all of which could have significant impacts on major life decisions.

Whether obtaining such results will provide benefits to the individual is still not known, but we believe that there is potential for significant societal impacts resulting from the use of unregulated personal genetic-testing technologies. The creation of a new social group of the 'at-risk well'; the requirement for health professionals to understand and communicate the implications of the 'new knowledge'; and the demands that might be placed on medical practitioner consultations and use of the diagnostic services will increase as more genetic information becomes available and disease linkages are made with specific genes.

Rabinow (1999)⁶ predicted of this time of rapidly increasing personal genetic knowledges as the age of biosociality in which the most minute of social interchanges will be governed by our biological identities and their associated risk benefits. Rose and Novas (2005) talk of it as 'biological citizenship'.⁷

Many of the genes may ultimately have significant social implications—such as genes associated with mental illness, alcohol susceptibility, and infectious diseases such as HIV and hepatitis—thus creating the potential for the increasing misuse of this genetic information.

These dramatic societal impacts of this style of genetic testing suggest that empirical research in New Zealand should be undertaken before this new area of applied health biotechnology becomes embedded into public practice.

Competing interests: None.

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Since presenting the last annual report, 52 new members have been added to our roll. This is the largest increase in any one year.

It is with the deepest regret that your Council is called upon to record the death of Sir James Hector, who has been an honorary member of the Branch since its inception; and of Dr. W. A. Logan, one of our most active members. The late Sir James Hector's work in the field of science is well known to every member of the Branch, and it is gratifying to note that steps are being taken to establish a fitting memorial. Dr. Logan has for several years represented the Otago Division on the Council, and the Branch as a whole has profitted by the keen interest he has always shown in its welfare. By his death the profession in New Zealand sustains a severe loss.

FRIENDLY SOCIETIES.—On 18th. June last a Conference was held between your Council and delegates representing the Friendly Societies of New Zealand, a full report of which has already been circulated -in the Supplement to the N.Z. Medical Journal of July, 1907. The resolutions arrived at by the Conference have since been submitted to the several Divisions of the Branch, and are in the main approved. The Divisions, however, agree that an income limit should be insisted on, and that decision has been conveyed to the Colonial Executive of the Friendly Societies. The reply of the Colonial Executive has not yet come to hand.

REGISTRATION.—The annual general meeting in March last decided by a large majority against the proposal to register under “The Unclassified Societies’ Registration Act,” the feeling of the meeting being that the proposed Royal Charter would give to the Branch and its Divisions the liberty they desired in the management of their own affairs.

BRANCH RULES.—The new Branch Rules as passed by the special general meeting held in November, 1906, and adopted by your Council, have in the main been approved by the Central (Council. The rule, “annual subscription,” is held over pending application for Royal Charter.

A capitation of 7/- per member on subscriptions for 1907 has been paid to the several Divisions, and as the expenses of the annual meeting are now defrayed by the Branch, the position of the Divisions financially has been considerably strengthened.

N.Z. MEDICAL JOURNAL.—The Journal has been published regularly each quarter, and though the Editor has still to regret a good many misprints, the number of these is steadily decreasing; the printer has had considerable difficulty in getting efficient typesetters at times. There has been no lack of papers for publication during the past year, but the usual annual meeting not being held this year the Editor anticipates some lack of material for the coming numbers, and earnestly hopes that members will send for publication the papers which they would have read had there been the usual meeting. The financial position of the Journal continues satisfactory.

The special attention of members is again called to the instruction from Head Office, London, that all Branch subscriptions are to be collected in New Zealand. Those who have not paid are asked to send their cheques to the Branch Secretary, P.O. Box 156, Wellington.

Your Council desires to thank the Government, the Manawatu Railway Co. and the U.S.S. Co. for concessions to travelling members.

The attention of members is directed to the reports of the N.Z. Defence Union and Medical Benevolent Funds.

NZMJ Note: Read more about Sir James Hector at <http://www.teara.govt.nz/1966/H/HectorSirJames/HectorSirJames/en>



Proceedings of the 188th Scientific Meeting of the Otago Medical School Research Society, Thursday 5 July 2007

Pathogenicity of a missense mutation in *ALDH18A1*, encoding Δ^1 -pyrroline-5-carboxylate synthase (P5CS) in a consanguineous NZ family. L Bicknell¹, A Sutherland-Smith², J Pitt³, M Maw⁴, R Ramadas⁵, S Aftimos⁶, S Robertson¹.

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To investigate genetic contributors to congenital joint dislocation, we have characterised a consanguineous family segregating an autosomal recessive connective tissue disorder (lax skin and joints) with neurological abnormalities.

We performed a 400-microsatellite genome screen under a hypothesis of homozygosity for a common ancestral disease allele. Multipoint linkage analysis identified a 50 cM region at 10q23.1-23.4 with a peak logarithm of odds (LOD) score of $Z = 2.99$. Fine mapping refined this to a 14 Mb critical region which demonstrated homozygosity by descent exclusively in affected individuals with a maximal LOD of $Z = 3.63$. Eighty-five genes within this interval were prioritised for disease gene candidacy. One gene *ALDH18A1*, encoding Δ^1 -pyrroline-5-carboxylate synthase (P5CS), was focused on since a missense mutation causes progressive neurodegeneration, joint dislocations, lax skin and metabolic derangement in a consanguineous Algerian family. Sequencing of *ALDH18A1* in an affected individual identified the transition, 2350C>T, predicting the substitution H784Y. Comparative sequence analysis showed H784 is conserved across all phyla within a novel C-terminal tail motif.

P5CS is a bifunctional enzyme that converts glutamate to proline and ornithine upstream of the urea cycle. Proline, a major constituent of connective tissue, has also been implicated in neurotransmission. Therefore, impaired synthesis could lead to abnormal joint, skin and brain development. However, *in vivo* enzymatic assays we performed suggest proline biosynthesis is not perturbed, correlating with the normal metabolic profiles found in affected individuals. A partial P5CS crystal structure is available and hints towards roles for H784 in P5CS dimerisation and modulation of an active site cleft. Moonlighting roles (i.e. the evolutionary adoption of an unrelated function by an enzyme) exist for other metabolic enzymes. P5CS may therefore possess additional uncharacterised functions. The pathogenic effect of H784Y on P5CS suggests novel roles for the C-terminal domain in P5CS stability or function within the cell.

Supported by a University of Otago PhD Scholarship and a University of Otago Research Grant.

Distribution of fibroblast growth factor-2 within excisional wounds following topical application in rats. R Braund, N Medicott, S Hook. School of Pharmacy, University of Otago, Dunedin.

Chronic wounds may in part result from a deficiency in crucial growth factors. To compensate for this deficiency the topical application of growth factors has been studied. Fibroblast growth factor 2 (FGF-2, or basic FGF) has been well studied for this purpose. The aim was to determine the concentration profiles of this growth factor within experimental wounds following topical administration in different formulations.

A dosage of 0.3 µg FGF-2 was incorporated into three formulations (solution, gel or dried gel film on Melolin™ backing). FGF-2 formulations or PBS was administered to punch biopsy wounds in rats (6 animals per group: total n = 72). At two, five or eight hours, the animals from each group were euthanised by CO₂ inhalation and cervical dislocation. Wound tissue was dissected horizontally to surface granulation, subcutaneous fat, superficial muscle and deep muscle layers and the amount of FGF-2 at various wound depths was quantified via ELISA. Tissue FGF-2 concentrations were compared using a repeated measures ANOVA (Minitab Version 14.1).

The highest concentrations of FGF-2 were seen in the surface granulation tissue of rats two hours after receiving the solution formulation (2275 ± 787 pg/g; mean ± SD, > 1000 pg/g higher than control levels). Concentrations decreased with increasing tissue depth and were significantly greater than the PBS control in the surface granulation and subcutaneous fat layers ($P < 0.05$, ANOVA). There was a statistically significant difference in the mean FGF-2 levels with respect to formulation and time following application of the formulation ($P < 0.05$, ANOVA).

In conclusion, elevated FGF-2 could be measured in superficial wound tissues up to eight hours post-application of a solution. However, application of a comparable amount (0.3 µg FGF-2) in hypromellose gels or films did not give appreciable elevation of FGF-2 in wound tissues.

Supported by a University of Otago Research Grant.

Cell-wide homeostatic regulation of long-term potentiation by prior synaptic activity. S Hulme, W Abraham. Department of Psychology, University of Otago, Dunedin.

It has been suggested that homeostatic regulation of synaptic plasticity is required to maintain the overall strength of synaptic inputs to a cell within a dynamic range. This has been implemented in the Bienenstock, Cooper and Munro (BCM) computational model by θ_M , a cell-wide threshold for long-term potentiation (LTP) that is modulated by previous levels of postsynaptic cell firing. The aim of this research was to test the predictions of the model regarding θ_M for hippocampal LTP.

Field excitatory postsynaptic potentials (fEPSPs) were recorded in response to stimulation of the Schaffer collaterals in area CA1 of acute hippocampal slices from 6-7-week-old male Sprague-Dawley rats. Priming stimulation of one pathway significantly reduced the level of LTP induced 30 min later by 100 Hz stimulation of

a second (heterosynaptic) pathway (mean \pm SEM, $12 \pm 5\%$, $n = 6$, $P < 0.05$, unpaired t -test) compared with control LTP ($27 \pm 5\%$, $n = 8$). In accord with predictions of the BCM model of cell-wide changes in θ_M , priming stimulation of synapses on the basilar dendrites significantly inhibited LTP induced at synapses on the apical dendrites ($16 \pm 4\%$, $n = 6$, $P < 0.05$) compared with control LTP ($30 \pm 3\%$, $n = 6$). Contrary to the predicted role of cell-firing in changes of θ_M , hyperpolarising cells (by direct current injection) during priming to completely prevent somatic action potentials, did not prevent the priming effect (control LTP: $40 \pm 10\%$, $n = 5$; primed LTP: $-6 \pm 6\%$, $n = 5$, $P < 0.05$).

These results confirm that synaptic plasticity is homeostatically regulated by the cell-wide history of activity. However, postsynaptic cell firing does not mediate this regulatory process.

Supported by a University of Otago PhD Scholarship and the Health Research Council of New Zealand.

Mitochondrial redox-active species participate in the modulation of nuclear gene expression. R Jarvis, E Ledgerwood. Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin.

Tumour necrosis factor- α (TNF α) is an important pro-inflammatory cytokine that is released from activated immune cells. An important part of the TNF α response is modulation of gene expression, predominantly via nuclear factor- κ B (NF- κ B) and activator protein-1 (AP1) transcription factors. Several key TNF α responses have been linked to the intracellular accumulation of redox-active species (RAS). A major source of intracellular RAS is the mitochondrial respiratory chain. We have found that a mitochondrially targeted antioxidant delays TNF α -induced transcription factor activation. In the current study we have investigated whether mitochondrial RAS participate in TNF α -induced gene expression.

The human monocyte-like leukaemic U937 cell line was used as a model system to investigate TNF α -induced redox-mediated gene expression by microarray analysis. Total RNA was isolated from U937 cells treated with either 5 ng/mL human TNF α , 2 μ M mitoE (a mitochondrially targeted version of vitamin E), or a combination of both for 45 and 120 min. Total RNA was reverse transcribed to cDNA with poly-dT anchored oligo primers and applied to human 20K oligo arrays as biological triplicates.

MitoE was found to repress the TNF α -induced expression of a subset of genes by approximately 50%, including *inhibitory κ B-a* (I κ Ba), *inhibitory κ B-z* (I κ Bz), *monocyte chemoattractant protein-1* (MCP-1) and *manganous superoxide dismutase* (MnSOD), which are known targets of NF- κ B. MitoE was also found to repress the basal expression of a small number of genes by two-fold, including MCP-1. qRT-PCR or western blotting has confirmed the effect of mitoE on TNF-induced and basal expression of MCP-1, I κ Ba and MnSOD.

This study suggests that TNF α -induced RAS production from the mitochondria contributes to the induction of NF- κ B-mediated gene expression, and that RAS from the mitochondria help maintain gene expression in resting cells. These findings lend

weight to the emerging idea that strict modulation of intracellular RAS levels is an important element of cellular signalling.

Supported by a University of Otago PhD Scholarship and the Otago Medical Research Foundation.

Mechanisms by which the copper metabolism gene MURR1 domain 1 (COMMD1) protein down-regulates human epithelial sodium channel activity. Y Ke, T Chang, F McDonald. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

The epithelial sodium channel (ENaC) is located at the apical membrane of polarised epithelia and mediates transport of sodium ions into cells. Tight control of ENaC function is essential for maintaining sodium homeostasis, blood volume and pressure. Controlling the number of active channels present at the cell surface is important for regulating ENaC activity. The neural precursor cell expressed, developmentally downregulated gene 4 (Nedd4) family of proteins (e.g. Nedd4-2) ubiquitinate ENaC and decrease its cell surface expression. The activity of Nedd4-2 is modulated by serum and glucocorticoid regulated kinase 1 (SGK1), which phosphorylates Nedd4-2 and increases cell surface expression of ENaC. COMMD1 is a recently identified ENaC binding partner, and negative regulator of channel activity. Other studies suggest that COMMD1 is also involved in intracellular protein trafficking and ubiquitin-dependent protein degradation. In this project we aim to characterise the interaction between ENaC and COMMD1, and identify the mechanism(s) by which COMMD1 down-regulates ENaC activity.

Glutathione S-transferase (GST) pull-down and coimmunoprecipitation assays were used to identify the binding interface between COMMD1 and ENaC. Cell surface biotinylation and ENaC ubiquitination assays were developed to investigate if COMMD1 affects the cell surface expression and ubiquitination of ENaC respectively.

The results showed that the conserved C-terminal COMM domain in COMMD1 is essential for binding to ENaC. The binding site for COMMD1 in bENaC was located at its N-terminal domain. COMMD1 down-regulated ENaC by increasing ubiquitin modification of ENaC and removing ENaC from the cell surface. COMMD1 also bound to SGK1 and prevented Nedd4-2 mediated degradation of SGK1.

It is suggested that COMMD1 might affect the interaction between SGK1 and Nedd4-2 and this pathway is likely to be involved in the COMMD1-mediated ubiquitination and down-regulation of ENaC activity.

Supported by the Marsden Fund and a University of Otago Research Grant.

The orf virus protein ORFV125 acts in a Bcl-2-like manner to inhibit apoptosis. D Westphal¹, E Ledgerwood², S Fleming¹, A Mercer¹. ¹Department of Microbiology and Immunology, ²Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin.

Apoptosis is one of the host cell's responses in its fight against virus infection. Therefore, many viruses have developed strategies to circumvent apoptosis; one of

these includes the expression of Bcl-2 homologs. The Bcl-2 family of proteins are regulators of the mitochondrial pathway of apoptosis. It has been proposed that the pro-apoptotic family members are activated by various apoptotic signals and thereupon induce mitochondrial apoptosis, while the anti-apoptotic family members prevent this process by inhibiting the activity of their pro-apoptotic counterparts. We have shown that orf virus can express an inhibitor of apoptosis, ORFV125, which shows some similarities to the cellular anti-apoptotic protein Bcl-2. However, the mechanism by which ORFV125 inhibits apoptosis is still unknown. The present study investigates whether ORFV125 inhibits the activation of the pro-apoptotic Bcl-2 proteins Bax and Bak.

TK143B cells stably expressing either ORFV125, Bcl-2 or the empty-vector were incubated with 50 μ M caspase inhibitor (Z-VAD-FMK), added 1 h before UV-C treatment (80 J/m²). Eight hours after UV irradiation cells were stained with anti-Bax or -Bak antibodies and visualised by fluorescence microscopy. The antibodies used recognise an N-terminal epitope, which is exposed only when the proteins are activated by an apoptotic stimulus. While the empty-vector cell line showed a substantial number of cells expressing active Bax ($30 \pm 3\%$, mean \pm SD, $n = 3$), almost no active Bax was detected in cells expressing either ORFV125 ($0.6 \pm 0.1\%$, $P < 0.001$, ANOVA multiple comparison test) or Bcl-2 ($2 \pm 0.6\%$, $P < 0.001$). A similar result was obtained for the activation of Bak, showing that ORFV125 can fully inhibit the activation of both proteins in a manner comparable with Bcl-2.

These results suggest that ORFV125 acts in a Bcl-2-like manner, and supports our predictions that ORFV125 may be a distant member of the Bcl-2 family.

Supported by a University of Otago PhD Scholarship and the Health Research Council of New Zealand.

Multiple effects of estrogen on intracellular calcium levels in adult gonadotropin-releasing hormone neurons. N Romanò, C Jasoni, A Herbison. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

Gonadotropin-releasing hormone (GnRH) neurons are the principal regulators of reproductive function and are strongly modulated by estrogen (E₂). In addition to transcriptional effects of E₂, rapid non-transcriptional actions of E₂ have also been demonstrated to occur in GnRH neurons. The aim of this study was to evaluate the rapid effects of E₂ on intracellular calcium concentration ([Ca²⁺]_i) in adult GnRH neurons.

Calcium imaging experiments were undertaken using acute brain slices from transgenic mice ($n = 68$) in which the genetically-encoded calcium indicator ratiometric-pericam is expressed selectively in GnRH neurons. GnRH neurons were tested with: (1) 1-100 nM E₂, both in pericam and pericam x estrogen receptor- β (ER- β) knockout mice; (2) the selective ER- α agonist 3,17-dihydroxy-19-nor-17 α -pregna-1,3,5(10)-triene-21,16 α -lactone (16 α -LE₂) and (3) a membrane-impermeable, bovine serum albumin conjugate of E₂ (E₂-6-BSA).

In 13 of 27 GnRH neurons exhibiting low frequency spontaneous [Ca²⁺]_i transients, treatment with 100 nM E₂ increased the frequency of the transients ($P < 0.001$, one-

way ANOVA, Tukey post-hoc test); lower doses were not effective. In 9 of 11 GnRH neurons showing high frequency spontaneous $[Ca^{2+}]_i$ transients, 1 nM E_2 significantly reduced the frequency of the transients ($P < 0.01$, one-way ANOVA, Tukey post-hoc test). ER- β knockout mice did not respond to E_2 differently to wild-type mice ($n = 16$, two-way ANOVA). Ten of 20 silent neurons were stimulated by 100 nM 16α -LE $_2$. E_2 -6-BSA reproduced the inhibitory (1 nM, $n = 3$), but not the stimulatory (100 nM, $n = 6$) effect of E_2 .

In summary, these results show that E_2 produces two opposite effects on $[Ca^{2+}]_i$; a stimulatory effect mediated by ER- α , and an inhibitory effect mediated by a membrane receptor. These data provide evidence in favour of the rapid control of adult GnRH neurons by E_2 . This might be involved in generating the pulsatile activity of the GnRH system.

Supported by a University of Otago PhD Scholarship and the Wellcome Trust.

Altered muscle activation during a weight-bearing task following hamstring injuries. G Sole¹, A Gray², S Milosavljevic¹, H Nicholson³, SJ Sullivan¹. ¹Centre for Physiotherapy Research, School of Physiotherapy, ²Department of Preventive and Social Medicine, Dunedin School of Medicine, ³Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin.

Altered electromyographic (EMG) patterns of trunk, gluteal and thigh muscles have been found in groups of subjects with lumbopelvic or knee disorders and their presence may contribute towards injury prolongation or recurrence. This study aimed to investigate whether differences in EMG patterns of selected muscles exist when comparing subjects with a recent hamstring injury (HI) and control subjects during a weight-bearing task.

Sixteen sportsmen with a recent clinically diagnosed HI were compared to an uninjured control group (CG) of 18 men. Surface EMG activity was recorded from the gluteus maximus, gluteus medius, biceps femoris (BF), medial hamstring (MH), and the quadriceps muscles of the weight-bearing leg during contralateral hip flexion. Muscle onsets were expressed relative to the start of the anticipatory postural adjustments seen in force platform data.

There were no significant differences for muscle onsets for the injured versus uninjured sides (HI group) and the preferred versus non-preferred sides (CG, $P > 0.05$, paired t -tests). In the HI group, onsets of BF and MH of the injured side, and onsets of MH of the uninjured side, were significantly earlier when compared to the CG bilateral average (mean difference \pm SEM, injured BF 208.1 ± 75.0 ms, $P < 0.01$; injured MH 114.0 ± 44.5 ms, $P < 0.02$, uninjured MH 103.3 ± 49.3 ms, $P < 0.05$, ANCOVA controlling for age and activity level). There were no between-group differences for the gluteal and quadriceps muscles onsets, and the uninjured BF.

The earlier onset of the hamstring muscles in preparation for single leg stance of the injured and uninjured leg of the HI group in comparison to the bilateral average of the CG suggests an alteration in the motor control of these muscles. These changes may be an important factor to be considered in the rehabilitation of hamstring injuries.

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Poxvirus ankyrin repeat proteins represent a novel class of F-box proteins that associate with functional cellular ubiquitination ligases. S Sonnberg, S Fleming, A Mercer. Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin.

The ankyrin repeat is a commonly observed motif that mediates interactions between cellular proteins. Almost all chordopoxviruses encode multiple ankyrin repeat proteins of unknown function. We have identified a potential F-box-like domain at the C-terminus of most poxviral ankyrin repeat proteins. Cellular F-box proteins function as adaptors in the multisubunit ubiquitin ligase S-phase kinase associated protein 1 (Skp1), Cullin1 (Cul1), F-box protein (SCF1) complex of the ubiquitin-proteasome system. F-box proteins recruit substrate proteins to the SCF1 complex for polyubiquitination and proteasomal degradation. The interaction between F-box proteins and the SCF1 component Skp1 is mediated by the F-box domain. We tested the five ankyrin proteins of the parapoxvirus Orf virus for their ability to interact with Skp1.

Co-immunoprecipitation was used to determine possible interactions of the five Orf virus ankyrin repeat proteins with the SCF1 components Skp1, Cul1, and (Ring-box 1) Rbx1. Each of the orf virus proteins was transiently expressed in human embryonic kidney 293 cells and then immunoprecipitated. The samples were analyzed by western blotting showing that each orf virus ankyrin protein co-precipitated endogenous Skp1, Cul1 and Rbx1. An F-box deletion construct of one orf virus ankyrin/F-box protein did not co-precipitate any SCF1 components demonstrating that the interaction of the full-length protein is F-box-dependent. The co-precipitated SCF1 complexes retained their intrinsic activity in an *in vitro* non-specific poly-ubiquitination assay.

The results indicate that the large class of poxviral ankyrin proteins function as F-box proteins. The extensive number of poxviral ankyrin/F-box proteins suggests cellular proteins from multiple pathways could be targeted. These poxviral F-box proteins could target the cellular anti-viral response or other cellular physiological processes whose manipulation could enhance viral survival and replication.

Supported by a University of Otago PhD Scholarship and the Health Research Council of New Zealand.

Generic medicines and their use: Perceptions of South African consumers. A Patel¹, P Norris¹, R Gauld². ¹School of Pharmacy, ²Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin.

Many developing countries have introduced policies encouraging the use of generic medicines in order to improve access to affordable essential medicines. Successful implementation of these policies requires acceptance by all stakeholders, including the consumer. The present, qualitative, study explores South African consumers'

perceptions regarding generic medicines and their impact on their medicine purchasing behaviour.

Data were collected through focus group discussions (n = 12 groups) conducted in three cities within South Africa during December 2005 to January 2006. Key informants were purposively sampled according to their socio-economic status. Key informants recruited other participants through snowball sampling, yielding a total of 72 participants. During the discussions participants were asked whether they would select between brands of paracetamol (i.e. PanadoR, innovator brand; PacimolR, generic) to treat a headache. A second scenario required them to select between brands of amoxicillin (i.e. AmoxilR, innovator brand; MoxypenR, generic) for treatment of an infection. Discussions were tape-recorded and transcribed. Content analysis of the transcriptions was undertaken by the first author and reviewed jointly by the research team for confirmation.

Across all income and age groups, participants selected the original paracetamol for their headache. For amoxicillin, participants relied on the prescriber to decide which product to use. They agreed with generic substitution provided the prescriber supported this. Participants felt that cheaper generic products were of inferior quality. They reported they would pay higher prices to obtain the original medicines to treat their minor ailments, and that they would rely on the advice of their doctor and pharmacist for the prescription medicines.

Governments have to ensure that adequate information campaigns, which target consumers and healthcare providers, accompany implementation of policies for generic medicines. This is needed to achieve success in the overall goal of improving access to affordable, quality medicines.



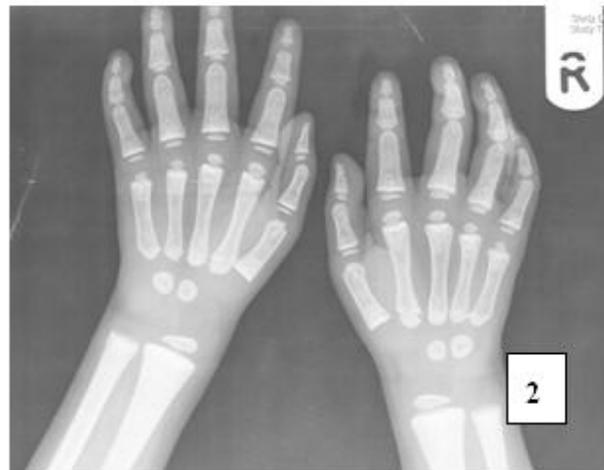
Dense bones and brain stones

Suresh Prabhu, Jubbin J Jacob, Nihal Thomas

A 4-year-old boy presented with delay in developmental milestones and aggressive behaviour. An axial CT scan of the brain was done (Figure 1).

Subsequent evaluation revealed normal serum calcium and inorganic phosphorus values with an elevated serum alkaline phosphatase. His arterial blood gas analysis was suggestive of metabolic acidosis with anionic gap of minus 15.1.

His skeletal X-rays were done (Figures 2 and 3).



What is your diagnosis?

Diagnosis

The axial CT scan of the brain (Figure 1) shows dense calcification (brain stones) in the region of the basal ganglia and cerebral cortex.

Dense bones characteristic of osteopetrosis (Figures 2 and 3) are seen in the skeletal and skull X-rays. Investigation in this patient had documented metabolic acidosis suggesting a renal tubular defect.

The triad of cerebral calcification, renal tubular acidosis, and dense bone is seen in *carbonic anhydrase-II (CA-II) deficiency*.

Discussion

CA-II deficiency is an autosomal recessive disorder in which CA-II enzyme activity is lost. This enzyme activity is necessary for osteoclast-mediated bone resorption. Skeletal disease in CA-II deficiency resembles other forms of osteopetrosis and may in some cases be associated with multiple pathological fractures.

Mental subnormality of variable severity is present in over 90% of patients. Cerebral calcifications appear early by 2 to 5 years of age and are more pronounced in childhood.

In the kidney, this enzyme is necessary for bicarbonate reclamation. Patient with CA-II deficiency present with metabolic acidosis and high urine pH. Hyperchloraemic metabolic acidosis may be noted at birth and in some patients can be profound.

There is no established medical treatment for CA-II deficiency. Bone marrow transplantation from a human leukocyte antigen (HLA)-identical donor is an accepted treatment for the malignant form of osteopetrosis.

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Osteolytic jaw lesion in metastatic breast cancer: not always metastases

Iñaki Alvarez-Busto, Luis Martínez-Moya, Rodrigo Lastra, Javier Alcedo, Dámaris Quiles, Antonio Lobo-Escolar, Carlos Vázquez, Miguel Burillo, Carla Toyas-Miazza, Rosario Ortas-Nadal

A 64-year-old woman with a personal history of breast carcinoma and multiple bone metastases to the skull, sternum, and sacrum was treated with an aromatase inhibitor. Due to her bone pain, we started intravenous zoledronic acid therapy in December 2004: 4 mg was administered every 28 days. The pain was successfully controlled a few months later, and she ceased taking analgesics.

During this treatment period she didn't have any complications related to the bone metastases. However, after 16 drug infusions, she consulted us in October 2006 because of pain at the left lower jawbone.

The CT scan (Figure 1) showed an osteolytic lesion with central and peripheral areas of bone sclerosis. The gammagraphic study (Figure 2) revealed an intense hypercaptation at the left jaw in addition to that known at the skull and spinal column.

Figure 1

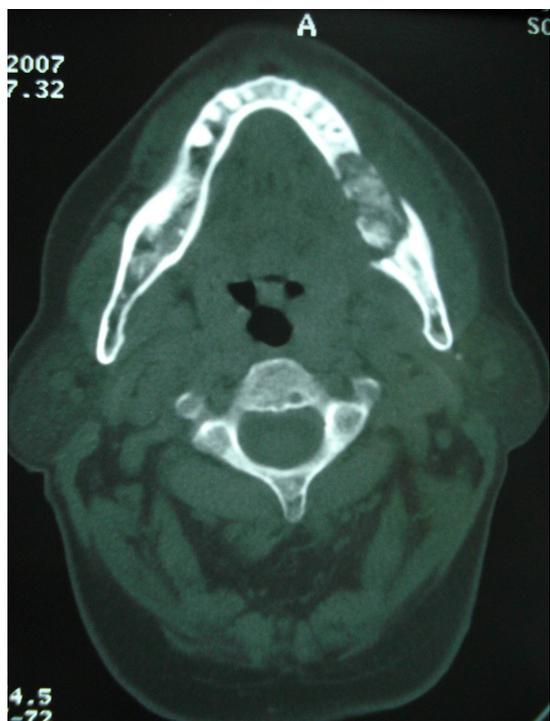


Figure 2



What is the diagnosis?

Diagnosis and Discussion

The diagnosis was *osteonecrosis of the jaw* (ONJ) due to the intravenous bisphosphonate treatment—as confirmed after surgical exeresis.

Accumulating evidence reveals that bisphosphonate therapy has a significant effect in preventing skeletal complications in a variety of cancers, and in preventing bone loss resulting from cancer or its therapy. The major risks of bisphosphonate therapy include nephrotoxicity, electrolyte abnormalities, and ONJ.¹

The incidence of ONJ in this population (breast cancer patients receiving intravenous bisphosphonates) is almost 2.5%.² However, with increased recognition of the condition, longer exposure to bisphosphonates, and more follow-up, the reported incidence is likely to increase.³

Management of ONJ is controversial since there is no effective treatment; the most recommended strategy is to simply stop the administration of bisphosphonates, although improvements in the osteonecrosis may not be observed with drug discontinuation as measurable levels of bisphosphonates may persist in bone for up to 12 years after cessation of therapy.⁴

Surgical treatment is usually reserved for refractory cases such as the present one. At present, the treatment modality of choice may be the removal of only symptomatic boney sequestra with minimal disturbance of overlying soft tissues along with topical and systemic antibiotics.³

Our patient has minimal residual jaw pain 1 year after the surgical procedure and cessation of the bisphosphonates.

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Modernising Medical Careers (MMC) in the UK—a debacle—are the royal colleges at fault?

Attempts to modernise postgraduate medical training in the United Kingdom have been a spectacular failure. In particular the activities of the Medical Training Application Service (MTAS) resulted in mass demonstrations by junior doctors. Justifiably it seems because of the failure of a computerised system to process job applications of some 30,000 for 22,000 positions.

A spin-off for us is an influx of UK graduates to bolster our ailing hospital staffing situation. However, as reported in the *BMJ*, some believe that both the British Medical Association (BMA) and the royal colleges let the young doctors down.

In particular “the question the royal colleges have to answer is how and why they became complicit in a system for postgraduate education that meant they had no influence on MTAS until it was too late.”

The chairman of BMA resigned over the issue.

BMJ 2007;334:724

Aspirin dose for the prevention of cardiovascular disease—low dose is best

Placebo-controlled trials to confirm the benefit of aspirin in the treatment and prevention of atherosclerotic disease complications have used dosages ranging from 50 mg to 1300 mg/d. So what is the best dose and why is it best?

The authors of this paper did a systematic review of the English-language literature on this topic and have come up with an unequivocal recommendation that dosages greater than 75 to 81 mg/d do not enhance efficacy, whereas larger doses are associated with an increased incidence of bleeding events, primarily related to gastrointestinal tract toxicity.

I think that we could settle for 100 mg daily in New Zealand.

JAMA 2007;297:2018–24

Antiplatelet agents for prevention of pre-eclampsia—more good news about low-dose aspirin

Pre-eclampsia is a multisystem disorder of pregnancy that is usually associated with hypertension and proteinuria and may lead to risks for the baby including poor intrauterine growth and premature birth. The cause of pre-eclampsia remains unclear but antiplatelet agents (particularly low-dose aspirin) may prevent or delay it.

This meta-analysis of 31 randomised trials confirms that antiplatelet agents during pregnancy are associated with moderate but consistent reductions in the relative risk

of pre-eclampsia, of birth before 34 weeks' gestation, and of having a pregnancy with a serious adverse outcome.

Lancet 2007;369:1791–8

Tonsillectomy and adenoidectomy

In the not too distant past these operations were regarded as routine for the under 5 year old. Tonsillectomy is no longer so popular but what about adenoidectomy?

In this review article, the authors examine the evidence and conclude that adenoidectomy alone improves nasal airflow and the sense of smell and taste. Growth after adenoidectomy may in part be due to an improved appetite associated with the improvement in smell and taste.

And as part of the surgical management of glue ear where watchful waiting has failed and the child is over three years of age, adenoidectomy with grommet surgery appears to be more effective than adenoidectomy alone.

Finally, adenoidectomy appears to be effective as part of the management of childhood sleep apnoea syndrome, when combined with tonsillectomy, although high-level evidence of efficacy is lacking.

The Journal of Laryngology and Otology 2007;121:209–14

Human pheromone responses—sex and the nose

In this very interesting paper it is pointed out that the olfactory neurones and the limbic system are phylogenetically very 'old' part of the mammalian brain that governs emotions and behaviours, such as aggression, fear or mating responses.

Pheromones, being chemical messengers related to reproduction, are sensed by olfaction, hence the nose is or could be a sexual organ. Apparently young babies can identify, and are attracted to, both the axillary and the breast odours of their own mother but not of other mothers, and that this is not based upon memory of that odour. Mothers too can recognise the odour of their own baby.

Furthermore, several studies have shown that women are far better at odour detection than men. It is biologically more important for a woman to choose the correct mate than a man, as women have a much larger parental investment; their better sense of smell may reflect this.

So, what about perfumes, deodorants, and after-shave?

J R Soc Med 2007;100:268–74



A stroke rehabilitation unit 6 years on

In 2002, I reported on the first 6 months of a dedicated stroke rehabilitation unit (SRU) for older patients.¹ Length of stay in hospital was shortened by a median of 8.0 days, without compromising patient outcomes.² However with new initiatives, there is always a danger that the initial enthusiasm diminishes over time. Furthermore there is inevitably attrition of key staff either through retirement or rotation to other clinical areas, with the effect that some of the original energy and/or vision is lost.

Consequently, efficiency gains previously made may be reduced or even lost. I wished to investigate whether the progress made by introducing a SRU have been sustained over time.

In Christchurch, patients with an acute stroke are initially admitted to Christchurch Hospital (CH) for their acute care. Older patients (generally 65+ years old) who need ongoing inpatient rehabilitation are transferred CH to the SRU based at The Princess Margaret Hospital (TPMH). Approximately 45–50% of all acute stroke patients require this inpatient rehabilitation.³

Data from all patients admitted to the SRU over a 6-year period (2001–2006 inclusive) was collected prospectively. These data are for those patients admitted to SRU only, and so exclude the less severe strokes that are able to be discharged directly from CH. Trends in numbers of patients admitted to the SRU, length of stay (LOS), functional scores, and discharge domicile were reviewed.

During the study period, the numbers of patients admitted annually to SRU rose from 186 to approximately 250 (Table 1). Mean LOS in CH, SRU, and total LOS (CH and TPMH combined) all showed a steady reduction over time. The age of the patients, severity of stroke (as assessed by FIM⁴ score on admission), and FIM on discharge did not alter.

Discharge domicile over the study period is shown in Figure 1 with the proportion of patients returning to live in the community remaining between 50 and 60% of all SRU patients.

These data confirms that the SRU has not only maintained but improved its performance. More patients are now admitted, with a lower average LOS, whilst patient outcomes are maintained. This has major benefits for both patients and the Canterbury District Health Board (DHB). Other recent initiatives have probably impacted on these results. These include the development of an acute stroke unit at CH (opened October 2004)³ and more recently a pilot, community-based stroke specific rehabilitation team (started March 2006 but yet to be expanded beyond pilot phase).

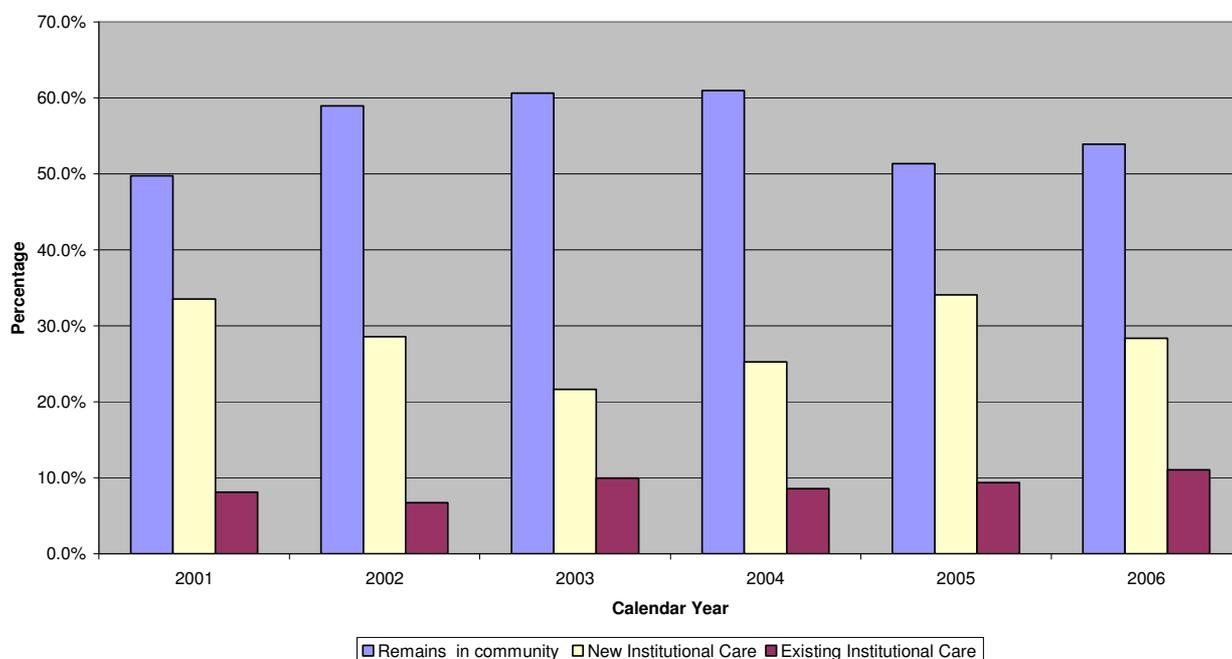
Table 1

Variables	2001	2002	2003	2004	2005	2006
N	186	224	231	210	267	254
Age (mean in years)	78.8	78.6	75.8	79.6	80.0	79.7
LOS CH (mean in days)	10.7	11.4	7.6	7.8	8.4	7.4
LOS SRU (mean in days)	34.1	37.0	31.8	31.6	28.0	28.3
LOS Total (mean in days)	44.7	48.2	39.0	39.0	35.8	35.4
Admission FIM (median)	67.0	74.5	71.0	62.0	65.0	69.0
Discharge FIM (median)	101.0	103.0	107.0	100.0	96.0	96.5

LOS=Length of stay; CH=Christchurch Hospital; SRU=Stroke Rehabilitation Unit; FIM=Functional independence measure (score).

Figure 1

**Change in Domicile Trends 2001-6
for stroke patients admitted to SRU.**



Unfortunately despite local and international evidence,^{1,2,5-7} many stroke patients in New Zealand are still unable to benefit from such stroke unit care.^{8,9}

Stroke Units (SUs) are a win-win scenario for patients and DHBs. Therefore the question needs to be asked “Why haven’t all DHBs developed organised stroke services, with SUs in all the medium to large DHBs?”

National Stroke Awareness Week (10–16 September 2007) is a timely reminder that we can, and should, do better for all stroke patients in New Zealand.

H Carl Hanger

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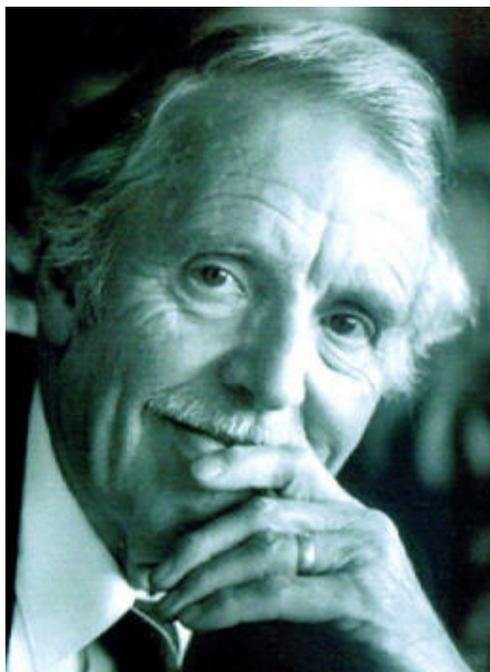
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Ellison James McInnes

2 March 1923 – 16 January 2007

Dr Ellison James McInnes died after a long illness.



Ellison was born in Temuka and his subsequent career in psychiatry was strongly influenced by his general practitioner father who enjoyed a close relationship with his community. It was enlightening to learn from Ellison that matriculation in Latin was a prerequisite for medical intermediate acceptance.

He was a Knox College Old Boy in Dunedin between 1941 and 1948 and, as was required at the time, in the Otago University Medical Corp.

Officers were fifth-year medical students and he wryly stated that the late Dr John Dobson, psychiatrist, was his lieutenant, who in later years, was his senior at Ashburn Hall.

He was a house surgeon in Timaru Hospital when the anaesthetic Boyle machine was introduced. With the late Dr John McLeod, chest physician, they had a few days of training in Dunedin Hospital to be acquainted with the modern innovation and subsequently responsible with a part-time general practitioner/anaesthetist for anaesthesia in Timaru Hospital. There is no question that Ellison's appetite for technology was whetted, whereupon he and his former wife Gaye set off to England in pursuit of his postgraduate studies.

On their return to Dunedin in 1961, he embarked upon a major career change into psychiatry under the tutelage of the late Professor Reg Medlicott. Ellison modestly makes light of his involvement during the infancy phase of modern anaesthesiology and psychiatry. His biological and pharmacological background would have equipped him for his contributing partnership to the well-thumbed Ashburn Hall manual on psychotropic medications much valued by generations of doctors.

He was subsequently recruited into public psychiatry as a Consultant and Deputy Medical Superintendent of Cherry Farm Hospital, but felt somewhat disillusioned by the deinstitutionalisation process as he was not convinced that patient care was adequately safeguarded.

Ironically, when he became my Deputy Medical Superintendent at Sunnyside, we in turn engaged in the final and major deinstitutionalisation process when his genuineness, compassion, and equanimity proved most helpful to me over what could

have been very turbulent years. His administrative experience was reassuring to me. He was one of the very few psychiatrists who enjoyed working with long-stay patients at a time when they received little specialist attention.

Following a brief retirement in 1987, he accepted the invitation to return to Sunnyside Hospital as a locum psychiatrist until his final retirement in 1991. This heralded a very satisfying and settled period in his life when he married Mildred.

Ellison was an educated man in the true sense of the word. His interests included the classics, genealogy, personal computers, the environment, historic places, birds and forests, photography, bush walks, gardening, and he was a member of the Landrover Club before the word 4WD was popularised. He was highly valued for his many years as a member and administrator of the Photographic Society and for his membership of the New Zealand Historic Places Trust and Forest and Bird.

He was philosophical, and true to character was quietly courageous through his terminal illness and had the delight of carrying their first great-grandchild in June of 2006.

Notwithstanding the marital separation, Ellison was effective in his dedication to his extended and blended family. He is survived by Gaye and Mildred, their children and stepchildren, grandchildren, and a great-granddaughter.

Dr Ellison James McInnes was formally a consultant anaesthetist in Melbourne in 1957 to 1960 and Assistant Medical Director, Ashburn Hall, (Psychiatric) Dunedin 1961 to 1973. He was Acting Medical Superintendent, Cherry Farm Hospital, 1980 to 1983, and Deputy Medical Superintendent of Sunnyside Hospital, 1984 to 1987. He was a locum psychiatrist at Sunnyside Hospital from 1988 to 1991.

Dr Ellison's qualifications: MBChB from the Otago University in 1949, DA(RACP, RACS) 1953, MFARACS 1960, MANZCP 1968, FRANZCP 1998, and FANZCA in 1992.

His publications include Medlicott and McInnes, *Drugs in Psychiatry*, An Ashburn Hall Manual, 1971.

Dr Les Ding (Consultant Psychiatrist, Avenue Consultancy, Christchurch) wrote this obituary.



James (Jim) Frederick Moodie

Jim Moodie saw more war than most New Zealanders, but he never ceased to be affected by it.



After fighting through North Africa and Italy in World War 2, Moodie served in Malaya and Vietnam as a medical officer.

His close friend, Bill Hunter, says Moodie almost never mentioned war. However, he once explained the overwhelming distress he felt on hearing the Viet Cong had strung up residents of the Vietnamese village of Bon Song, where Moodie had been based with New Zealand forces.

Moodie rose from the ranks to command a tank squadron as a major in World War 2. He received the Military Cross (MC) for bravery at Minqar Qaim, in North Africa.

He retired from the army in 1972 with the rank of Lieutenant Colonel.

A doctor and cardiologist, Moodie served as physician and consultant at Ashburton Hospital for 12 years. He moved to Christchurch's Rannerdale War Veterans' Home a year ago and died there recently. He was 90.

The good all-round sportsman, who also played piano and ukulele, was born in Dunedin and attended Maori Hill School and Otago Boys' High School. He left at 17 to train as a teacher but joined the army soon after war was declared in 1939. He was selected for officer training and sent to North Africa with the 20th Battalion of Infantry (which later became a tank regiment).

As a lieutenant, he was heavily involved in action at Minqar Qaim to halt the German advance on Cairo. His courage in driving across open country to retrieve abandoned German equipment brought him the MC, which was presented to him later at Cassino in Italy.

The New Zealanders became surrounded at Minqar Qaim and staged their famous night-time breakout. Moodie spent some time in hospital recovering from wounds.

After the war, he studied medicine at Otago University, graduating in 1951. He married Barbara Aitken, of Dunedin, in 1952 and worked as a doctor in Nelson and Christchurch before rejoining the army in 1956. He then took his family to Scotland, where he completed studies in his specialty of cardiology.

Moodie was stationed at Burnham Camp until the army posted him as a medical officer to Malaya from 1962 to 1964. The family lived in the Terendak Military Camp, from which Moodie travelled with the troops on jungle patrols against insurgents. He carried a heavy medical pack and attended to the men's health needs in the most difficult conditions.

On return from Malaya, he was awarded the MBE for his services. He continued with the army, treating Territorial soldiers at Tekapo and becoming Chief Medical Officer

for the NZ armed forces. He went into active service again, treating soldiers and civilians at Bon Song Hospital during the Vietnam War for 6 months in 1971.

Moodie left the army soon after serving in Vietnam and spent the next 12 years at Ashburton Hospital. His wife died in 1984 and he retired in 1986. He then found time for his hobbies of golf, fishing, gardening, and travel. He indulged his passion for jazz and wide-ranging reading. He revisited Cassino for the 50th and 60th anniversaries of the battle and enjoyed sharing experiences with old foes, one of whom he hosted on a tour of the South Island in 1997.

Bill Hunter says Moodie was "a man who did not like to sit in the front, always in the back. He did not like any smart alics. He was actually a shy person, though he had lived a great life. He was a grand fellow."

Hunter says Moodie loved army life and kept in touch with army mates. However, his only reference to the war was to comment, when the topic of tanks arose, that they were the workhorse of the war.

Moodie never told him he had won the MC, Hunter says. When Hunter, an interior decorator, was asked to paint the Moodies' lounge, he found a photo of his friend wearing the medal. If he had not noticed it, he would never have known about the award.

Moodie valued physical fitness and was a good golfer who got his handicap as low as 5. He was very methodical in golf, as in all things. "He was Mr Steady. He never got excited," Hunter says.

Moodie's daughter, Annabel, says her father was "incredibly loyal" to family members, friends, and military contemporaries. He had a great sense of humour but also "upheld the fundamental principles of life". "He was extremely principled. He stuck to his principles. He was extremely modest. He loved animals and was interested in all people."

He could speak five languages (besides English): French, German, Italian, Arabic, and Indonesian.

James Frederick Moodie was born in Dunedin on 13 January 1917 and died in Christchurch on 23 August 2007. Pre-deceased by wife Barbara; survived by daughters Victoria and Annabel, sons Jamie and Hamish, and five grandchildren.

This obituary entitled *War hero modest and loyal* originally appeared in *The Press* newspaper (Christchurch) on September 8 and was written by Mike Crean. We are also grateful to Bruce Rennie of *The Press*.