Metabolic markers of hyperinsulinaemia in normotensive Maori and Caucasian New Zealanders

T Maling, MD, FRACP, K van Wissen, RN, R Toomath, MBCLB, FRACP, and R Siebers, FNZIMCS, MIBiol

Wellington School of Medicine and Capital Coast Health, Wellington Hospital Wellington, New Zealand

New Zealand Maori are hyperinsulinaemic and insulin resistant, compared with age- and blood pressure-matched Caucasians and are therefore an important group in which to study previously described metabolic correlates of insulin resistance, including plasma urate, triglycerides and erythrocytic sodium. Only fasting triglycerides were associated with hyperinsulinaemia. Erythrocyte sodium and plasma urate were not correlated with fasting or stimulated insulin in either race. The reduced fractional urate clearance in Maori, compared with Caucasians, was positively correlated with fractional lithium clearance (proximal tubular sodium reabsorption), suggesting an ethnically expressed dependence of urate clearance on proximal tubular sodium reabsorption. Our findings indicate the need for caution in the generalisability of the variously described "markers" of hyperinsulinaemia.

Introduction

An increase in body weight, serum triglycerides, urate, blood pressure, and the prevalence of NIDDM, has been shown to occur in Polynesian migrants to New Zealand, within 2-3 years after migration. These effects are compatible with the phenotypic expression of a "thrifty" genotype in response to modernisation of life-styles. Prior *et al*[1], have postulated that the "metabolic malady" of New Zealand Maori represents the fully developed spectrum of expression of the Polynesian "thrifty" genotype, the Maori having been subjected to Western life styles for much longer periods than other more recent Polynesian migrants to New Zealand.

We have also described erythrocytic hypernatraemia and increased proximal tubular sodium reabsorption, in healthy young Maori males, compared with age-matched Caucasians[2]. All of these metabolic features have been variously described[3,4] as associated with insulin resistance.

We have hypothesised that Maori are ethnically predisposed to insulin resistance[5] and we have subsequently confirmed hyperinsulinaemia and insulin resistance as an ethnically expressed predisposition in healthy young Maori[6]. In this paper we examine the relationships between fasting and stimulated plasma insulin levels and the previously described metabolic markers of hyperinsulinaemia, in Maori compared with age- and sex-matched Caucasian New Zealanders. We postulate that the functional validity of these relationships should be most clearly expressed in Maori who have been shown to be insulin resistant.

Methods

We have compared plasma urate, fasting triglycerides, erythrocyte sodium, body mass index and fasting and glucose-stimulated plasma insulin, in normotensive non-obese Maori (35) and Caucasians (39). Maori and Caucasians were drawn from the same residential area, as part of a health screening programme. Individuals with an abnormal glucose tolerance test were excluded. All were unmedicated. Proximal tubular sodium reabsorption was measured indirectly as fractional lithium clearance[5], 12 hours after 600 mg oral lithium. Fractional urate clearance was estimated after heating urine to redissolve precipitated urate[7]. The central body fat index was calculated from the ratio of skin-fold thicknesses (biceps + triceps)/ (sub-scapular + supra-iliac). Plasma insulin was measured fasting, 1 hour and 2 hours after 75 g polycose, by RIA (Phadeseph). Fasting and stimulated plasma C peptide levels were measured similarly, by RIA (Novo Nordisk Human C Peptide). Relationships between variables were defined using standard regression techniques, with appropriate correction for non parametric distribution. Ethnic differences were tested by the Mann Whitney U or Student's t test. All values are reported as means and 95% confidence limits.

Results

The ethnic groups were similar for blood pressure, sex ratio and age (mean age for Maori 29.8 years, and Caucasian 31.8 years, range 16-40 years). A family history of non-insulin dependent diabetes was present in a first degree relative in 11 Maori and 10 Caucasians.

There was a marked ethnic difference in body build. Central body fat was increased in Maori, mean (95% confidence interval) 0.64 (0.55-0.72), compared with

Correspondence address: Assoc Prof T J B Maling, Dept of Medicine, Wellington School of Medicine, PO Box 7343, Wellington South, Wellington, New Zealand.
Fax: +64-4-389-5725 Tel: +64-4-385-5999

Caucasians 0.88 (0.77-0.99), p = 0.002.

Fasting insulin levels were higher in Maori 10.1 mU/ml (8.3 mU/ml - 11.8 mU/ml) compared with Caucasians, 7.6 mU/ml (6.8 mU/ml - 8.4 mU/ml) p < 0.05.

Two hour stimulated insulin levels were also higher in Maori 32.4 mU/ml (24.3 mU/ml - 40.5 mU/ml), compared with Caucasians 20.9 mU/ml (17.2 mU/ml - 24.7 mU/ml) , p = 0.02. The differences remained after correction for body build covariates.

Fasting C peptide levels were not significantly different at 1 and 2 hours. There were also no ethnic differences in C peptide levels. C peptide levels were not correlated with any of the previously described metabolic markers of hyperinsulinaemia in either race.

Fasting triglycerides were higher in Maori 1.19 mmol/l (1.00 mmol/l - 1.38 mmol/l), compared with Caucasians 0.98 mmol/l (0.82 mmol/l - 1.15 mmol/l), p < 0.05. After correction for body build covariates, fasting triglycerides were correlated with fasting insulin r = 0.45 (p = 0.02), only in Maori.

Erythrocyte sodium was higher in Maori 7.4 mmol/l (6.7 mmol/l - 8.0 mmol/l), compared with Caucasians 6.5 mmol/l (6.1 mmol/l - 7.0 mmol/l), p = 0.02, confirming our previous findings. As expected, plasma urate was also higher in Maori 0.35 mmol/l (0.32 mmol/l - 0.38 mmol/l), compared with Caucasians 0.31 mmol/l (0.28 mmol/l - 0.34 mmol/l), p < 0.05. Erythrocyte sodium and plasma urate were not correlated with fasting or stimulated insulin in either race. There was no correlation between erythrocyte sodium and proximal tubular sodium reabsorption in either race.

Mean fractional urate clearance was lower in Maori 7.1% (6.4% - 7.6%), compared with Caucasians 9.2% (7.8% - 10.6%), p = 0.006. Fractional lithium clearance was also reduced in Maori (increased proximal tubular sodium reabsorption) , confirming earlier findings, but was not related to fasting or stimulated insulin. Fractional urate clearance was inversely correlated with plasma urate in both races, but was positively correlated with proximal tubular sodium reabsorption only in Maori r = 0.51 (p < 0.002), suggesting an ethnically expressed dependence of urate clearance on proximal tubular sodium reabsorption.

Discussion

Modan *et al*[3], have described the association of raised intracellular sodium (>7 mmol/l) and lowered intracellular potassium (< 92.5 mmol/l) in erythrocytes in a subsample of individuals with all combinations of abnormal glucose tolerance, obesity and hypertension, compared with individuals without these conditions. Using the same intracellular electrolyte criteria the same group[8] also confirmed the presence of this cation "imbalance" in association with glucose-stimulated hyperinsulinaemia and increased serum triglyceride and urate concentrations. We have been unable to replicate their findings in a Maori population, ethnically predisposed to erythrocytic hypernatraemia and we question the generalisability of the concept of erythrocytic hypernatraemia as a marker of hyperinsulinaemia.

Hypertriglyceridaemia and hyperuricaemia are established markers of hyperinsulinaemia in European[9] and Israeli[4] populations, respectively. Serum urate and triglycerides are also increased in Maori, compared with Caucasians and the same is found in insulin resistant and hyperinsulinaemic Caucasians[10,11]. The association between serum urate and triglycerides in non-Polynesian populations has also been known for many years[12]. In our healthy young Maori study population, only fasting triglycerides were correlated with insulin level.

Despite the Maori predisposition to hyperinsulinaemia, there was no correlation between plasma urate and insulin level. A possible explanation for this arises from our finding of a strongly positive correlation between urate clearance and proximal tubular sodium reabsorption in Maori, but not in Caucasians. Since plasma urate is inversely correlated with urate clearance it must also be dependent on proximal tubular sodium reabsorption which is increased in Maori, independently of insulin level. In Maori, urate clearance is reduced due to increased proximal tubular sodium reabsorption. This mechanism has not been described previously and may account in part for the Maori predisposition to hyperuricaemia and gout. It also accounts for the lack of dependence of plasma urate on insulin level in Maori.

Our findings emphasise the ethnic specificity of biochemical correlates with hyperinsulinaemia and insulin resistance and indicate the need for caution in the generalisability of previously described markers of hyperinsulinaemia.

Acknowledgements

We would like to thank the many Maori Health workers who paved the way for Maori to participate with cultural safety in this study. The study was funded in part by a grant from the National Heart Foundation of New Zealand.

References

1 Prior I, Rose B, Harvey H Davidson F. Hyperuricaemia, gout and diabetic abnormality in Polynesian people. Lancet 1966; i: 333-338.

2 Maling T, Siebers R. Membrane sodium transport and renal proximal tubular sodium clearance in Maori and Caucasian normotensives. J Hypertens 1989: 7 (Suppl 6): S28.

3 Modan M, Halkin H, Almog S *et al*. Hyperinsulinaemia. A link between hypertension, obesity and glucose intolerance. J Clin Invest 1985; 75: 809-817.

4 Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid: a facet of hyperinsulinaemia. Diabetologia 1987; 30: 713-718.

5 Maling T. Clinical Studies of Cation Transport in Hypertension. MD thesis. University of Otago, 1993.

6 Maling T, van Wissen K, Siebers R. Hyperinsulinaemia and blood pressure in normotensive Maori and Caucasian New Zealanders. J Hypertens 1994; 12 (Suppl 3): S186.

7 Siebers R, Jackson M, Lim C, Maling T. Stability of urate in urine. Clin Biochem Revs 1993; 14(4): 308.

8 Halkin H, Modan M, Shefi M, Almog S. Altered erythrocyte and plasma sodium and potassium in hypertension, a facet of hyperinsulinaemia. Hypertension 1988; 11: 71-77.

9 Reaven G, Greenfield M. Diabetic hypertriglyceridaemia: evidence for three clinical syndromes. Diabetes 1981; 30 (Suppl 2): 66-75.

10 Castelli W. The triglyceride issue: a view from Framingham. Am Heart J 1986; 112: 432- 430.

11 McKeigue P, Marmot M, Syndercombe Court Y, Cottier D, Rahman S, Riemersma R. Diabetes hyperinsulinaemia and coronary risk factors in Bangladeshis in East London. Br Heart J 1988; 60: 390-396.

12 Berkovitz D. Blood lipid and uric acid inter-relationships. J Am Med Assoc 1964; 190: 856-858.