Clinical Endocrinology (2007) **66**, 000–000 doi: 10.1111/j.1365-2265.2007.02801..x

ORIGINAL ARTICLE

Interleukin-6, tumour necrosis factor-alpha and insulin relationships to body composition, metabolism and resting energy expenditure in a migrant Asian Indian population

Elaine C. Rush*, Lindsay D. Plank† and Chittaranjan S. Yajnik‡

**Institute of Sport and Recreation Research New Zealand, Faculty of Health and Environmental Sciences, Auckland University of Technology, Auckland, New Zealand, †Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand and ‡Diabetes Unit, King Edward Memorial Hospital and Research Centre, Pune, India*

Summary

Objective Systemic inflammation and insulin resistance may play important roles in the pathogenesis of obesity-related diseases for which migrant Asian Indians are at particularly high risk. We examined relationships between markers of insulin resistance and inflammation, resting energy expenditure (REE), and body composition.

Design and methods Measurements were made of total and regional body composition, including regional fat mass (FM) and appendicular skeletal muscle mass (ASMM) by dual-energy X-ray absorptiometry (DXA), REE by indirect calorimetry and fasting interleukin (IL)-6, tumour necrosis factor (TNF)-α, glucose and insulin, in 79 healthy Asian Indians (38F, 41M; age 30–49 years) from urban Auckland, New Zealand. Beta-cell function (HOMA B%) and insulin sensitivity (HOMA S%) were derived using homeostatic model assessment.

Results Men had a more central distribution of body fat than women. REE was strongly correlated with IL-6 concentrations in men but not in women. In both sexes, IL-6 was associated positively with percentage body fat and HOMA B% and inversely with ASMM and HOMA S%. Insulin increased and HOMA S% decreased with increasing waist-to-hip ratio and abdominal-to-thigh fat ratio in men but not in women. TNF-α was not significantly associated with any of the variables examined.

Conclusion Relationships between body fat distribution and HOMA S% were strongly sex dependent and may indicate a greater propensity for development of the metabolic syndrome among male Asian Indians than females in the age group examined.

(Received 23 August 2006; returned for revision 15 September 2006; finally revised 5 October 2006; accepted 28 November 2006)

Correspondence: Elaine Rush, Auckland University of Technology, Private Bag 92006, Auckland 1128, New Zealand. Tel.: + 64 9 921 9999 x8091; Fax: + 64 9 921 9960; E-mail: elaine.rush@aut.ac.nz

Introduction

A number of recent studies (reviewed by Grimble[1]) have shown significant associations between markers of systemic inflammation and the metabolic syndrome and its components. In particular, elevated levels of C-reactive protein (CRP), tumour necrosis factor (TNF)-α and interleukin (IL)-6 appear to be associated with obesity and insulin resistance and the development of obesity-related diseases, including diabetes, hypertension and cardiovascular disease.[2] In the control of energy homeostasis through complex endocrine signalling pathways, adipose and skeletal muscle tissues play major roles. The adipocyte is recognized as both a source and a recipient of paracrine and endocrine signals that interact with many other tissues in association with variations in body composition and metabolism.[3,4] IL-6 has been shown to increase energy expenditure[5] and to increase lipolysis during exercise,[4] decrease food intake, and is implicated in the pathogenesis of insulin resistance.[6] IL-6 may also regulate regional adipose tissue metabolism as suggested by the high rates of secretion of this cytokine from omental tissue compared to subcutaneous tissue in obese subjects.[7] Similarly, TNF-α correlates with body fat mass and hyperinsulinaemia[3] and induces insulin resistance in skeletal muscle.[8]

Research on the links between inflammation and the metabolic syndrome is especially relevant for Asian Indian populations because of their high propensity for the development of insulin resistance and abdominal obesity, risk factors for diabetes and cardiovascular disease.[9,10] Compared with European populations, urban dwellers within India and migrant Indian populations worldwide are at increased risk of obesity-related diseases with consequent economic implications.[11] A survey conducted in New Zealand[12] showed that the Asian Indian population had a much higher age-standardized prevalence of known diabetes (9·9%) than all other major ethnic groups. Studies on migrant Asian Indians have shown higher levels of subclinical inflammation (assessed by CRP) than in Europeans,[13,14] despite similar percentage body fat and lower waist circumference.[15] Within India, proinflammatory cytokine levels were higher in urban than in rural Indians.[16] For Asian Indian populations, limited information is available on the relationships between markers of inflammation and other key factors associated with risk of obesity-related disease.

The aim of the current study was to investigate, in a group of Asian Indians resident in New Zealand, the interrelationships between systemic cytokine levels, insulin resistance and sensitivity, lipid profiles, resting energy expenditure, substrate oxidation and body composition.

Research design and methods

Seventy-nine apparently healthy volunteers (38 women and 41 men) aged 30–49 years, self-identified as Indian (30F, 32M), Sri Lankan (2F, 2M) or Fijian Indian (6F, 7M), participated in the study. All had resided in New Zealand for at least 3 (range 3–42) years and four were born in New Zealand. The maximum age of the women was 47 and none identified that they were postmenopausal. Subjects with pregnancy, known diabetes or any other condition or medications that would affect body weight or body water, or doing weight training more than once a week were excluded from the study. The experimental procedure was explained to all subjects before recruitment and written informed consent was obtained. The study was approved by the Auckland Regional Ethics Committee.

Anthropometry and body composition

Anthropometry and body composition measurements were carried out on overnight-fasted (> 10 h) subjects during an early morning visit to the Body Composition Laboratory, Department of Surgery, University of Auckland. Height and weight were measured with participants wearing light clothing or standard hospital gown and no shoes. Waist, hip and skinfold thicknesses (biceps, triceps, subscapular and suprailiac) were measured using standard techniques. Body composition (fat, fat-free soft tissue and bone mineral content) measurements were made by dual-energy X-ray absorptiometry (DXA; model DPX+ with software version 3·6y, Lunar Radiation Corp., Madison, WI, USA). Fat-free mass (FFM) was calculated as the sum of the values for fat-free soft tissue and bone mineral content. Percentage body fat was calculated as 100 × fat mass (FM)/(FM + FFM).

For assessing regional fat distribution the whole-body DXA scans were analysed. Abdominal and thigh regions of interest were defined by the criteria of Ley *et al.*[17] Abdominal fat was obtained from analysis of a region of interest positioned with the lower horizontal border on top of the iliac crest and the upper border approximately parallel with the junction of the T12 and L1 vertebrae. The sides of this region were adjusted to include the maximum amount of abdominal tissue. A region of interest of identical height placed over the thighs with the upper horizontal border positioned immediately below the ischial tuberosities was used to obtain fat content of the thighs. The lateral margins were adjusted to follow the shape of the thighs.

Appendicular skeletal muscle mass (ASMM) was derived from the DXA scans as total limb mass minus the sum of limb fat mass and wet bone mass, estimated as bone mineral content divided by 0·55.[18] In this model, mass of the skin and associated dermal tissues is assumed to be negligible relative to the skeletal muscle component.

The length of the body and the legs was calculated from the *x* and *y* coordinates on the digitized image of proximal to distal points on the bones. Total skeletal length was measured as the distance from the apex of the cranium to the plantar surface of the calcaneus bone (i.e. bottom of the heel). Femur bone length was measured from the top of femoral head (greater trochanter) to middle patellar surface, and tibia bone length was measured from the superior intercondylar eminence to inferior surface medial malleolus. Dimensions were measured in pixels and converted to centimetres after scanning a standard ruler. One pixel was equal to 0·48 cm on the *x*-axis and 0·96 cm on the *y*-axis. These dimensions do not correspond precisely to anatomical bone lengths, although all measurements were consistent among our subjects.

The equation used to derive length from proximal (P_x, P_y) and distal (D_x, D_y) coordinates was:

$$\text{Bone length (cm)} = \sqrt{\{[0{\cdot}96(D_y - P_y)]^2 + 0{\cdot}48(D_x - P_x)^2\}}$$

Leg lengths were determined by measuring the lengths of the femur plus tibia bones on the scan. The ratio of tibia plus femur length to total subject length (as measured by DXA as DXA height) was used as an index of relative leg length.

Resting energy metabolism and activity

Resting energy expenditure (REE) and respiratory exchange ratio (RER) were measured following the DXA scan. Measurements were made over a period of 30 min using a ventilated canopy, connected to an open circuit indirect calorimeter (Deltatrac, Datex, Finland). The calorimeter was calibrated with standardized gases before each measurement and accuracy tested regularly using alcohol combustion. Participants completed a questionnaire detailing number of hours slept per day and whether they perceived themselves as active or sedentary.

Biochemistry

Plasma from fasting blood samples, collected in ethylenediaminetetraacetic acid (EDTA) tubes, was separated within 5 min of collection and aliquots were immediately frozen at −80 °C until analysis. Glucose, triglycerides, low density lipoprotein (LDL) and total cholesterol were measured using standard enzymatic kits (Roche-Hitachi) and high density lipoprotein (HDL) was assayed directly using a Hitachi 911 analyser (Hitachi Limited, Tokyo, Japan). All assays were within target limits specified by the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program. These assays were carried out by a local laboratory (Diagnostic Medlab) that has IANZ ISO9002 Accreditation.

Insulin levels were measured at the Waikato District Health Board laboratory using the Abbott IMx Insulin assay (list No2A10, Abbott Laboratories, Japan). Markers of β-cell function (HOMA B%) and insulin sensitivity (HOMA S%) were calculated using the homeostasis model assessment (HOMA) index algorithm[19] derived from the fasting glucose and the insulin concentrations (using a DOS algorithm supplied by Jonathan Levy, Oxford University). Aliquots were transported in dry ice to the Diabetes Unit, KEM Hospital, Pune, India, for the analysis of cytokines, IL-6 and TNF-α, using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Inc.,

Minneapolis, MN, USA). For IL-6, the sensitivity was 0·094 pg/ml and the interassay coefficient of variation (CV) 12·2%, and for TNF-α, the sensitivity was 0·12 pg/ml and the CV 7·5%.

Statistical methods

Results are presented as mean ± SD or median and interquartile range (IQR). Student's *t*-test was used to compare male and female groups. Variables were compared between activity groups (active or sedentary) for males and females by two-factor analysis of variance (ANOVA). Pearson correlation analysis was used to examine relationships between body composition, metabolic risk variables, and cytokines. Prediction of REE was examined by stepwise multiple regression analysis using an alpha level of 5% for retention in the model. Potential predictors considered were FFM, FM, body mass index (BMI), hip girth, abdominal fat mass, ASMM, IL-6 and smoking status. All biochemistry variables, except cholesterol concentration, were logarithmically transformed prior to analyses to reduce their positive skewness. Data were analysed using SPSS software, version 13.

Results

Physical characteristics and body composition results are shown in Table 1. At the time of study six men and one woman were smokers. Compared to women, men were taller, heavier, and had less subcutaneous fat thickness on their arms. Central skinfolds were not different but men had larger waists and smaller hips than the women. The DXA analysis showed that women had, relative to body weight, more body fat and less ASMM than the men. Percentage fat in both the abdominal and thigh regions was higher in women than men but proportionately more fat was in the thigh area than the abdominal area for the women.

Absolute REE was higher in men than women (Table 2). In men, 72% of the variation in REE could be explained by FFM (60%) and FM (12%), while in women, these two variables explained only 36% (of which 26% was accounted for by FM). Abdominal fat mass in place of FM improved the prediction of REE for both men (74% explained) and women (38% explained). For men, inclusion of smoking status in this model increased the R^2 to 77% and IL-6 concentration as an additional predictor increased R^2 to 84%. However, smoking status and IL-6 were not independently predictive of REE. Circulating IL-6 concentrations were significantly higher in the male smokers than the nonsmokers ($P = 0{\cdot}019$). For women, IL-6 did not significantly improve prediction of REE. Stepwise regression analysis considering all possible covariates yielded the following significant predictors of REE:

Women

$$\text{REE (kcal/day)} = 697 + 8{\cdot}7\ \text{FFM (kg)} + 0{\cdot}06\ \text{abdominal FM (kg)}$$
(adjusted $R^2 = 0{\cdot}35$, standard error of estimate = 95 kcal/day)

Men

$$\text{REE (kcal/day)} = 729 + 32{\cdot}1\ \text{FFM (kg)} + 205{\cdot}5\ \log[\text{IL-6 (pg/ml)}] + 23{\cdot}3\ \text{BMI (kg/m}^2) - 9{\cdot}6\ \text{hip girth (cm)} - 30{\cdot}9\ \text{ASMM (kg)}$$
(adjusted $R^2 = 0{\cdot}87$, standard error of estimate = 73 kcal/day)

In the latter model, FFM and IL-6 accounted for, respectively, 60% and 20% of the explained variance.

RER at rest was higher for those with more percentage ASMM ($r = 0{\cdot}26$, $P = 0{\cdot}024$), relatively longer legs ($r = 0{\cdot}25$, $P = 0{\cdot}029$) and a lower percentage of abdominal fat ($r = -0{\cdot}24$ $P = 0{\cdot}038$), indicating greater carbohydrate utilization.

Table 1. General characteristics, anthropometry and body composition of female and male adult Asian Indians

	Women ($n = 38$)	Men ($n = 41$)	*P*
Age (years)	39 ± 5	39 ± 5	0·88
Height (cm)	157·6 ± 5·5	169·0 ± 7·7	< 0·0001
Weight (kg)	66·1 ± 10·2	75·2 ± 14·1	0·002
Leg length/height	0·476 ± 0·012	0·476 ± 0·015	0·89
Biceps skinfold (mm)	15·7 ± 7·5	8·1 ± 4·2	< 0·0001
Triceps skinfold (mm)	30·7 ± 9·6	21·4 ± 10·0	< 0·0001
Subscapular skinfold (mm)	36·7 ± 12·6	36·1 ± 12·4	0·81
Suprailiac skinfold (mm)	32·9 ± 10·3	30·7 ± 13·3	0·42
Subscapular/triceps skinfold	1·24 ± 0·40	1·82 ± 0·56	< 0·0001
Waist girth (cm)	84·8 ± 8·6	93·6 ± 11·9	< 0·0001
Hip girth (cm)	103·2 ± 10·0	99·2 ± 7·0	0·036
Waist/hip	0·82 ± 0·07	0·94 ± 0·08	< 0·0001
Fat mass (kg)	28·7 ± 8·1	24·9 ± 9·7	0·064
Percentage body fat	42·7 ± 6·7	32·3 ± 7·8	< 0·0001
Fat-free mass (kg)	37·4 ± 4·4	50·4 ± 7·8	< 0·0001
Appendicular skeletal muscle mass (%)	22·9 ± 3·1	29·0 ± 3·6	< 0·0001
Abdominal fat (%)	45·8 ± 6·8	40·5 ± 7·9	< 0·0001
Thigh fat (%)	49·6 ± 8·0	35·0 ± 8·4	0·002
Abdominal/thigh fat	0·872 ± 0·213	1·244 ± 0·212	< 0·0001

Data are means ± SD.

Table 2. Biochemical and metabolic variables for female and male adult Asian Indians

	Women ($n = 38$)	Men ($n = 41$)	P
Interleukin-6 (pg/ml)	1·73 (0·93–2·67)	1·31 (0·80–2·24)	0·71
Tumour necrosis factor-α (pg/ml)	3·27 (2·49–5·40)	4·098 (2·91–5·40)	0·53
Glucose (mmol/l)	5·0 (4·7–5·3)	5·3 (5·1–5·8)	0·006
Insulin (pmol/l)	86·5 (52·4–78·9)	78·9 (62·8–126·6)	0·44
Insulin sensitivity (HOMA S%)	66·9 (48·9–99·3)	66·1 (41·7–83·5)	0·32
β-cell function (HOMA B%)	125·8 (88·7–156·6)	107·5 (81·0–156·2)	0·42
Cholesterol (mmol/l)	5·2 ± 0·9	5·3 ± 0·9	0·49
HDL (mmol/l)	1·20 (1·00–1·40)	1·00 (0·90–1·20)	0·009
LDL (mmol/l)	3·2 (2·9–4·0)	3·3 (3·0–4·0)	0·40
Triglycerides (mmol/l)	1·3 (0·9–1·9)	1·8 (1·2–2·4)	0·014
Resting energy expenditure (kcal/day)	1181 ± 118	1371 ± 199	< 0·0001
Respiratory exchange rate	0·90 ± 0·05	0·91 ± 0·04	0·047
Resting heart rate (beats/min)	67 ± 8	62 ± 8	0·021
Sleep hours	6·9 ± 1·7	7·2 ± 1·0	0·37
Number active	20	31	0·095

Data are mean ± SD or median (interquartile range).

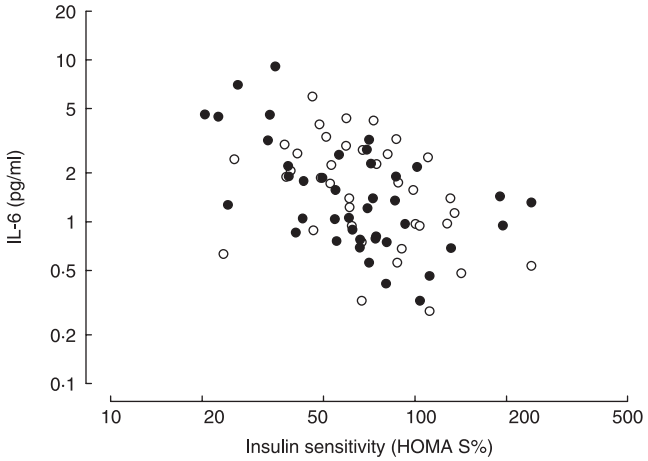

Fig. 1 Associations between circulating interleukin (IL)-6 concentrations and insulin sensitivity in 38 women (open symbols, $r = -0{\cdot}40$, $P = 0{\cdot}013$) and 41 men (closed symbols, $r = -0{\cdot}54$, $P = 0{\cdot}0002$).

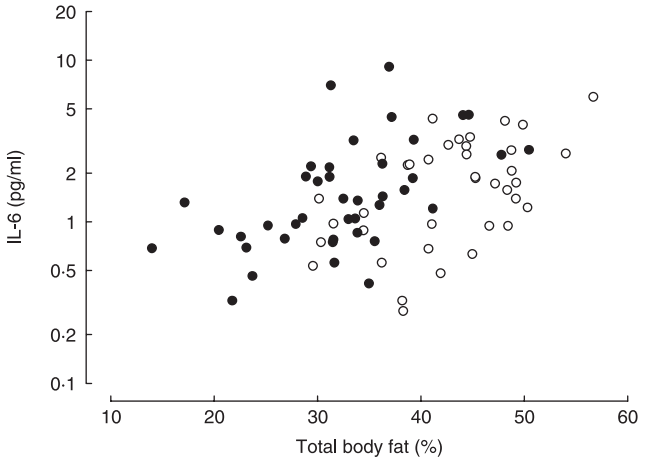

Fig. 2 Associations between circulating interleukin (IL)-6 concentrations and percentage body fat in 38 women (open symbols, $r = 0{\cdot}50$, $P = 0{\cdot}002$) and 41 men (closed symbols, $r = 0{\cdot}55$, $P = 0{\cdot}0002$).

Men and women who defined themselves as active had a lower heart rate (62·6 ± 8·6 *vs.* 69·1 ± 9·6 beats/min, $P = 0{\cdot}015$) and lower triglyceride levels [median (IQR) 1·5 (1·0–1·9) *vs.* 1·6 (1·0–2·6) mmol/l, $P = 0{\cdot}03$].

HOMA S%, HOMA B% and fasting insulin levels did not differ between men and women, while fasting glucose and HDL were lower and triglycerides were higher in men than in women (Table 2).

In men, IL-6 levels were significantly associated with insulin ($r = 0{\cdot}55$, $P = 0{\cdot}0002$), HOMA B% ($r = 0{\cdot}49$, $P = 0{\cdot}0011$) and HOMA S% ($r = -0{\cdot}54$, $P = 0{\cdot}0002$, Fig. 1). In women, these relationships were less strong ($r = 0{\cdot}40$, $P = 0{\cdot}013$; $r = 0{\cdot}32$, $P = 0{\cdot}052$; $r = -0{\cdot}40$, $P = 0{\cdot}013$, respectively).

The results of correlation analysis between biochemical factors (insulin, IL-6, HOMA S% and HOMA B%) and factors related to body composition, glucose and blood lipids are summarized in Table 3 for women and in Table 4 for men. Insulin and IL-6 were positively correlated with subcutaneous fat, total body and abdominal fat and negatively correlated with ASMM. Relationships between IL-6 and percentage body fat are shown in Fig. 2. Waist-to-hip ratio and abdominal-to-thigh fat ratio were correlated with insulin levels in men but not in women. For both men and women there were no correlations between these ratios and IL-6 levels. Triglyceride levels were correlated with both insulin and IL-6 levels in men but not in women. HOMA S% was higher in those with less subcutaneous and total fat and higher percentage ASMM. In men this parameter increased with reduction in waist-to-hip ratio, abdominal-to-thigh fat ratio and triglyceride levels. In women, there were no significant associations between HOMA S% and these variables. Relatively longer legs were associated with higher HOMA S% and lower insulin levels in women. In men, a similar pattern was seen, although these associations did not reach statistical significance. HOMA B% was positively associated in women with subcutaneous fat, abdominal fat, waist girth and ASMM but was not related to triglyceride concentration. These associations with HOMA B% were not seen in men. TNF-α was not associated with any of the variables measured.

Table 3. Correlation coefficients for 38 female adult Asian Indians

	Insulin	Interleukin-6	Insulin sensitivity (HOMA S%)	β-cell function (HOMA B%)
Triceps skinfold	0·528 (0·001)	0·312 (0·056)	−0·525 (0·001)	0·482 (0·002)
Subscapular skinfold	0·594 (< 0·0001)	0·538 (0·001)	−0·591 (< 0·0001)	0·594 (< 0·0001)
Subscapular/triceps skinfold	0·049 (0·77)	0·273 (0·097)	−0·048 (0·78)	0·121 (0·47)
Waist girth	0·525 (0·001)	0·382 (0·018)	−0·521 (0·001)	0·530 (0·0006)
Waist/hip	−0·015 (0·93)	−0·210 (0·21)	0·020 (0·90)	0·109 (0·51)
Heart rate	0·174 (0·30)	0·266 (0·11)	−0·178 (0·29)	0·028 (0·87)
Percentage body fat	0·487 (0·002)	0·496 (0·002)	−0·490 (0·002)	0·323 (0·048)
Abdominal fat (%)	0·536 (0·0005)	0·486 (0·002)	−0·538 (0·0005)	0·412 (0·010)
Abdominal/thigh fat	0·165 (0·32)	0·030 (0·86)	−0·164 (0·33)	0·155 (0·35)
Appendicular skeletal muscle mass (%)	−0·403 (0·012)	−0·398 (0·013)	0·406 (0·011)	−0·260 (0·114)
Leg length/height	−0·345 (0·034)	0·104 (0·53)	0·353 (0·030)	0·005 (0·98)
Glucose	0·252 (0·13)	0·119 (0·48)	–*	–*
HDL	−0·587 (< 0·0001)	−0·040 (0·81)	0·584 (0·0001)	−0·641 (< 0·0001)
Triglycerides	0·232 (0·16)	−0·008 (0·96)	−0·234 (0·16)	0·124 (0·46)

P-values are given in parentheses. *Glucose used in HOMA calculation.

Table 4. Correlation coefficients for 41 male adult Asian Indians

	Insulin	Interleukin-6	Insulin sensitivity (HOMA S%)	β-cell function (HOMA B%)
Triceps skinfold	0·343 (0·028)	0·500 (0·0008)	−0·345 (0·027)	0·189 (0·24)
Subscapular skinfold	0·623 (< 0·0001)	0·443 (0·004)	−0·627 (< 0·0001)	0·371 (0·017)
Subscapular/triceps skinfold	0·191 (0·23)	−0·240 (0·13)	−0·193 (0·23)	0·103 (0·52)
Waist girth	0·585 (< 0·0001)	0·352 (0·024)	−0·589 (< 0·0001)	0·270 (0·087)
Waist/hip	0·576 (< 0·0001)	0·278 (0·079)	−0·580 (< 0·0001)	0·329 (0·036)
Heart rate	0·300 (0·064)	0·403 (0·011)	−0·300 (0·064)	0·166 (0·31)
Percentage body fat	0·473 (0·002)	0·550 (0·0001)	−0·475 (0·002)	0·278 (0·078)
Abdominal fat (%)	0·535 (0·0003)	0·486 (0·001)	−0·538 (0·0003)	0·349 (0·026)
Abdominal/thigh fat	0·392 (0·011)	0·152 (0·34)	−0·394 (0·011)	0·226 (0·16)
Appendicular skeletal muscle mass (%)	−0·420 (0·006)	−0·509 (0·0007)	0·423 (0·006)	−0·237 (0·14)
Leg length/height	−0·296 (0·061)	0·190 (0·23)	0·299 (0·057)	−0·088 (0·59)
Glucose	0·163 (0·31)	0·003 (0·99)	–*	–*
HDL	−0·241 (0·13)	−0·108 (0·50)	0·246 (0·12)	−0·125 (0·43)
Triglycerides	0·439 (0·004)	0·312 (0·047)	−0·441 (0·004)	0·298 (0·059)

P-values are given in parentheses. *Glucose used in HOMA calculation.

Discussion

This study is the most comprehensive to date examining, in adult Asian Indians, the relationships between body composition, energy expenditure and markers of inflammation and insulin resistance. The key findings of this work are: (1) men showed a more central distribution of body fat than women, as judged by both anthropometry and DXA regional analysis; (2) REE was strongly correlated with circulating IL-6 concentrations in men but not in women; (3) in both men and women, IL-6 levels were associated positively with percentage body fat and insulin resistance and inversely with ASMM and insulin sensitivity; and (4) insulin levels increased and insulin sensitivity decreased with increasing waist-to-hip ratio and abdominal-to-thigh fat ratio in men while no such associations were seen in women.

Features of the metabolic syndrome, inflammation and obesity are closely linked but the aetiology of the development of this syndrome is not well understood. Compared with European populations, higher inflammatory marker (CRP) levels are observed in migrant Asian Indians.[13–15] This difference was accounted for by the greater central obesity and insulin resistance in the Asian Indians.[13] Comparison between urban and rural populations in India showed higher circulating IL-6 and TNF-α in the former group.[16] Others have shown positive correlations between inflammatory markers and body fat levels, in both Europeans and Asian Indians.[13,15,20] In a European population, Fernandez-Real *et al.*[21] showed that IL-6 and insulin sensitivity or resistance were strongly associated in men but not in women. The relatively poor correlation between insulin sensitivity and waist-to-hip ratio or abdominal-to-thigh fat ratio in

women may be related to the fact that premenopausal women have relatively much less visceral fat (in relation to total fat mass) than men or postmenopausal women.[22] Thus, visceral fat may make a relatively low contribution to abdominal fat and metabolic rate[23] in this group of relatively inactive women, and might explain the rather poor correlations.

The stronger relationship between FFM and REE found in the men compared to the women is surprising. Other studies, not restricted to Asian populations, have found similar correlations between FFM and REE for men and women.[24,25] We do not have an explanation for this difference. Further studies are needed to determine factors that may contribute to REE in Asian Indian women that would help to explain this anomaly.

Smoking is known to increase markers of inflammation[26] and REE[27,28] and we confirmed this in our group of males. Lyngso *et al.*[28] have also shown that infusion of IL-6 increases fat oxidation in splanchnic and subcutaneous adipose tissue. Thus it would seem that external and internal stressors that promote the inflammatory response, increase metabolic rate and change the balance of substrate oxidation are also associated with metabolic syndrome markers. While we were not able to show in the fasting state a relationship between IL-6 level and RER, there was a significant relationship between RER and percentage fat in the abdominal region. Differences in substrate oxidation measured by the RER were seen between the sexes; women burnt more fat and they also had more total and abdominal body fat than men. Conversely, more glucose was apparently burnt at rest as relative leg length increased, abdominal percentage fat decreased and percentage ASMM increased. Increased relative leg length and lower abdominal fat are known to be associated with lower risk for metabolic syndrome.[29] We have been able to confirm that a greater proportion of ASMM and longer legs are associated with lower levels of insulin and increased insulin sensitivity.

It is well-established that IL-6 can induce raised metabolic rate and ACTH concentrations.[26] IL-6 is also capable of inducing insulin resistance in the fat cells that produce it.[21] Insulin resistance in turn increases adipose mass and subsequently BMI. Stephens *et al.*[30] examined 'IL-6-174GC', a common functional gene variant, in 571 subjects who already had type 2 diabetes and found that the presence of this allele was associated with a higher BMI. In a healthy population this association was not found, so it was concluded that this allele has a role in inflammatory insulin resistance.

We were not able to demonstrate any metabolic or risk factor associations with plasma TNF-α. Others, however, have found that circulating TNF-α levels are elevated in subjects with obesity, insulin resistance and obesity-related diseases.[1,31]

It should be recognized that a large number of exploratory analyses have been carried out in this report and adoption of an arbitrary 5% threshold for statistical significance will yield a number of significant results by chance alone. We have provided *P*-values so that the results can be viewed in the context of a lower threshold for significance.

In summary, we have shown that the relationships between body fat distribution and insulin sensitivity were strongly sex dependent and may indicate a greater propensity for development of the metabolic syndrome among male Asian Indians than females (premenopausal) in the age group examined. Lowered risk for this syndrome and an increased oxidation of carbohydrate were seen in those with more appendicular skeletal muscle, relatively longer legs and less abdominal fat. These associations may have important implications for understanding the increasing incidence of diabetes and cardiovascular disease in migrant and urban Indian populations.

Acknowledgements

This study was supported by the Auckland University of Technology Contestable Research Fund. We thank Dr Vishnu Chandu for the subject measurements and Dattatraya Bhat for analysing the samples for IL-6 and TNF-α.

References

1 Grimble, R.F. (2002) Inflammatory status and insulin resistance. *Current Opinion in Clinical Nutrition and Metabolic Care*, **5**, 551–559.
2 Das, U.N. (2004) Metabolic syndrome X: an inflammatory condition? *Current Hypertension Reports*, **6**, 66–73.
3 Cancello, R., Tounian, A., Poitou, C. & Clement, K. (2004) Adiposity signals, genetic and body weight regulation in humans. *Diabetes and Metabolism*, **30**, 215–227.
4 Orban, Z., Remaley, A.T., Sampson, M., Trajanoski, Z. & Chrousos, G.P. (1999) The differential effect of food intake and beta-adrenergic stimulation on adipose-derived hormones and cytokines in man. *Journal of Clinical Endocrinology and Metabolism*, **84**, 2126–2133.
5 Kubaszek, A., Pihlajamaki, J., Punnonen, K., Karhapaa, P., Vauhkonen, I. & Laakso, M. (2003) The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes*, **52**, 558–561.
6 Rotter, V., Nagaev, I. & Smith, U. (2003) Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *Journal of Biological Chemistry*, **278**, 45 777–45 784.
7 Fried, S.K., Lavau, M. & Pi-Sunyer, F.X. (1982) Variations of glucose metabolism by fat cells from three adipose depots of the rat. *Metabolism*, **31**, 876–883.
8 Plomgaard, P., Bouzakri, K., Krogh-Madsen, R., Mittendorfer, B., Zierath, J.R. & Pedersen, B.K. (2005) Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes*, **54**, 2939–2945.
9 Misra, A. & Vikram, N.K. (2004) Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition*, **20**, 482–491.
10 Yajnik, C.S. (2004) Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *Journal of Nutrition*, **134**, 205–210.
11 Popkin, B.M., Horton, S., Kim, S., Mahal, A. & Shuigao, J. (2001) Trends in diet, nutritional status, and diet-related noncommunicable diseases in China and India: the economic costs of the nutrition transition. *Nutrition Reviews*, **59**, 379–390.
12 Simmons, D., Gatland, B., Fleming, C., Leakehe, L. & Scragg, R. (1994) Prevalence of known diabetes in a multiethnic community. *New Zealand Medical Journal*, **107**, 219–222.
13 Chambers, J.C., Eda, S., Bassett, P., Karim, Y., Thompson, S.G., Gallimore, J.R., Pepys, M.B. & Kooner, J.S. (2001) C-reactive protein,

insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation*, **104**, 145–150.

14 Forouhi, N.G., Sattar, N. & McKeigue, P.M. (2001) Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *International Journal of Obesity and Related Metabolic Disorders*, **25**, 1327–1331.

15 Chandalia, M., Cabo-Chan, A.V. Jr, Devaraj, S., Jialal, I., Grundy, S.M. & Abate, N. (2003) Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. *Journal of Clinical Endocrinology and Metabolism*, **88**, 3773–3776.

16 Yudkin, J.S., Yajnik, C.S., Mohamed-Ali, V. & Bulmer, K. (1999) High levels of circulating proinflammatory cytokines and leptin in urban, but not rural, Indians. A potential explanation for increased risk of diabetes and coronary heart disease. *Diabetes Care*, **22**, 363–364.

17 Ley, C.J., Lees, B. & Stevenson, J.C. (1992) Sex- and menopause-associated changes in body-fat distribution. *American Journal of Clinical Nutrition*, **55**, 950–954.

18 Heymsfield, S.B., Smith, R., Aulet, M., Bensen, B., Lichtman, S., Wang, J. & Pierson, R.N. Jr (1990) Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *American Journal of Clinical Nutrition*, **52**, 214–218.

19 Hermans, M., Levy, J., Morris, R. & Turner, R. (1999) Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. *Diabetologia*, **42**, 678–687.

20 Heliovaara, M.K., Teppo, A.M., Karonen, S.L., Tuominen, J.A. & Ebeling, P. (2005) Plasma IL-6 concentration is inversely related to insulin sensitivity, and acute-phase proteins associate with glucose and lipid metabolism in healthy subjects. *Diabetes, Obesity and Metabolism*, **7**, 729–736.

21 Fernandez-Real, J.M., Vayreda, M., Richart, C., Gutierrez, C., Broch, M., Vendrell, J. & Ricart, W. (2001) Circulating interleukin-6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. *Journal of Clinical Endocrinology and Metabolism*, **86**, 1154–1159.

22 Zamboni, M., Armellini, F., Milani, M.P., De Marchi, M., Todesco, T., Robbi, R., Bergamo-Andreis, I.A. & Bosello, O. (1992) Body fat distribution in pre- and post-menopausal women: metabolic and anthropometric variables and their inter-relationships. *International Journal of Obesity*, **16**, 495–504.

23 Toth, M.J., Sites, C.K., Cefalu, W.T., Matthews, D.E. & Poehlman, E.T. (2001) Determinants of insulin-stimulated glucose disposal in middle-aged, premenopausal women. *American Journal of Physiology. Endocrinology and Metabolism*, **281**, E113–E121.

24 Owen, O.E., Holup, J.L., D'Alessio, D.A., Craig, E.S., Polansky, M., Smalley, K.J., Kavle, E.C., Bushman, M.C., Owen, L.R., Mozzoli, M.A., Kendrick, Z.V. & Boden, G.H. (1987) A reappraisal of the caloric requirements of men. *American Journal of Clinical Nutrition*, **46**, 875–885.

25 Owen, O.E., Kavle, E., Owen, R.S., Polansky, M., Caprio, S., Mozzoli, M.A., Kendrick, Z.V., Bushman, M.C. & Boden, G. (1986) A reappraisal of caloric requirements in healthy women. *American Journal of Clinical Nutrition*, **44**, 1–19.

26 Zhang, J., Liu, Y., Shi, J., Larson, D.F. & Watson, R.R. (2002) Side-stream cigarette smoke induces dose–response in systemic inflammatory cytokine production and oxidative stress. *Experimental Biology and Medicine (Maywood)*, **227**, 823–829.

27 Collins, L.C., Cornelius, M.F., Vogel, R.L., Walker, J.F. & Stamford, B.A. (1994) Effect of caffeine and/or cigarette smoking on resting energy expenditure. *International Journal of Obesity and Related Metabolic Disorders*, **18**, 551–556.

28 Lyngso, D., Simonsen, L. & Bulow, J. (2002) Metabolic effects of interleukin-6 in human splanchnic and adipose tissue. *Journal of Physiology*, **543**, 379–386.

29 Gunnell, D., Whitley, E., Upton, M.N., McConnachie, A., Smith, G.D. & Watt, G.C. (2003) Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. *Journal of Epidemiology and Human Health*, **57**, 141–146.

30 Stephens, J.W., Hurel, S.J., Cooper, J.A., Acharya, J., Miller, G.J. & Humphries, S.E. (2004) A common functional variant in the interleukin-6 gene is associated with increased body mass index in subjects with type 2 diabetes mellitus. *Molecular Genetics and Metabolism*, **82**, 180–186.

31 Kershaw, E.E. & Flier, J.S. (2004) Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology and Metabolism*, **89**, 2548–2556.

