

Ethnicity, Insulin Resistance, and Inflammatory Adipokines in Women at High and Low Risk for Vascular Disease

JOSEF V. SILHA, MD, PHD¹
B.L. GRÉGOIRE NYOMBA, MD, PHD, FACE^{1,2}

WILLIAM D. LESLIE, MD, FRCPC, MSC^{1,3}
LIAM J. MURPHY, MB, FRACP, FRCPC^{1,2}

OBJECTIVE — We sought to compare the relationship between body composition, insulin resistance, and inflammatory adipokines in Aboriginal Canadian women, who are at high risk of vascular disease, with white women.

RESEARCH DESIGN AND METHODS — A subgroup of the First Nations Bone Health Study population, consisting of 131 Aboriginal women and 132 matched white women, was utilized. Body composition was determined by whole-body dual X-ray absorptiometry, and blood analytes were measured after an overnight fast.

RESULTS — After excluding individuals with diabetes, A1C, BMI, percent trunk fat, and homeostasis model assessment of insulin resistance (HOMA-IR) were greater in First Nation women compared with white women, whereas adiponectin, retinol binding protein (RBP)4, and insulin-like growth factor binding protein-1 (IGFBP-1) were lower. First Nation women had more trunk fat for any given level of total fat than white women. There were no differences in resistin, leptin, tumor necrosis factor (TNF)- α , or C-reactive protein (CRP) levels between First Nation and white women. Insulin resistance correlated with leptin and inversely with adiponectin levels in both First Nation and white women. There were weak correlations between insulin resistance and TNF- α , interleukin-6, and CRP, but these were not significant after correction for body fat. No correlation was found between RBP4 and insulin resistance. ANCOVA revealed a higher HOMA-IR adjusted for total body fat in First Nation women than in white women ($P = 0.015$) but not HOMA-IR adjusted for trunk fat ($P > 0.2$).

CONCLUSIONS — First Nation women are more insulin resistant than white women, and this is explained by trunk fat but not total fat. Despite the increased insulin resistance, inflammatory adipokines are not significantly increased in First Nation women compared with white women.

Diabetes Care 30:286–291, 2007

An increased prevalence of vascular disease in insulin-resistant states such as pre-diabetes, type 2 diabetes, and the metabolic syndrome has been long recognized (1). There is considerable debate whether insulin resistance is the primary event in atherosclerosis, with consequent activation of proinflammatory signaling pathways, or, alternatively,

whether low-grade inflammation and subsequent insulin resistance accounts for the association of diabetes and vascular disease (2).

Aboriginal Canadian populations, which include First Nation, Metis, and Inuit individuals (3), have an increased prevalence of atherosclerosis and cardiovascular and peripheral vascular disease

(4,5). First Nations are Aboriginal individuals signatory to treaties and/or recognized by the Canadian Federal Government as a fiduciary responsibility and represent the large majority of Aboriginal individuals living in Canada (3). While type 2 diabetes is more prevalent among Canadian men than women in the general population, the reverse is true for the First Nation population (6,7). In the First Nation population, obesity is more prevalent among men than women, but the prevalence of metabolic syndrome and type 2 diabetes appears to be greater for women than men, suggesting that First Nation women may be more insulin resistant than their male counterparts (6,8). Studies in Canadian Aboriginal populations have found elevated adipocytokines such as tumor necrosis factor (TNF)- α , C-reactive protein (CRP), and leptin (9,10), whereas adiponectin levels were found to be reduced (11). In some of these studies, percent body fat determined by electric impedance was reported to be elevated. However, there have been no reports of a systematic comparison of body composition and insulin resistance in women from ethnic groups at high risk of vascular disease with the general female population.

In this study, we have compared body composition, insulin resistance, and adipokines in a large cohort of First Nation women with an age-matched cohort of white women from the general Canadian population.

RESEARCH DESIGN AND METHODS

The study population was based on the urban participants from a population-based, cross-sectional survey of osteoporosis: the First Nations Bone Health Study. The design and recruitment of this study is described in detail elsewhere (12). All subjects completed an entrance questionnaire that included information about health status and medications. We excluded individuals with either a history of diabetes or a fasting plasma glucose level >6.9 mmol/l. In addition, we excluded individuals with an elevated A1C ($>6.0\%$) to minimize the number of subjects with normal fasting plasma glucose (but impaired glucose tol-

From the ¹Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; the ²Department of Physiology, University of Manitoba, Winnipeg, Manitoba, Canada; and the ³Department of Radiology, University of Manitoba, Winnipeg, Manitoba, Canada.

Address correspondence and reprint requests to Liam J. Murphy, University of Manitoba, 715 McDermott Ave., Room 843, Winnipeg, R3E 3P4 Canada. E-mail: ljmurph@cc.umanitoba.ca.

Received for publication 24 May 2006 and accepted in revised form 20 October 2006.

Abbreviations: CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IGFBP-1, insulin-like growth factor binding protein-1; IL, interleukin; RBP, retinol binding protein; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1073

© 2007 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Comparison of demographic, anthropomorphic, and biochemical parameters

	White women	First Nation women	P value
n	132	131	
Age (years)	45.6 ± 14.1	41.1 ± 10.2	
Pre-/transitional/postmenopausal	67/36/29	77/44/10	0.005
Weight (kg)	73.9 ± 16.3	77.8 ± 16.4	0.040
BMI (kg/m ²)	27.52 ± 6.29	29.20 ± 5.87	0.011
Total fat (kg)	26.78 ± 10.63	29.37 ± 9.74	0.022
Total lean mass (kg)	42.59 ± 6.33	43.72 ± 7.05	
Trunk fat (kg)	12.90 ± 5.99	15.63 ± 5.96	<0.001
Trunk fat (%)	16.69 ± 4.68	19.53 ± 4.13	<0.001
Plasma glucose (mmol/l)	5.03 ± 0.41	5.16 ± 0.53	
A1C (%)	5.50 ± 0.29	5.58 ± 0.29	0.013
Insulin (pmol/l)	49.65 (31.66)	59.0 (48.2)	0.002
HOMA-IR	1.54 (1.07)	1.93 (1.66)	0.002
Resistin (ng/ml)	16.74 ± 6.36	16.81 ± 6.03	
Adiponectin (μg/ml)	17.67 ± 9.26	14.95 ± 8.37	0.012
Leptin (ng/ml)	33.93 ± 25.90	33.77 ± 24.21	
TNF-α (pg/ml)	5.45 ± 1.25	5.60 ± 1.33	
IL-6 (ng/ml)	1.18 (1.08)	1.51 (1.43)	<0.001
CRP (μg/ml)	2.05 (3.09)	2.37 (3.49)	
RBP4 (ng/ml)	47.59 (20.88)	44.24 (15.31)	0.008
IGFBP-1 (ng/ml)	12.45 (19.55)	11.92 (10.33)	0.002

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

erance) or undiagnosed type 2 diabetes. After these exclusions, data from a total of 132 white and 131 First Nation women were available for analysis. All participants provided written informed consent. The study was approved by the University of Manitoba's Research Ethics Board.

Assays and measurements

Dual-energy X-ray absorptiometry measurements. Body composition (lean, fat, and bone mass) was derived from whole-body dual-energy X-ray absorptiometry (Hologic QDR-4500; Hologic, Waltham, MA). A single trained operator was used to perform all dual-energy X-ray absorptiometry scans. Fat mass and lean tissue mass parameters were analyzed using the manufacturer's software. Trunk fat, defined as the absolute amount of fat in the trunk region, including thorax, abdomen, and pelvis, was calculated.

Glucose and insulin assays and homeostasis model assessment of insulin resistance calculations. Blood samples were obtained after an overnight fast, separated, and stored in aliquots at -70°C until analysis. Blood glucose was measured with a glucose oxidase method (Yellow Springs). Insulin was measured using a two-site chemiluminescent immunometric assay (Immulin insulin; Diagnos-

tic Products Corporation), which has 8.5% cross-reactivity with proinsulin. All samples were assayed in a single run with reagent pooled from several kits. Insulin resistance was calculated using homeostasis model assessment of insulin resistance (HOMA-IR) (13). Insulin-like growth factor binding protein-1 (IGFBP-1) was measured with reagents from Diagnostic Systems Laboratories (Webster, TX).

Adipokines and inflammatory markers. Total adiponectin was measured by radioimmunoassay using reagents from Linco Research (St. Charles, MO), whereas resistin and leptin were measured by enzyme-linked immunoassay kits obtained from Biovendor Laboratory Medicine (Brno, Czech Republic). The specificity, sensitivity, and coefficient of variation of these assays in our laboratory have been previously reported (14). TNF-α and interleukin (IL)-6 were measured by a Quantikine HS assay from R&D Systems (Minneapolis, MN). The sensitivity of the assay was 0.12 and 0.039 pg/ml, and the within-assay coefficients of variation were 5 and 7%, respectively. Serum retinol binding protein (RBP)4 was measured with an enzyme-linked immunosorbent assay kit from Alpco Diagnostics (Windham, NH). The sensitivity and interassay coefficients of variation were

100 pg/ml and 5%, respectively. C-reactive protein (CRP) was measured with a high-sensitivity assay kit from BioQuatt (San Diego CA). The sensitivity and coefficients of variation of the assay were 100 ng/ml and 4%, respectively.

Statistical analysis

Normally distributed data are expressed as means ± SD. Measurements that were non-normally distributed (such as HOMA-IR) are reported as median (quartile range). Group differences in continuous measurements were identified with the Wilcoxon's rank-sum test. χ^2 analysis was used to compare the frequency of various conditions in the two populations. The relationship between two variables was assessed with Spearman's rank correlation coefficient. Partial correlations were computed on ranks after controlling for ethnicity, trunk fat, and total fat (15). ANCOVA was used to compare covariate relationships between the two populations (regression line intercepts and parallelism). Non-normally distributed variables were log transformed to obtain normal distributions before ANCOVA. Statistical analysis was performed using SPSS 11.0 for Windows software.

RESULTS

Differences in demographic, anthropomorphic, and biochemical parameters

Weight, BMI, total fat, trunk fat, A1C, fasting insulin, IL-6, and HOMA-IR were significantly greater in First Nation women compared with white women, while adiponectin, RBP4, and IGFBP-1 were significantly lower in First Nation women (Table 1). However, there were no significant differences in resistin, leptin, TNF-α, or CRP levels. There were significantly fewer postmenopausal First Nation women, and, as a group, the First Nation women were slightly younger than the white population, suggesting that age itself was not a major cause of the increased insulin resistance apparent in the First Nation women.

First Nation women had a larger percentage of their total fat as trunk fat than nondiabetic white women (52.5 ± 5.9 vs. $46.9 \pm 5.7\%$, $P < 0.001$). In both groups, there was a significant relationship between trunk fat and total fat. First Nation women had a significantly greater increment in trunk fat for each additional kilogram of total fat (ANCOVA $P = 0.028$ for comparison of regression slopes) and sig-

Table 2—Spearman correlation coefficients between HOMA-IR and other parameters in non-diabetic populations

	White women	First Nation women	All women
BMI	0.569*	0.660*	0.634*
IGFBP-1	-0.585*†	-0.554*†	-0.592*†
Total fat	0.576*	0.623*†	0.607*†
Trunk fat	0.603*	0.697*	0.668*
Resistin	0.008	0.180‡	0.097
Adiponectin	-0.415*†	-0.451*†	-0.451*†
Leptin	0.525*	0.672*†	0.595*†
TNF- α	0.042	0.186‡	0.107
IL-6	0.272§	0.373*	0.347*
CRP	0.250§	0.390*	0.324*
RBP4	0.088	0.005	0.008

* $P < 0.005$, † $P < 0.05$, § $P < 0.01$. †Significant after controlling for trunk fat.

nificantly greater trunk fat computed at the covariate means ($P < 0.001$ for comparison of regression least-squares means).

Determinants of insulin resistance

HOMA-IR was strongly correlated with BMI, total body fat, and trunk fat in both groups and when the population was considered as a whole (Table 2). The strongest correlation was observed with trunk fat. ANCOVA regression analysis for HOMA-IR and trunk fat for the two populations showed no significant ethnicity effect. While regression analysis for HOMA-IR and total fat indicated that there was no difference in the regression slopes, the intercept was significantly higher in First Nation compared with white women ($P > 0.2$ for comparison of regression slopes; $P = 0.015$ for comparison of intercepts). That is, for any given amount of total fat, First Nations had a higher HOMA-IR than white women (Fig. 1). When total fat was replaced by trunk fat in the ANCOVA model, no ethnicity difference was seen ($P = 0.19$ for comparison of regression slopes; $P > 0.2$ for comparison of intercepts).

A significant inverse correlation was observed between IGFBP-1 and HOMA-IR and between adiponectin and HOMA-IR, while leptin showed a strong positive correlation in all groups. Interestingly, even after correction for trunk fat, the relationships between HOMA-IR and both adiponectin and leptin remained significant (in all comparisons except for HOMA-IR versus leptin in the white women). Resistin, TNF- α , and CRP showed a weak, but significant, positive correlation with HOMA-IR, but none of these correlations remained significant af-

ter correction for trunk fat. RBP4 did not correlate with HOMA-IR in either group or the entire study population.

The contribution of adipose tissue to adipokine levels

The correlations between fat mass and adipokines are shown in Table 3. RBP4 levels did not correlate with either total or trunk fat in either group, and there were only weak correlations for TNF- α in First Nation women. Leptin strongly corre-

lated with total body and trunk fat, and in each group, the correlation was slightly greater with total than trunk fat. Similarly, adiponectin levels were inversely correlated with fat mass in all groups, and, in contrast with leptin, the correlation was stronger for trunk than total fat. Resistin correlated with total and trunk fat only in the First Nation women, while IL-6 levels correlated with total and trunk fat in both groups. CRP correlated with both total and trunk fat in both control and First Nation women. All of these correlations remained significant after controlling for HOMA-IR.

CONCLUSIONS— Several epidemiological studies (4–8,16) have reported a higher prevalence of diabetes, insulin resistance, and cardiovascular disease in various ethnic groups including Native Americans and Canadians. Some studies (9,10) have reported increased levels of inflammatory markers and their association with insulin resistance or percent body fat in Aboriginal versus white populations. However, there are no reports that specifically address markers of insulin resistance and inflammatory markers in Aboriginal women compared with white women.

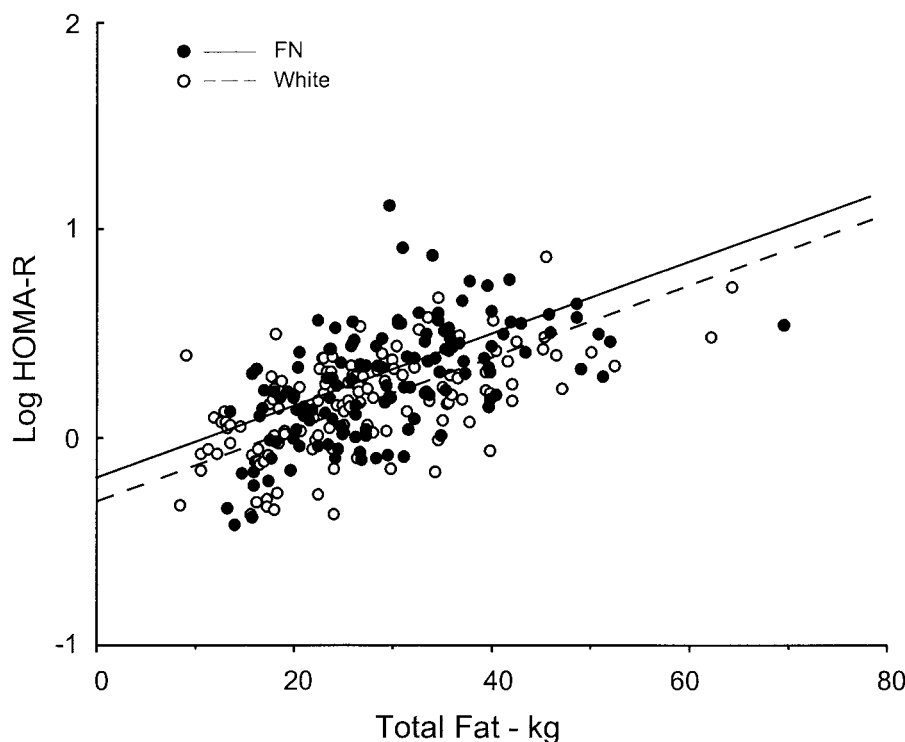


Figure 1— The relationship between insulin resistance and total fat in First Nation (FN) and white women. ANCOVA was used to examine differences in the slope and intercept of the lines of best fit. The slopes did not differ significantly, whereas the intercepts were significantly different. The predicted regression lines based on the ANCOVA model are shown.

Table 3—Spearman correlation coefficients between adipose tissue and adipokine levels in nondiabetic populations with and without correction for insulin resistance

	White women		First Nation women		All women	
	Total fat	Trunk fat	Total fat	Trunk fat	Total fat	Trunk fat
Resistin	0.162	0.146	0.203*†	0.192†‡	0.203*†	0.192†‡
Adiponectin	−0.366*†	−0.406*†	−0.423*†	−0.483*†	−0.423*†	−0.483*†
Leptin	0.781*†	0.743*†	0.782*†	0.748*†	0.782*†	0.748*†
TNF- α	0.128	0.124	0.139§	0.137§	0.139§	0.137§
IL-6	0.528*†	0.574*†	0.513*†	0.566*†	0.513*†	0.566*†
CRP	0.514*†	0.533*†	0.543*†	0.548*†	0.543*†	0.548*†
RBP4	0.088	0.112	0.022	0.013	0.022	0.013

* $P < 0.005$, † $P < 0.01$, § $P < 0.05$. †Significant after controlling for HOMA-IR.

First Nation women had significantly greater total fat mass than white women and a greater proportion of their adipose mass as trunk fat. Differences in trunk fat explained the difference in insulin resistance observed between First Nation and white women. While there was no significant difference in the slope of the relationship between log HOMA-IR and total body fat in the two groups of women, First Nation women had a significantly higher intercept, indicating that at any given level of total body fat, First Nation women were more significantly insulin resistant than white women.

Consistent with increased insulin resistance, First Nation women had lower adiponectin and IGFBP-1 but greater IL-6 levels than white women. However, the majority of inflammatory markers such as resistin, TNF- α , or CRP were not significantly increased in First Nation women and would not explain the difference in insulin sensitivity between the two study groups.

Although we recognize that dysglycemia and type 2 diabetes represent a continuum and that excluding subjects with type 2 diabetes might have biased our results against finding differences between the First Nation and control women, we chose to concentrate our analysis of insulin resistance on subjects who did not have self-reported diabetes or biochemical evidence of type 2 diabetes because the validity of the HOMA-IR determinations in type 2 diabetes patients is questionable (17,18).

In both First Nation and white women, as in other reports (19,20), leptin levels directly correlated with insulin resistance and body fat. However, despite significantly greater amounts of body fat in First Nation compared with white women, leptin levels were not significantly increased. This may reflect the rel-

atively lower expression of leptin in visceral fat compared with subcutaneous fat (21) and the tendency for First Nation women to have a significantly larger proportion of their fat as trunk fat.

In this study, as previously observed (14), the adipokine that correlated best with insulin resistance was leptin. The magnitude of the correlation coefficient for HOMA-IR and leptin was comparable with HOMA-IR and IGFBP-1, a sensitive marker of insulin resistance (22), and was significantly higher than that observed for the relationship between HOMA-IR and adiponectin. While there was no difference between resistin levels in First Nation and white women, resistin levels did significantly correlate with both total fat and trunk fat in First Nation women but not in white women consistent with previous reports (14,23). In First Nation women alone, there was a weak positive correlation between HOMA-IR and resistin levels. This correlation was not seen in the white women and was lost when data were controlled for trunk fat, suggesting that this association was due to the correlation of both HOMA-IR and resistin levels with trunk fat in First Nation women. In contrast to the rodent, where resistin appears to be important in modulating hepatic insulin sensitivity (24,25), the contribution of resistin to insulin resistance in human subjects appears to be relatively minor. While a few studies have reported a weak positive association between insulin resistance and resistin levels (14,26,27), the majority of studies have not (23,28–33). Resistin levels in human subjects are thought to correlate more closely with inflammation than with insulin resistance (28,30,34).

RBP4 has recently been proposed to be an adipocytokine (35,36) and was elevated in insulin-resistant mice (36). These authors also found that plasma RBP4 lev-

els determined by Western blot were elevated in a small sample of obese diabetic and nondiabetic subjects compared with lean subjects, but there was no difference between obese nondiabetic and obese diabetic subjects despite the latter being more insulin resistant (36). Other studies found RBP4 levels to correlate with poor metabolic control in both type 2 (37) and type 1 diabetic patients (38). These observations suggest that elevated RBP4 concentrations result from hyperglycemia, rather than insulin resistance, which is consistent with the lack of correlation between RBP4 levels and either fat mass or HOMA-IR in the present study.

TNF- α levels have been reported to be significantly elevated in insulin-resistant type 2 diabetic subjects (39,40). Although First Nation and control women had similar levels of TNF- α , a weak correlation was found between TNF- α and HOMA-IR but only in the First Nation individuals.

First Nation women had elevated IL-6 levels, but they did not have significantly higher CRP or TNF- α levels. This contrasts with previous reports where CRP levels have been found to be elevated in diabetic and insulin-resistant individuals (9,10,39,41). However, in the Diabetes Heart Study, there was no difference in CRP levels between type 2 diabetic subjects and their unaffected siblings (42), although a significant relationship was found between BMI and CRP in the same study as in the data reported here. Although First Nation women had elevated IL-6 levels, the correlation of IL-6 with HOMA-IR became insignificant after correction for trunk fat. This is consistent with the concept that truncal obesity precedes inflammation in the development of insulin resistance (43).

Significant limitations to this study include the cross-sectional design and

lack of prospectively defined clinical end points such as the development of diabetes. Although the sample sizes were adequate for the analyses undertaken, a much larger population would be required to assess cardiovascular events. Our finding may not be applicable to men since they were not the target of the First Nations Bone Health Study. We used an indirect measure of insulin resistance, HOMA-IR, since it is well suited to epidemiological studies and shows a satisfactory correlation with other quantitative measures such as the euglycemic-hyperinsulinemic glucose clamp (17). Correlations were adjusted for trunk fat and total fat, but no adjustment was made for other potentially important covariates such as physical activity. Although we excluded women with known or biochemical evidence of type 2 diabetes, this is unlikely to have excluded all women who were destined to develop diabetes in the future, particularly since women with impaired fasting glucose were included in the study.

In summary, our observations in First Nation women, a population that is at high risk for vascular disease, suggest that these women are more insulin resistant due in part to their tendency to accumulate adipose tissue in the truncal region. However, despite the increase in insulin resistance, we observed no significant increase in inflammatory cytokines, with the exception of IL-6. Although limited by cross-sectional nature, these data suggest that inflammation is unlikely to be the primary cause of the insulin resistance, as has been suggested by some investigators (44,45).

Acknowledgments— This research was supported by funds from the Health Science Centre Foundation, Canadian Institutes for Health Research, and the Manitoba Health Research Council. L.J.M is a recipient of the Henry G. Friesen Chair in Endocrine and Metabolic Research.

We thank the rest of the First Nations Bone Health Study Research Group: Dr. C.R. Greenberg, Dr. L. Lix, Dr. C.J. Metge, Dr. J.D. O'Neil, Dr. A. Tenenhouse, Dr. H.A. Weiler, Dr. M. Doupe, Dr. J. Krahn, Dr. L. Roos, Dr. E.A. Salamon, A. Walker Young, and P. Wood Steiman. The authors are indebted to Health Information Management of Manitoba Health and to the First Nations and Inuit Health Branch and Indian and Northern Affairs Canada for permission to use the Status Verification System, as well as to the Health Information Research Committee of the As-

sembly for Manitoba Chiefs for actively supporting this work.

References

1. Rosenberg DE, Jabbour SA, Goldstein BJ: Insulin resistance, diabetes and cardiovascular risk: approaches to treatment. *Diabetes Obes Metab* 7:642–653, 2005
2. Bloomgarden ZT: Inflammation, atherosclerosis, and aspects of insulin action. *Diabetes Care* 28:2312–2319, 2005
3. Young TK: Review of research on aboriginal populations in Canada: relevance to their health needs. *BMJ* 327:419–422, 2003
4. Anand SS, Yusuf S, Jacobs R, Davis AD, Yi Q, Gerstein H, Montague PA, Lonn E: Risk factors, atherosclerosis, and cardiovascular disease among Aboriginal people in Canada: the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP). *Lancet* 358:1147–1153, 2001
5. Goulet S, Trepman E, Mmath MC, Koulack J, Fong H, Duerksen F, Martin B, Simonsen JN, Nicolle L, Embil J: Revascularization for peripheral vascular disease in Aboriginal and non-Aboriginal patients. *J Vasc Surg* 43:735–741, 2006
6. Kelly C, Booth GL: Diabetes in Canadian women. *BMC Womens Health* (Suppl. 1): S16, 2004
7. Green C, Blanchard JF, Young TK, Griffith J: The epidemiology of diabetes in the Manitoba-registered First Nation population: current patterns and comparative trends. *Diabetes Care* 26:1993–1998, 2003
8. Pollex RL, Hanley AJ, Zinman B, Harris SB, Khan HM, Hegele RA: Metabolic syndrome in aboriginal Canadians: prevalence and genetic associations. *Atherosclerosis* 184:121–129, 2006
9. Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, Lonn E, Teo K, McQueen M, Yusuf S: C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol* 24:1509–1515, 2004
10. Liu J, Young TK, Zinman B, Harris SB, Connelly PW, Hanley AJ: Lifestyle variables, non-traditional cardiovascular risk factors, and the metabolic syndrome in an Aboriginal Canadian population. *Obesity (Silver Spring)* 14:500–508, 2006
11. Hanley AJ, Connelly PW, Harris SB, Zinman B: Adiponectin in a native Canadian population experiencing rapid epidemiological transition. *Diabetes Care* 26:3219–3225, 2003
12. Leslie WD, Metge CJ, Weiler HA, Doupe M, Wood SP, O'Neil JD: Bone density and bone area in Canadian Aboriginal women: the First Nations Bone Health Study. *Osteoporos Int* 17:1755–1762, 2006
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Ho-

- meostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
14. Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL, Murphy LJ: Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *Eur J Endocrinol* 149:331–335, 2003
15. Conover WJ, Iman RL: Analysis of covariance using the rank transformation. *Biometrics* 38:715–724, 1982
16. Butler J, Rodondi N, Zhu Y, Figaro K, Fazio S, Vaughan DE, Satterfield S, Newman AB, Goodpaster B, Bauer DC, Holvoet P, Harris TB, de RN, Rubin S, Ding J, Kritchevsky SB: Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol* 47:1595–1602, 2006
17. Rabasa-Lhoret R, Bastard JP, Jan V, Ducruzeau PH, Andreelli F, Guebre F, Bruzeau J, Louche-Pellissier C, Maltrepierre C, Peyrat J, Chagne J, Vidal H, Laville M: Modified quantitative insulin sensitivity check index is better correlated to hyperinsulinemic glucose clamp than other fasting-based index of insulin sensitivity in different insulin-resistant states. *J Clin Endocrinol Metab* 88:4917–4923, 2003
18. Katsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Morioka K, Kitagawa N, Tanaka T, Raki-Sasaki R, Hori Y, Nakatani K, Yano Y, Adachi Y: Neither homeostasis model assessment nor quantitative insulin sensitivity check index can predict insulin resistance in elderly patients with poorly controlled type 2 diabetes mellitus. *J Clin Endocrinol Metab* 87: 5332–5335, 2002
19. Hanley AJ, Harris SB, Gao XJ, Kwan J, Zinman B: Serum immunoreactive leptin concentrations in a Canadian aboriginal population with high rates of NIDDM. *Diabetes Care* 20:1408–1415, 1997
20. Smith J, Al-Amri M, Sniderman A, Cianflone K: Leptin and adiponectin in relation to body fat percentage, waist to hip ratio and the apoB/apoA1 ratio in Asian Indian and Caucasian men and women. *Nutr Metab (Lond)* 3:18, 2006
21. Montague CT, Prins JB, Sanders L, Zhang J, Sewter CP, Digby J, Byrne CD, O'Rahilly S: Depot-related gene expression in human subcutaneous and omental adipocytes. *Diabetes* 47:1384–1391, 1998
22. Mohamed-Ali V, Pinkney JH, Panahloo A, Cwyfan-Hughes S, Holly JM, Yudkin JS: Insulin-like growth factor binding protein-1 in NIDDM: relationship with the insulin resistance syndrome. *Clin Endocrinol (Oxf)* 50:221–228, 1999
23. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, Xiao Q, Mistry JS, Retzlaff BM, Knopp RH, Kahn SE: Resistin is not associated with insulin

- sensitivity or the metabolic syndrome in humans. *Diabetologia* 48:2330–2333, 2005
24. Patel SD, Rajala MW, Rossetti L, Scherer PE, Shapiro L: Disulfide-dependent multimeric assembly of resistin family hormones. *Science* 304:1154–1158, 2004
 25. Satoh H, Nguyen MT, Trujillo M, Imamura T, Usui I, Scherer PE, Olefsky JM: Adenovirus-mediated adiponectin expression augments skeletal muscle insulin sensitivity in male Wistar rats. *Diabetes* 54:1304–1313, 2005
 26. Koebnick C, Wagner K, Garcia AL, Gruendel S, Lahmann PH, Weickert MO, Mohlig M, Harsch IA, Einig C, Speth M, Katz N, Trippo U, Zunft HJ: Increase in serum resistin during weight loss in overweight subjects is related to lipid metabolism. *Int J Obes (Lond)* 30:1097–1103, 2006
 27. Burnett MS, Devaney JM, Adenika RJ, Lindsay R, Howard BV: Cross-sectional associations of resistin, coronary heart disease, and insulin resistance. *J Clin Endocrinol Metab* 91:64–68, 2006
 28. Bahr MJ, Ockenga J, Boker KH, Manns MP, Tietge UJ: Elevated resistin levels in cirrhosis are associated with the proinflammatory state and altered hepatic glucose metabolism but not with insulin resistance. *Am J Physiol Endocrinol Metab* 291:E199–E206, 2006
 29. Axelsson J, Bergsten A, Qureshi AR, Heimbürger O, Barany P, Lonnqvist F, Lindholm B, Nordfors L, Alvestrand A, Stenvinkel P: Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int* 69:596–604, 2006
 30. Pagano C, Soardo G, Pilon C, Milocco C, Basan L, Milan G, Donnini D, Faggian D, Mussap M, Plebani M, Avellini C, Feder-spil G, Sechi LA, Vettor R: Increased serum resistin in nonalcoholic fatty liver disease is related to liver disease severity and not to insulin resistance. *J Clin Endocrinol Metab* 91:1081–1086, 2006
 31. Chu MC, Cosper P, Orio F, Carmina E, Lobo RA: Insulin resistance in postmenopausal women with metabolic syndrome and the measurements of adiponectin, leptin, resistin, and ghrelin. *Am J Obstet Gynecol* 194:100–104, 2006
 32. Reinehr T, Roth CL, Menke T, Andler W: Resistin concentrations before and after weight loss in obese children. *Int J Obes (Lond)* 30:297–301, 2006
 33. Heilbronn LK, Rood J, Janderova L, Albu JB, Kelley DE, Ravussin E, Smith SR: Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *J Clin Endocrinol Metab* 89:1844–1848, 2004
 34. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ: Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 111:932–939, 2005
 35. Tamori Y, Sakaue H, Kasuga M: RBP4, an unexpected adipokine. *Nat Med* 12:30–31, 2006
 36. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB: Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 436:356–362, 2005
 37. Basualdo CG, Wein EE, Basu TK: Vitamin A (retinol) status of first nation adults with non-insulin-dependent diabetes mellitus. *J Am Coll Nutr* 16:39–45, 1997
 38. Baena RM, Campoy C, Bayes R, Blanca E, Fernandez JM, Molina-Font JA: Vitamin A, retinol binding protein and lipids in type 1 diabetes mellitus. *Eur J Clin Nutr* 56:44–50, 2002
 39. Natali A, Toschi E, Baldeweg S, Ciociaro D, Favilla S, Sacca L, Ferrannini E: Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. *Diabetes* 55:1133–1140, 2006
 40. Miyazaki Y, Pipek R, Mandarino LJ, DeFronzo RA: Tumor necrosis factor alpha and insulin resistance in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord* 27:88–94, 2003
 41. Di Benedetto A, Russo GT, Corrado F, Di Cesare E, Alessi E, Nicocia G, D'Anna R, Cucinotta D: Inflammatory markers in women with a recent history of gestational diabetes mellitus. *J Endocrinol Invest* 28:34–38, 2005
 42. Bowden DW, Lange LA, Langefeld CD, Brosnihan KB, Freedman BI, Carr JJ, Wagenknecht LE, Herrington DM: The relationship between C-reactive protein and subclinical cardiovascular disease in the Diabetes Heart Study (DHS). *Am Heart J* 150:1032–1038, 2005
 43. Esposito K, Pontillo A, Di PC, Giugliano G, Masella M, Marfella R, Giugliano D: Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 289:1799–1804, 2003
 44. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B: Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 17:4–12, 2006
 45. Houstis N, Rosen ED, Lander ES: Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* 440:944–948, 2006