Int J Diabetes & Metabolism (2008) 16: 1-6

Susceptibility to insulin resistance in indigenous Australians may be down stream of resistin.

David A Good[1], John Cardinal[2], Robert S Ware,[3] Lisa Marks[2], Janine B Kesting[1], Lionel CK Chan,[1] Joanne TE Shaw[1]

Discipline of Medicine, The University of Queensland, The Prince Charles Hospital, Brisbane, Queensland 4032[1],Chemical Pathology, Queensland Health Pathology Service, Brisbane, Queensland 4029,[2] School of Population Health, The University of Queensland, Brisbane, Queensland 4006[3], Australia

Abstract

Objective: Obesity is thought to be a major risk factor for the development of insulin resistance and type 2 diabetes mellitus. However, not all obese or insulin resistant individuals develop T2DM suggesting additional factors are required to cause disease. In order to identify additional mechanisms leading to insulin resistance and T2DM, we measured plasma adipokines as well as established biochemical risk factors for developing T2DM in a large indigenous Australian family. **Results:** We found T2DM individuals had higher insulin resistance (as measured by HOMA-IR) ($p< 0.001$), triglyceride ($p= 0.003$), cholesterol ($p=0.02$) and TNFα ($p=0.03$) levels than normoglycaemic controls, independent of age, gender and BMI. The alterations in insulin resistance could not be attributed to TNFα, as we did not find a correlation between TNFα and HOMA-IR in either normoglycaemic or T2DM individuals. In contrast, resistin correlated strongly to HOMA-IR in T2DM ($p<0.001$) but not normoglycaemic individuals despite the lack of significant differences in circulating levels. We also showed obese T2DM individuals had significantly lower leptin levels ($p<0.001$) and ß cell function (as measured by HOMA-%B) ($p<0.001$) compared to obese normoglycaemic family members. **Conclusion:** These results suggest that events downstream of resistin signalling warrant further investigation to identify the cause for increased susceptibility to insulin resistance in this family. The lower leptin levels in obese T2DM individuals may be explained by a reduced ß cell function. Longitudinal studies are required to assess the utility of TNFα and leptin levels in relation to BMI as risk factors for T2DM.

***Key Words**: Adipokines, Adiponectin, Diabetes, Leptin, Obesity, Resistin, TNFα*

Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly common condition associated with reduced life expectancy and considerable morbidity. It may remain undetected for a number of years, and consequently, a significant proportion of people with newly diagnosed T2DM have established complications at the time of diagnosis.[1]

Obesity is thought to be a major risk factor for T2DM. A major complication of obesity is the development of insulin resistance. The mechanisms underlying insulin resistance are unclear. It has been suggested that increased adiposity induces a chronic inflammatory state characterized by elevated circulating levels of adipokines produced from adipocytes or macrophages infiltrating the fat pad.[2-4] Many of these cytokines have been shown to antagonize insulin signalling in rodent models leading to an increased secretion of insulin by pancreatic beta cells. T2DM is thought to occur when the internal *milieu* governing glucose homeostasis is disrupted to such a degree that it overrides residual pancreatic beta cell function[5].

Although obesity increases the risk of developing T2DM, not all obese or insulin resistant individuals develop T2DM. There is also a significant role for genetic differences in determining the level of insulin resistance and T2DM susceptibility. A previous study identified three distinct regions of genetic linkage to T2DM in a large indigenous Australian family with a high prevalence of T2DM and obesity[6]. In this present study, we aim to better delineate the phenotype of individuals who are susceptible to insulin resistance and T2DM in this family. As adipokines have been implicated in the pathogenesis of diabetes, we measured plasma adipokine levels along with established biochemical risk factors for developing T2DM and compared these variables between individuals with and without T2DM.

Methods

Subjects and study design

The study participants included 166 individuals of a single large indigenous Australian family of which 28% had been diagnosed as having T2DM. Individuals were regarded as overweight if they had a BMI > 25 and ≤ 30 and obese if they had a BMI > 30 as per WHO recommendations. Data analysis for BMI groups was performed on 144 individuals, as we were unable to obtain BMI data for 22 individuals.

Received on: 6/08/07
Accepted on: 21/02/08

Correspondence to: Dr John Cardinal, Department of Chemical Pathology, Queensland Health Pathology Service, Herston Rd, Herston, Brisbane, QLD 4029, Australia, Tel: +617 36360165, Fax: +617 36363417, Email: john_cardinal@health.qld.gov.au or scardina@bigpond.net.au

The study was approved by the Human Ethics Review Board of the Indigenous Community and the Human Research Ethic Committee of the Princess Alexandra Hospital.

Clinical and Biochemical data

Baseline measurements included a medical history, physical examination and laboratory testing. Presence of T2DM was defined according to WHO criteria.[7] Clinical history was validated by examination of medical charts in local health centers.

Procedures for measuring physical parameters like body mass index (BMI) have been previously described.[8] Biochemical investigations of fasting blood samples included: fasting plasma glucose, insulin, total cholesterol, triglycerides and high density lipoprotein (HDL), leptin, adiponectin, resistin and TNFα..

All blood samples were collected from subjects after 8 hours of fasting and abstinence from smoking and caffeinated beverages. Plasma glucose was measured using a hexokinase method, cholesterol and triglycerides were measured using a peroxidase mediated oxidative reaction in a Dimension RxL automated Clinical Chemistry Analyser (Dade Behring Inc, Illinois, USA). Hb_{A1c} was measured by ion-exchange high performance liquid chromatography in the Variant 2 Analyser (Biorad, Sydney, Australia). Insulin levels were determined using an enzyme immunoassay (Tosoh Bioscience San Francisco, CA, USA). Adipokine levels were measured by a commercially available immunoassay (Linco Research Inc, St. Charles, Missouri, USA) using a Luminex 100 system (Luminex, Austin, Texas, USA). HOMA-IR was calculated as insulin x fasting glucose / 22.5 and HOMA-%B as 20 x insulin / (Glucose – 3.5) as previously described[9].

Statistical Analysis

Variables were checked for normal distribution using the Shapiro-Wilk test; variables not normally distributed were natural log transformed and retested for normality before entry into parametric models. Physical and biochemical characteristics were compared using Student's t-tests according to T2DM status, BMI category and insulin resistance. The association between adipokines and physical parameters was analysed using Spearman's correlation coefficient. Analysis of variance techniques were used to detect relationships between adipokines and BMI, plasma insulin, HOMA-IR, HOMA-%B and TNFα, after adjusting for BMI, age, gender and T2DM status. BMI was categorized as BMI ≤25**,** >25 to ≤30 and >30. Age was categorized into tertiles. Analyses were performed using SPSS version 12.0 for Windows (SPSS Inc, IL, USA) and Stata version 9.2 for Windows (StataCorp, College Station, TX, USA).

Results:

Association between obesity, HOMA-IR, HOMA-%B and T2DM

There was a significantly higher proportion of overweight or obese individuals with T2DM than normal weight individuals with 39.0% of over weight or obese family members having T2DM compared with only 12.8% in normal weight individuals (Chi squared p=0.003). T2DM individuals were more likely to be overweight or obese than normoglycaemic individuals with 10.9% of T2DM individuals being normal weight compared with 34.7% of normoglycaemic individuals (chi squared p= 0.003). Although T2DM individuals were significantly older (p<0.001), the association between BMI and T2DM remained significant after correcting for age and gender (p<0.001). After adjusting for gender and age, the odds of having T2DM in this family for overweight or obese individuals is 5.98 (95%CI 1.73 to 20.64) times the odds for the normal weight individuals.

Both HOMA-IR and log HOMA-%B increased between normal and obese individuals by 5.68 (95%CI: 1.87 to 9.51) (p=0.004) and 0.83 (0.36 to 1.30) (p=0.001) respectively, in normoglycaemic individuals after correcting for age and gender. In the normoglycaemic group, there was a significant correlation between both HOMA-IR and HOMA-%B and BMI (Table 1). In contrast, the T2DM group had a significantly higher overall HOMA-IR (16.5 vs 7.2; p<0.001) and lower log HOMA-%B (4.4 vs 5.4; p<0.001) than the normoglycaemic group. There was no significant difference in HOMA-IR or HOMA-%B between normal, overweight and obese T2DM individuals after correcting for age and gender. There was no significant correlation between HOMA-IR and BMI or between HOMA-%B and BMI in T2DM individuals (Table 2).

Associations between traditional biochemical markers and T2DM

When the family was analysed as a whole, T2DM individuals had significantly higher total cholesterol (6.1 vs 5.3; p=0.002) and triglyceride (5.4 vs 2.1; p=0.001) than normoglycaemic family members (Table 3). After adjusting for age, BMI and gender, triglycerides levels of T2DM individuals were 3.5 mM (95%CI 1.2-5.9) higher (p = 0.003) than the normoglycaemic group. Cholesterol was 0.66 (95%CI 0.10-1.22) higher in T2DM group, after adjustement for age, BMI, gender (p=0.02)). Total cholesterol and triglyceride levels of T2DM individuals correlated with glucose (Table 1).

Adiponectin

There were no significant differences in adiponectin levels between normoglycaemic and T2DM groups, however there was a significant difference in adiponectin levels between normal weight and obese individuals and this remained significant after adjusting for T2DM, age and gender (p < 0.001) (Table 3). Adiponectin levels of normoglycaemic individuals showed a negative correlation with BMI, triglyceride, insulin, HOMA-IR and HOMA-%B and a positive correlation with HDL (Table 1). Adiponectin levels were associated with HOMA-IR (p< 0.001), triglyceride (p< 0.001) and HDL (p< 0.001) in normoglycaemic individuals but changed to p = 0.16, 0.05 and 0.65 respectively after adjusting for BMI. Similarly, adiponectin levels of T2DM individuals showed a negative correlation with BMI and insulin and a strong correlation with HDL. Adiponectin levels of T2DM individuals were associated with HDL (p=

Table 1: Adipokine correlations according to glycaemic status and lipids for normoglycaemic individuals (n=119). Correlations expressed as Spearman's correlation coefficient (*p-value*)

Variable	BMI	Insulin (mU/L)	Glucose (mM)	HOMA-IR	HOMA %B	Total cholesterol (mM)	HDL cholesterol (mM)	Triglyceride (m
Insulin (mU/L)	0.306 (0.003)		0.359 (<0.001)	0.941 (<0.001)	0.873 (<0.001)	-0.073 (0.440)	-0.272 (0.004)	0.241 (0.010)
Glucose (mM)	0.098 (0.344)	0.359 (<0.001)		0.514 (<0.001)	-0.105 (0.286)	-0.014 (0.880)	0.030 (0.756)	0.096 (0.320)
HOMA-IR	0.393 (<0.001)	0.941 (<0.001)	0.514 (<0.001)		0.776 (<0.001)	-0.067 (0.513)	-0.301 (0.003)	0.220 (0.030)
HOMA %B	0.308 (0.003)	0.873 (<0.001)	-0.105 (0.286)	0.776 (<0.001)		-0.114 (0.249)	-0.347 (<0.001)	0.221 (0.024)
Adiponectin (µg/mL)	-0.511 (<0.001)	-0.276 (0.027)	0.016 (0.870)	-0.310 (0.002)	-0.289 (0.003)	-0.046 (0.622)	0.360 (<0.001)	-0.457 (<0.001)
Resistin (ng/mL)	0.112 (0.271)	0.007 (0.941)	0.020 (0.832)	0.075 (0.461)	-0.014 (0.888)	-0.074 (0.428)	-0.330 (<0.001)	0.015 (0.875)
Leptin (ng/mL)	0.642 (<0.001)	0.391 (<0.001)	0.089 (0.353)	0.415 (<0.001)	0.394 (<0.001)	-0.029 (0.759)	-0.291 (0.002)	0.127 (0.174)
TNF (pg/mL)	0.177 (0.083)	0.171 (0.068)	-0.049 (0.606)	0.093 (0.359)	0.199 (0.041)	0.071 (0.450)	-0.201 (0.033)	0.215 (0.021)
Total cholesterol (mM)	0.105 (0.309)	-0.073 (0.440)	-0.015 (0.880)	-0.067 (0.513)	-0.114 (0.249)		0.154 (0.104)	0.465 (<0.001)
HDL cholesterol (mM)	-0.495 (<0.001)	-0.272 (0.004)	0.030 (0.756)	-0.301 (0.003)	-0.347 (<0.001)	0.154 (0.105)		-0.449 (<0.001)
Triglyceride (mM)	0.417 (<0.001)	0.241 (0.010)	0.096 (0.320)	0.220 (0.030)	0.221 (0.024)	0.465 (<0.001)	-0.449 (<0.001)	

Table 2: Adipokine correlations according to glycaemic status and and lipids for T2DM individuals (n = 47). Correlations expressed as Spearman's correlation coefficient (*p-value*)

Variable	BMI	Insulin (mU/L)	Glucose (mM)	HOMA-IR	HOMA %B	Total cholesterol (mM)	HDL cholesterol (mM)	Triglyceride (mM)
Insulin (mU/L)	0.120 (0.432)		0.255 (0.091)	0.866 (<0.001)	0.420 (0.004)	-0.010 (0.948)	-0.257 (0.110)	0.204 (0.179)
Glucose (mM)	0.257 (0.085)	0.255 (0.091)		0.637 (<0.001)	-0.725 (<0.001)	0.155 (0.305)	-0.120 (0.460)	0.288 (0.055)
HOMA-IR	0.258 (0.095)	0.866 (<0.001)	0.637 (<0.001)		0.052 (0.739)	-0.018 (0.909)	-0.259 (0.116)	0.185 0.241)
HOMA %B	-0.141 (0.357)	0.420 (0.004)	-0.725 ((<0.001)	0.052 (0.739)		-0.164 (0.282)	-0.070 (0.674)	-0.084 (0.586)
Adiponectin (µg/mL)	-0.321 (0.029)	-0.313 (0.034)	-0.081 (0.591)	-0.280 (0.069)	-0.079 (0.605)	0.050 (0.739)	0.504 (0.001)	-0.245 (0.100)
Resistin (ng/mL)	0.067 (0.669)	0.574 (<0.001)	0.224 (0.135)	0.600 (<0.001)	0.201 (0.186)	0.010 (0.944)	-0.322 (0.040)	0.149 (0.323)
Leptin (ng/mL)	0.284 (0.056)	0.338 (0.027)	-0.107 (0.480)	0.279 (0.071)	0.358 (0.018)	-0.207 (0.163)	-0.124 (0.440)	-0.024 (0.872)
TNFα (pg/mL)	0.157 (0.299)	0.279 (0.060)	-0.004 (0.977)	0.253 (0.102)	0.174 (0.252)	-0.200 (0.178)	-0.197 (0.218)	-0.227 (0.129)
Total cholesterol (mM)	0.138 (0.361)	-0.040 (0.948)	0.155 (0.305)	-0.018 (0.908)	-0.164 (0.282)		0.288 (0.068)	0.658 (<0.001)
HDL cholesterol (mM)	-0.369 (0.019)	-0.257 (0.110)	-0.120 (0.460)	-0.259 (0.116)	-0.070 (0.674)	0.288 (0.068)		-0.283 (0.077)
Triglyceride (mM)	0.331 (0.027)	0.204 (0.179)	0.288 (0.055)	0.185 (0.242)	-0.084 (0.586)	0.658 (<0.001)	-0.283 (0.077)	

Table 3: Cohort characteristics according to glycaemic status and BMI. Continuous variables expressed as mean (sd), categorical values expressed as n (%)

Variable`(unit)	All		*BMI ≤ 25 kg/m^2*		*BMI > 25 kg/m^2 and ≤ 30 kg/m^2*		BMI > 30 kg/m^2	
	No T2DM (n = 119)	*T2DM (n = 47)*	*No T2DM (n = 34)*	*T2DM (n = 5)*	*No T2DM (n = 31)*	*T2DM (n = 16)*	*No T2DM (n = 33)*	*T2DM (n = 25)*
Insulin (mU/L)	27.2 (25.2)	31.4 (26.5)	20.1 (22.4)	20.5 (4.1)	23.6 (18.2)	35.3 (33.8)	36.2 (29.5)	31.6 (23.4)
Glucose (mM)	5.3 (1.0)*	11.6 (6.4)	5.1 (0.8)*	7.7 (2.3)	5.2 (1.2)*	10.8 (5.9)	5.5 (0.9)***	12.8 (7.0)
HOMA-IR	7.2 (7.2)*	16.5 (14.8)	4.7 (5.8)	7.3 (3.6)	6.0 (4.7)*	18.7 (20.1)	10.0 (8.3)*	16.6 (11.1)
log HOMA %B	5.4 (1.0)***	4.4 (1.1)	5.0 (0.9)	4.7 (0.5)	5.4 (0.8)*	4.6 (1.3)	5.7 (0.9)***	4.3 (1.1)
Adiponectin (µg/mL)	16.3 (9.4)	15.0 (11.3)	21.4 (10.0)	22.9 (12.8)	13.1 (6.5)	14.0 (6.2)	10.9 (5.3)	13.6 (13.2)
Resistin (ng/mL)	16.4 (11.5)	20.3 (15.2)	16.8 (12.0)	21.3 (11.0)	16.4 (10.5)	20.7 (15.7)	16.4 (8.9)	20.0 (16.4)
Leptin (ng/mL)	16.9 (19.2)	13.4 (15.9)	7.3 (9.3)	4.8 (4.5)	13.6 (11.4)	17.1 (19.8)	33.4 (25.9)***	13.1 (14.4)
TNFα (pg/mL)	2.7 (1.1)*	3.7 (1.45)	2.7 (1.0)	3.1 (0.9)	2.8 (1.2)**	3.7 (1.3)	3.0 (1.0)*	3.8 (1.6)
Total cholesterol (mM)	5.3 (1.1)*	6.1 (1.9)	5.1 (1.3)	5.8 (2.0)	5.4 (1.2)	5.7 (1.4)	5.5 (0.9)*	6.4 (2.1)
HDL cholesterol (mM)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.5)	1.1 (0.3)	1.1 (0.2)	0.9 (0.2)	1.0 (0.3)
Triglyceride (mM)	2.1 (1.3)*	5.4 (9.9)	1.6 (0.8)	2.1 (2.1)	2.1 (1.0)	2.9 (3.1)	2.8 (1.7)*	7.8 (13.2)

Statistical significance levels using 2-tailed t-test; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Data analysis for BMI groups was performed on 144 individuals as 22 individuals did not have BMI data recorded.

0.001) and remain significant after adjusting for BMI (p= 0.007).

Resistin

Although there appeared to be a trend towards higher resistin levels in T2DM individuals, this association did not reach significance after adjusting for gender, age and BMI (p = 0.07). In normoglycaemic individuals, there was a weak correlation between resistin levels and BMI, but did not reach significance with insulin, HOMA-IR or HOMA-%B. In contrast, resistin levels of T2DM individuals did not correlate with BMI or HOMA-%B but correlated strongly with insulin and HOMA-IR. Resistin levels were negatively correlated with HDL in both normoglycaemic and T2DM individuals.

Leptin

Leptin levels of obese T2DM individuals were significantly lower compared with obese normoglycaemic individuals (13.1 vs 33.3; p=0.001). Overall, females had significantly higher leptin levels than males after adjusting for age and BMI (p<0.001). Leptin levels of normoglycaemic individuals correlated strongly with BMI and less strongly with insulin, HOMA-IR and HOMA-%B (Table 1). These relationships were altered in T2DM individuals with leptin correlating only with insulin and HOMA-%B (Table 2). Leptin levels of normoglycaemic individuals were associated with HOMA-IR but this association was not significant after adjusting for BMI. In order to further analyse associations between HOMA-%B and biochemical markers, HOMA-%B values of T2DM individuals were dichotomised into high and low HOMA-%B and compared. Leptin levels of low HOMA-%B

T2DM individuals were significantly lower than the high HOMA-%B group. There were no significant differences in any of the other biochemical markers. Leptin levels were negatively correlated to HDL in the normoglycaemic individuals but this correlation was not significant in the T2DM individuals (Tables 1 and 2).

TNFα

When the family was analysed as a whole, T2DM individuals had significantly higher TNFα (3.7 vs 2.7; p<0.001). After adjusting for age, BMI and gender, plasma TNFα levels of the T2DM group were 0.51 pg/mL(95%CI 0.05 – 0.97) higher ($p = 0.03$). TNFα levels increased with BMI in the family as a whole after adjusting for age and gender, by 0.034 (95%CI 0.005-0.063), p=0.024. However this association did not reach significance in normoglycaemic (0.017 (95%CI -0.011 – 0.046) p=0.24) or T2DM (0.085 (95%CI 0.000 – 0.171) p=0.05) individuals. TNFα levels of normoglycaemic individuals correlated with triglyceride, and HOMA-%B and negatively correlated with HDL. TNFα levels of T2DM individuals correlated with resistin (r= 0.338, p= 0.020) and leptin (r= 0.362, p= 0.017) but this was not seen in normoglycaemic individuals.

Discussion

In agreement with numerous other studies,[10,11] our results show that obesity, increased insulin resistance (as measured

by the HOMA-IR index), triglyceride and cholesterol are clearly associated with the presence of T2DM. We also confirm other reports showing TNFα levels are significantly increased in T2DM individuals compared to healthy controls.[12] Although increasing BMI is associated with increased HOMA-IR, triglyceride, cholesterol and TNFα, the association between these markers and T2DM remained significant after the effects of BMI were excluded. Thus we show in this family, T2DM is associated with an exaggerated insulin resistance, triglyceride, cholesterol and TNFα response to increasing adiposity.

Although numerous studies have shown TNFα as a potent inhibitor of insulin signalling,[13,14] it does not appear that TNFα is a major contributor to the abnormally high insulin resistance and dyslipidaemia seen in this family. TNFα levels did not associate with HOMA-IR, triglyceride or cholesterol after accounting for BMI. In addition, we did not see a significant correlation between TNFα and any of the other markers in normoglycaemic or T2DM individuals. However, these findings do not exclude the possibility that fat tissue derived TNFα may have significant local effects on insulin signalling.

In a striking contrast to healthy individuals, we found resistin correlated strongly with HOMA-IR in T2DM individuals, despite a lack of significant differences in circulating levels between normoglycaemic and T2DM individuals. These findings exclude differences in resistin expression as a candidate for the cause of increased susceptibility of T2DM individuals to insulin resistance and dyslipidaemia. Rather it suggests T2DM individuals in this family may have a heightened response to resistin.

The function of resistin in healthy individuals is unclear. Resistin has been reported to be expressed by fat tissue and be a significant contributor to insulin resistance in mice.[15] However, resistin levels of healthy or T2DM individuals did not correlate to BMI, suggesting that in this family, resistin is not exclusively expressed in fat tissue. This study and others [16] show a negative correlation between resistin and HDL, without a correlation to triglyceride or cholesterol, supporting studies suggesting a possible role for resistin in regulating lipoprotein release from the liver[17]. However, as this correlation was not altered in T2DM individuals, it is unlikely that an abnormality in lipolysis would explain the correlation between resistin and insulin resistance in T2DM individuals.

Resistin has been shown to attenuate multiple effects of insulin, including insulin receptor (IR) phosphorylation, IR substrate 1 (IRS-1) phosphorylation, phosphatidylinositol-3-kinase (PI3K) activation, phosphatidylinositol triphosphate production, and activation of protein kinase B/Akt.[18] Resistin is thought to act by up-regulating expression of suppressor of cytokine signalling 3 (SOCS-3), a known inhibitor of insulin signalling[19]. It is possible then that resistin's affects on SOCS-3 expression or function could be responsible for some of the differences in insulin resistance between the normoglycaemic and T2DM individuals. Overt diabetes is thought to occur when the ß cell function is exceeded.[20] The results from this study are consistent with this idea, as the ß cell function of obese T2DM individuals did not increase with BMI as seen in healthy obese individuals. When the T2DM individuals were dichotomised into high and low HOMA-%B levels, we found leptin levels to be lower in the low HOMA-%B group. Leptin was also the only marker that correlated with HOMA-%B in T2DM individuals. As leptin expression is stimulated by insulin,[21,22] it is possible then that the reduced leptin in obese T2DM individuals is a consequence of reduced ß cell function.

Although adiponectin was significantly associated with changes in BMI, we saw no significant differences in adiponectin levels between T2DM individuals and healthy controls, suggesting adiponectin levels are not indicative of T2DM risk in this family. This is surprising, as adiponectin has been shown to have sensitising effects on insulin signalling.[23] However, we did show a strong correlation between adiponectin and HDL in T2DM individuals supporting previous studies suggesting a role for adiponectin in the regulation of lipid storage. [24-26]

In conclusion, this study has added to existing findings showing indigenous Australian T2DM individuals are more insulin resistant and have a greater degree of dyslipidaemia than healthy controls and that obesity only partially explained these abnormalities. We suggest that signalling events downstream of resistin warrant further investigation to identify the cause of the increased susceptibility to insulin resistance in this family. In addition, we highlight the potential usefulness of TNFα and leptin as additional T2DM risk markers. Longitudinal studies are needed to confirm their utility and to evaluate the relative strength of these predictions. It would be of benefit to conduct further studies to compare associations among other Indigenous families and between the Indigenous and Caucasian populations with the aim of elucidating a T2DM risk algorithm. This will enable a more specific targeting of at risk individuals for multimodality intervention aimed at preventing the onset of T2DM.

Acknowledgements

This project was funded by a National Health and Medical Research Council of Australia Project Grant (#252719), a Prince Charles Hospital Foundation Grant (#FRC0205-11), private donation from Mrs Chryssa Aroney and a Novo Nordisk DAWN award for Associate Professor Joanne Shaw. Dr Lionel Chan was funded by the National Health and Medical Research Council (Postgraduate Medical Scholarship #301287). Dr Robert Ware was supported by a National Health and Medical Research Council of Australia Capacity Building Grant (#252834). We also acknowledge the enthusiasm and support of the Indigenous participants of this study.

References

1. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992;15: 815-819.
2. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005; 115:911-919.

3. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004; 25:4-7.
4. Hotamisligil GS. Inflammatory pathways and insulin action. Int J Obes Relat Metab Disord 2003; 27:S53-5.
5. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; 116:1802-1812.
6. Busfield F, Duffy DL, Kesting JB, et al. A genomewide search for type 2 diabetes-susceptibility genes in indigenous Australians. Am J Hum Genet 2002; 70:349-357.
7. Alberti KGMM, Aschner P, Assal J-P, et al. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications - Report of a WHO consultation. Geneva: World Health Organization, 1999: 1-59.
8. Chan L, Ware RS, Kesting J, et al. Association between anthropometric measures of obesity and cardiovascular risk markers in a self-selected group of Indigenous Australians. Eur Jl Cardiovasc Prevention Rehab 2007: (in press).
9. Matthews DR HJ, Rudenski AS, Naylor BA, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
10. Harrell JS JA, Greene N. Changing our future: obesity and the metabolic syndrome in children and adolescents. J Cardiovasc Nurs 2006; 21: 3 22-330.
11. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444: 840-846.
12. Zinman B, Hanley AJG, Harris SB, et al. Circulating Tumor Necrosis Factor-{alpha} Concentrations in a Native Canadian Population with High Rates of Type 2 Diabetes Mellitus. J Clin Endocrinol Metab 1999; 84: 272-278.
13. Borst S. The role of TNF-alpha in insulin resistance. Endocrine 2004; 23: 177-182.
14. Moller D. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab 2000; 11: 212-217.
15. Steppan CM BS, Bhat S, Brown EJ, et al . The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-312.
16. Pilz S, Weihrauch G, Seelhorst U, et al. Implications of resistin plasma levels in subjects undergoing coronaryangiography. The Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. Clinical Endocrinology 2007; 66: 380-386.
17. Sato N, Kobayashi K, Inoguchi T, et al. Adenovirus-Mediated High Expression of Resistin Causes Dyslipidemia in Mice. Endocrinology 2005; 146: 273-279.
18. Moon B, Kwan JJ-M, Duddy N, et al. Resistin inhibits glucose uptake in L6 cells independently of changes in insulin signaling and GLUT4 translocation. Am J Physiol Endocrinol Metab 2003; 285:E106-115.
19. Steppan CM, Wang J, Whiteman EL, et al. Activation of SOCS-3 by Resistin. Mol Cell Biol 2005;25:1569-1575.
20. Prentki M, Nolan CJ. Islet {beta} cell failure in type 2 diabetes. J Clin Invest 2006; 116(7): 1802-1812.
21. Moreno-Aliaga MJ, Stanhope KL, Havel PJ. Transcriptional Regulation of the Leptin Promoter by Insulin-Stimulated Glucose Metabolism in 3T3-L1 Adipocytes. Biochemical and Biophysical Research Communications 2001; 283: 544-548.
22. Kim JB, Sarraf P, Wright M, et al. Nutritional and Insulin Regulation of Fatty Acid Synthetase and Leptin Gene Expression through ADD1/SREBP1. J Clin Invest. 1998; 101: 1-9.
23. Wang C, Mao X, Wang L, et al. Adiponectin Sensitizes Insulin Signaling by Reducing p70 S6 Kinase-mediated Serine Phosphorylation of IRS-1. J Biol Chem 2007; 282: 7991-7996.
24. Baratta R, Amato S, Degano C, et al. Adiponectin Relationship with Lipid Metabolism Is Independent of Body Fat Mass: Evidence from Both Cross-Sectional and Intervention Studies. J Clin Endocrinol Metab 2004; 89: 2665-2671.
25. Bajaj M, Suraamornkul S, Piper P, et al. Decreased Plasma Adiponectin Concentrations Are Closely Related to Hepatic Fat Content and Hepatic Insulin Resistance in Pioglitazone-Treated Type 2 Diabetic Patients. J Clin Endocrinol Metab 2004; 89: 200-206.
26. Schneider JG, von Eynatten M, Schiekofer S, et al. Low Plasma Adiponectin Levels Are Associated With Increased Hepatic Lipase Activity In Vivo. Diabetes Care 2005; 28: 2181-2186.