Phenotypic Characteristics Associated With Insulin Resistance in Metabolically Obese but Normal-Weight Young Women

Roman V. Dvorak, Walter F. DeNino, Philip A. Ades, and Eric T. Poehlman

Metabolically obese, normal-weight (MONW) individuals are a hypothesized subgroup of the general population. These normal-weight individuals potentially display a cluster of obesity-related features, although this has not been systematically tested in young women. We hypothesized that MONW young women would display higher levels of total and visceral fat and lower levels of physical activity than normal women. In a cohort of 71 healthy nonobese women (21–35 years old), we identified MONW women based on cut points for insulin sensitivity (normal = glucose disposal >8 mg · min^{-1} · kg^{-1} of fat-free mass [FFM], n = 58; impaired = glucose disposal <8 ml · min^{-1} · kg^{-1} of FFM, n = 13). Thereafter, we measured body composition (dual energy X-ray absorptiometry) and body fat distribution (computed tomography), cardiorespiratory fitness (Vo_{2max} on a treadmill), physical activity energy expenditure (doubly labeled water and indirect calorimetry), glucose tolerance (oral glucose tolerance test), serum lipid profile, and dietary intake. We found a higher body fat percentage (32 ± 6 vs. 27 ± 6%, P = 0.01) and higher subcutaneous (213 ± 61 vs. 160 ± 78 cm^2, P = 0.03) and visceral (44 ± 16 vs. 35 ± 14 cm^2, P < 0.05) abdominal adiposity in the MONW group versus the normal group. The MONW group showed a lower physical activity energy expenditure (2.66 ± 0.92 vs. 4.39 ± 1.50 MJ/day, P = 0.01), but no difference in cardiorespiratory fitness was noted between groups. In conclusion, despite a normal body weight, a subset of young, apparently healthy women displayed a cluster of risky phenotypic characteristics that, if left untreated, may eventually predispose them to type 2 diabetes and cardiovascular disease. *Diabetes* 48:2210–2214, 1999

The existence of a subgroup of individuals who have normal body weight but display a cluster of obesity-related phenotypic characteristics was first proposed in the 1980s (1). Since this discussion, an accumulating body of evidence suggests a high prevalence of these individuals in the general population (2,3). These metabolically obese, normal-weight (MONW) individuals display early signs of insulin resistance, hyperinsulinemia, and dyslipidemia, despite having a normal weight based on traditional criteria (e.g., BMI, height/weight tables, etc.) (2). The presence of these metabolic and cardiovascular disease (CVD) risk factors may go undetected for years because young age, sex, and normal body weight mask the need for early detection and treatment. To our knowledge, however, the existence and prevalence of this syndrome in young women has not been systematically investigated. Moreover, the phenotypic characteristics that may be associated with the MONW syndrome in young women are unknown.

To this end, we identified MONW individuals (characterized by impaired insulin sensitivity) in a representative cohort of young nonobese women. Second, we compared the phenotypic characteristics implicated in the pathogenesis of insulin resistance between MONW and normal women. We hypothesized that MONW women would display higher levels of total and visceral adiposity and lower levels of cardiorespiratory fitness and physical activity than women with normal insulin sensitivity.

RESEARCH DESIGN AND METHODS

Patients. There were 71 young normal-weight women (67 of Caucasian, 2 of Asian, and 2 of Hispanic origin) who participated in the study. The inclusion criteria for participation were *1*) age 18–35 years, *2*) BMI ≤26, *3*) weight stable (±2 kg) over 6 months preceding the study, and *4*) no regular participation in exercise for 6 months before the study. Exclusion criteria for participation were *1*) smoking, *2*) acute illness, *3*) receiving any medication affecting energy expenditure (e.g., β-blockers), and *4*) alcohol consumption >15 g of alcohol/day. The presence or absence of a family history of diabetes was obtained during the physical examination. Because participants in our study were young women (<35 years old), parental age may have limited the detection of type 2 diabetes. Thus, we also considered the presence of type 2 diabetes among grandparents and the siblings of parents as indicators of a positive family history. The use of oral contraceptives was also obtained from the medical history. This study was approved by the Committee for Human Research at the University of Vermont and each participant gave written informed consent before the beginning of the study.

Overview of protocol. Each participant was first invited to a screening visit during which an oral glucose tolerance test (OGTT), medical history, physical examination, maximum oxygen consumption test, and complete blood chemistry and profile were performed. Two weeks later, participants were invited for an overnight visit to the General Clinical Research Center (GCRC) at the University of Vermont. For 3 days before the overnight visit, participants were provided with standardized diets prepared by the metabolic kitchen at the GCRC, containing 55% carbohydrates, 25% fat, and 20% protein. During the afternoon of admission, we administered doubly labeled water and conducted body composition and body fat distribution measurements. The following morning, the hyperinsulinemic-euglycemic clamp was performed. Subjects returned to the GCRC 10 days later to provide the final two urine samples to conclude the doubly labeled water measurement.

From the Divisions of Clinical Pharmacology and Metabolic Research (R.V.D., W.F.D., E.T.P.) and Cardiology (P.A.A.), Department of Medicine, College of Medicine, University of Vermont, Burlington, Vermont.

Address correspondence and reprint requests to Dr. Eric T. Poehlman, Clinical Pharmacology and Metabolic Research Unit, Given C-247, University of Vermont, Burlington, VT 05405. E-mail: epoehlma@zoo.uvm.edu.

Received for publication 22 April 1999 and accepted in revised form 23 September 1999.

CVD, cardiovascular disease; FFM, fat-free mass; GCRC, General Clinical Research Center; MONW, metabolically obese, normal-weight; OGTT, oral glucose tolerance test; PAEE, physical activity energy expenditure; RMR, resting metabolic rate; TEE, total daily energy expenditure.

Measurements

Glucose tolerance. An OGTT was performed in the morning after an overnight fast. A Teflon catheter was placed into an antecubital vein, and baseline samples for the measurement of insulinemia and glycemia were drawn. Thereafter, a standard glucose load (1.33 g/kg of body mass) was given orally (Ensure Plus; Ross Laboratories, Columbus, OH). Samples for repeated measurement of glycemia and insulinemia were then taken 120 min after baseline.

Body composition. We measured body composition by dual energy X-ray absorptiometry (Lunar DPX-L, Madison, WI), as previously described (4). The subjects were instructed to lay supine on a padded table with all metal objects removed. A total body scan takes ~30 min. This method uses a three-compartment model of body composition and provides an estimate of fat mass, fat-free mass (FFM), and bone mineral density. We analyzed all scans by the Lunar DPX-L extended analysis software, version 1.3. The test-retest reproducibility for body fat is 1.7% (six females) in our laboratory.

Body fat distribution. We measured body fat distribution by computed tomography (CT) using a General Electric High Speed Advantage CT Scanner (GE Medical Systems, Milwaukee, WI), as previously suggested by Sjostrom et al. (5) and reported by our laboratory (6). Visceral and subcutaneous abdominal fat accumulation was assessed at the level of L_4-L_5 intervertebral space. Scan position for the abdominal level was established using a scout view, positioning the scanner within the desired intervertebral space. The scans were 5 mm in thickness and performed at 120 kV and 220 mA. Visceral and subcutaneous adiposity was quantified by delineating the visceral cavity using the trace function and excluding the retroperitoneal area. The boundary was established at the innermost aspects of the abdominal and oblique muscle walls. Subcutaneous adipose tissue was selected as the area remaining between the visceral boundary and the skin. Retroperitoneal fat was excluded from both the subcutaneous and visceral adipose tissue areas. Adipose tissue was selected by the software at an attenuation range of –190 to –30 Hounsfield units. The visceral cavity was assessed using the "mask" function and then the subcutaneous area using the "contour" feature. The same individual analyzed all scans, and the interclass correlation for repeated analysis of 10 scans was 0.99 in 10 women.

Cardiorespiratory fitness. Maximum aerobic capacity (Vo_{2max}) was determined from an incremental exercise test on a treadmill to exhaustion, as previously described (7). After an initial 3-min warm-up, the speed was set so that the heart rate would not exceed 70% of the age-predicted maximum heart rate [220 – age (years)]. Thereafter, the speed was held constant, and the grade was increased by 2.5% every 2 min. The criteria for achieving a Vo_{2max} were *1*) a respiratory exchange ratio >1.0, *2*) a heart rate at or above the age-predicted maximum, and *3*) no further increase in oxygen consumption with an increasing workload. At least two of these criteria were reached by all volunteers. Test-retest conditions for nine individuals (on two occasions tested 1 week apart) yielded an intraclass correlation of 0.94 and a coefficient of variation of 3.8% in our laboratory.

Physical activity energy expenditure. We used doubly labeled water in combination with indirect calorimetry to measure free-living physical activity energy expenditure (PAEE). Total daily energy expenditure (TEE) was determined over a 10-day period. Each subject was dosed with a 1 g/kg body mass of $^2H_2{}^{18}O$ using the method of Schoeller and van Santen (8), as previously described (9). Briefly, a baseline urine sample was collected before dosing. The following morning, two additional urine samples were collected, and two more samples were collected 10 days later. Urine samples were stored frozen in vacutainers at –20°C until analyzed for ^2H and ^{18}O enrichments by isotope ratio mass spectrometry. ^{18}O isotopic enrichment was determined from the carbon dioxide (CO_2) equilibration technique, and ^2H enrichment was determined by the zinc catalyst method (10). Daily rate of CO_2 production (mol/day) was calculated using the equation of Speakman et al. (11): $rCO_2 = N/2.196 \times ({}^cO{}^kO - {}^cH{}^kH)$, where N is the total body water pool, ^kO and ^kH are the elimination rates of ^{18}O and ^2H tracers from the body, and ^cO and ^cH are the dilution spaces for ^{18}O and ^2H tracers, as recommended by Racette et al. (12). Assuming a respiratory quotient of 0.85 for the food consumed (13), total CO_2 production was converted to TEE (kJ/day) using the formula by Weir (14).

Resting metabolic rate (RMR) was determined from 45 min of indirect calorimetry using the ventilated hood technique, as previously described (15). Respiratory gas analysis was performed using a Deltatrac metabolic cart (Sensormedics, Yorba Linda, CA). RMR (kJ/day) was calculated from the equation by Weir (14). Assuming a thermic effect of feeding of 10% (16), total PAEE was then calculated from the equation: PAEE = [(TEE × 0.90) – RMR]. That is, PAEE represents the energy expenditure accumulated above basal levels, which include volitional and nonvolitional activities. We have previously reported an intraclass correlation of 0.90 and a coefficient of variation of 4.3% for the measurement of RMR in 17 older volunteers from two different occasions tested 1 week apart.

Insulin sensitivity. We measured insulin sensitivity by the hyperinsulinemic-euglycemic clamp technique, as proposed by DeFronzo et al. (17). Briefly, a Teflon catheter was inserted into the antecubital vein for the infusions of insulin and dextrose. Another Teflon catheter was retrogradely placed into the dorsal vein of the contralateral hand and used for the blood draws during the clamp procedure. This hand was placed in a "hot box" and warmed to 70°C for arterialization of blood. At time 0 min, a continuous infusion of insulin was started at a constant rate of 240 pmol · m^{-2} · min^{-1}. At the same time, a variable infusion of 20% dextrose was started to maintain fasting glycemia ±5%. Blood samples for glucose measurement were taken every 5 minutes for insulin measurements at –30, –10, 0, 30, 60, 70, 90, 105, and 120 min of the clamp. The insulin levels attained during the last 30 min of the clamp (minute 90–120) were 75 ± 23 μU/ml (mean ± SD). Insulin-stimulated glucose disposal rate (*M* value) was calculated as the average glucose infusion rate (mg/min) during the last 30 min of the 120-min clamp, adjusted for the total distribution volume of glucose (250 ml/kg). Hepatic glucose production has previously been shown to be fully suppressed, with the insulin dose used in our study to induce hyperinsulinemia (18).

Dietary intake. Dietary intake was measured for 3 days (one weekend and two weekdays), as previously described (19). Participants were instructed by a registered dietitian and encouraged to maintain their usual diet. Moreover, they were provided with dietary scales and measuring cups and spoons to further increase precision of obtained data. Diets were analyzed using the Nutritionist III software version 4.0 (N-Squared Computing, Salem, OR).

Blood pressure. Blood pressure was determined during the screening visit at the GCRC using a Dinamap automatic cuff machine (Critikon, Tampa, FL), as previously described (20). Subjects rested in the sitting position for 10 min and then the measurement was taken from their right arm. Appropriate cuff size was selected based on arm circumference.

Biochemical analyses. Plasma glucose concentrations were measured using the glucose oxidase method with an automated glucose analyzer (YSI Instruments, Yellow Springs, OH). Serum insulin was measured by a double antibody radioimmunoassay (Diagnostics Products, Los Angeles, CA). Plasma cholesterol, triglyceride, and HDL cholesterol concentrations were determined from standard enzymatic techniques at the Centers for Disease Control accredited laboratory of the Fletcher Allen Medical Center. Interassay coefficient of variation for the measurement of total and HDL cholesterol was 3.35 and 1.15%, respectively. LDL cholesterol was determined from the equation by Friedewald et al. (21).

Statistical analysis. To identify women classified as having impaired insulin sensitivity, we used a glucose disposal cut-point value of 8.0 mg · min^{-1} · kg^{-1} of FFM, based on previous data (22). Women with a glucose disposal rate greater than the cut-point value were classified as having normal insulin sensitivity and those women with values below the cut point as having impaired insulin sensitivity. The rationale for using glucose disposal as the criterion method to categorize individuals as normal or MONW is based on the notion that resistance to insulin-stimulated glucose uptake is suggested as a common pathogenic mechanism for type 2 diabetes, hypertension, and, ultimately, CVD (23,24). Differences in dependent variables between the groups (MONW vs. normal) were examined using an independent *t* test. Differences between groups in cardiorespiratory fitness were examined using analysis of covariance, with body weight as a covariate (7). Given the unequal sample size between groups, we examined the equality of variances in each variable using Levene's test. When the variances were unequal (HDL cholesterol and glucose disposal adjusted per kilogram of FFM), a *P* value based on Satterthwaite's (25) approximation for the degrees of freedom was used. A χ^2 test was used to compare the differences between the groups for the family history of diabetes and use of oral contraceptives. All values are reported as means ± SD. Significance was accepted at $P < 0.05$. Data were analyzed using the SPSS statistical software (Version 7.5.1, SPSS, Chicago).

RESULTS

Table 1 shows glucose disposal values and anthropometric variables for the normal and MONW groups. By design, the MONW women showed a lower absolute and adjusted (per kilogram of FFM) insulin-stimulated glucose disposal rate. The groups were similar with respect to age, BMI, body mass, FFM, and appendicular fat mass. Women classified as MONW, however, showed a greater total fat mass ($P < 0.05$), body fat percentage ($P = 0.01$), truncal fat ($P = 0.02$), and subcutaneous ($P < 0.05$) and visceral ($P < 0.05$) abdominal adiposity than women with normal insulin sensitivity.

We found no differences between groups in cardiorespiratory fitness on an absolute or adjusted basis (Table 2). On the other hand, we found a lower PAEE in the MONW women compared with normal women ($P < 0.001$, Table 2). No differences between groups were found for systolic or diastolic

TABLE 1
Comparison of glucose disposal and anthropometric variables between women with impaired (MONW) and normal insulin sensitivity

Variable value	MONW	Normal	*P*
n	13	58	—
Age (years)	29 ± 3	28 ± 4	0.97
Glucose disposal (mg/min)	250 ± 65	444 ± 112	0.001
Glucose disposal (mg · FFM^{-1} · min^{-1})	6.5 ± 1.7	11.0 ± 2.2	0.001
BMI (kg/m^2)	22.5 ± 2.0	21.5 ± 2.0	0.08
Body mass (kg)	60.1 ± 8.9	58.4 ± 6.9	0.42
FFM (kg)	38.9 ± 5.1	40.3 ± 4.0	0.28
Fat mass (kg)	18.4 ± 5.2	15.3 ± 4.4	0.03
Body fat (%)	31.8 ± 5.9	27.4 ± 5.5	0.01
Appendicular fat (kg)	8.9 ± 2.6	8.0 ± 2.3	0.23
Truncal fat (kg)	8.2 ± 2.6	6.5 ± 2.4	0.02
L_4-L_5 subcutaneous fat area (cm^2)	213 ± 61	160 ± 78	0.03
L_4-L_5 visceral fat area (cm^2)	44 ± 16	35 ± 14	0.046

Data are means ± SD. To identify women classified as having impaired insulin sensitivity, we used a glucose disposal cut-point value of 8.0 mg · min^{-1} · kg^{-1} of FFM, based on the data presented by Beck-Nielsen and Groop (22).

blood pressure, family history of diabetes, or the use of oral contraceptives (Table 2). Furthermore, we found no differences in total energy intake (8.28 vs. 8.32 MJ/day); percent intake of carbohydrate (53 vs. 56%), fat (33 vs. 30%), and protein (13 vs. 14%); and percent fat intake from saturated fat (36 vs. 34%) between the MONW and normal group, respectively.

In Table 3, we present the results of the OGTT and serum lipid profile. The MONW group showed a higher fasting (P = 0.03) and 2-h postload insulin ($P < 0.001$), 2-h postload glucose ($P < 0.01$), and total serum cholesterol ($P < 0.01$) than the normal group. We found no differences between groups in fasting serum glucose, HDL cholesterol, total–to–HDL cholesterol ratio, LDL cholesterol, or fasting triglycerides.

DISCUSSION

To our knowledge, this is the first study to comprehensively examine the phenotypic characteristics associated with the MONW syndrome in young women. Based on our approach, we found that 18% of our population was classified as having impaired insulin sensitivity, despite having normal body weight and BMI. Furthermore, young MONW women with impaired insulin sensitivity showed a cluster of risky phenotypic characteristics, including low PAEE and increased total and visceral adiposity.

The incidence of obesity and type 2 diabetes is increasing among women (26), which places them at high risk for the development of insulin resistance and associated comorbidities (27). Given that the deleterious consequences of compensatory hyperinsulinemia (i.e., microangiopathy, hypertension, and CVD) are present at the time of diagnosis of overt type 2 diabetes (28), a clear medical need exists to identify markers for early detection of these individuals before the onset of an established disease process.

We classified individuals above and below a glucose disposal cut point of 8 ml · min^{-1} · kg^{-1} of FFM. The use of glucose disposal to subdivide young women into normal and MONW groups is based on the notion that a decrease in insulin sensitivity may be a common pathogenic mechanism in the development of type 2 diabetes, hypertension, and CVD (23,24). Although this cut point may be considered somewhat arbitrary, women who were classified as having impaired insulin sensitivity (based on hyperinsulinemic-euglycemic clamp) also displayed an altered response to oral glucose load (Table 2). Furthermore, the chosen cut point was based on previous multicenter data (22) that examined insulin sensitivity data from a large sample of individuals. We were somewhat surprised that 18% (n = 13) was categorized as having impaired insulin sensitivity. This finding supports the hypothesis by Ruderman et al. (2) regarding the relatively high prevalence of individuals with impaired insulin sensitivity in apparently healthy normal-weight individuals. This finding prompted us to examine several obesity-related phenotypic characteristics that have been implicated in the development of impaired insulin sensitivity.

In the present study, we found that women with impaired insulin sensitivity were characterized by a higher body fat percentage and fat mass than women with normal insulin sensitivity, despite no difference in body mass or BMI between groups. This suggests that even small increases in body fatness (2–3 kg) within a normal range of BMI negatively affect insulin sensitivity. Indeed, in our cohort, the incidence of impaired insulin sensitivity reached almost 40% among women with a body fat percentage >30%. Therefore,

TABLE 2
Comparison of cardiorespiratory fitness, PAEE, blood pressure, oral contraceptives, and incidence of family history of diabetes between women with impaired (MONW) and normal insulin sensitivity

Variable	MONW	Normal	*P* value
n	13	58	—
$V_{O_{2max}}$ (ml/min)	2,228 ± 509	2,297 ± 426	0.61
Adjusted $V_{O_{2max}}$ (ml/min)*	2,197 ± 396	2,304 ± 395	0.38
PAEE (MJ/day) (*n*)	2.66 ± 0.92 (9)	4.39 ± 1.50 (41)	0.01
Systolic blood pressure (mmHg)	118 ± 12	118 ± 14	0.99
Diastolic blood pressure (mmHg)	69 ± 8	68 ± 10	0.73
Family history of diabetes (%) (yes/no)	31 (4/9)	32 (14/44)	0.53
Use of oral contraceptives (%) (yes/no)	60 (8/5)	47 (27/31)	0.33

Data are means ± SD or %. *Adjusted for kilogram of body weight, as previously described (7).

TABLE 3
Comparison of OGTT and blood lipid values between women with impaired (MONW) and normal insulin sensitivity

Variable	MONW	Normal	*P* value
n	13	58	—
Fasting glucose (mmol/l)	4.4 ± 0.4	4.4 ± 0.3	0.80
2-h postload glucose (mmol/l)	5.7 ± 1.1	4.6 ± 1.1	0.003
Fasting insulin (pmol/l)	60 ± 20	49 ± 15	0.03
2-h postload insulin (pmol/l)	481 ± 259	281 ± 186	0.001
Total cholesterol (mmol/l)	5.3 ± 0.9	4.5 ± 0.7	0.003
HDL cholesterol (mmol/l)	1.7 ± 0.5	1.5 ± 0.3	0.15
Total–to–HDL cholesterol	3.3 ± 0.9	3.3 ± 0.8	0.91
LDL cholesterol (mmol/l)	3.1 ± 0.9	2.7 ± 0.8	0.14
Triglycerides (mmol/l)	2.4 ± 0.7	2.4 ± 1.0	0.93

Data are means ± SD.

we suggest that young women with a BMI <26 but with a body fat percentage >30% are probably at a higher risk for impaired insulin sensitivity and a potentially early onset of type 2 diabetes, hypertension, and CVD. Our findings thus support the notion that BMI is a poor marker to identify women at risk for the development of insulin resistance and associated comorbidities.

The question as to whether body fat topography is "pathogenic" with respect to insulin sensitivity and type 2 diabetes is controversial (29). For example, some investigators found that abdominal subcutaneous adiposity is a stronger predictor of insulin sensitivity than visceral adiposity in middle-aged men and women (30) and in pre-menopausal women (31). On the other hand, others (32,33) reported that visceral adiposity is the stronger determinant of insulin sensitivity in obese women. In the present investigation, young women with impaired insulin sensitivity showed significantly higher subcutaneous as well as visceral abdominal fat accumulation than women with normal insulin sensitivity. Despite the fact that the levels of visceral fat accumulation in the MONW group were well below the suggested critical threshold of 130 cm^2 (34), it is possible that even relatively low levels of visceral adiposity in the presence of higher levels of total body fatness have a deleterious impact on insulin sensitivity. Nonetheless, our findings suggest that in young nonobese women, both subcutaneous and visceral abdominal fat accumulation may be associated with impaired insulin sensitivity.

Physical inactivity (35) and low cardiorespiratory fitness (36) have been implicated as important risk factors in the pathogenesis of type 2 diabetes. We found no differences in cardiorespiratory fitness between groups. This may be because only sedentary women were recruited for the study and thus limited our ability to find differences between the groups. On the other hand, we noted a significantly lower PAEE in the MONW group. To our knowledge, this is the first study that used a direct measurement of PAEE by the doubly labeled water methodology in the examination of risk factors for insulin resistance and CVD in free-living individuals. Previous investigations have reported an inverse relationship between physical activity and incidence of type 2 diabetes (37); however, physical activity levels were only estimated from a self-reported questionnaire, which has been shown to be inaccurate (38). These results suggest that PAEE, and not cardiorespiratory fitness, may be a more important predictor of impaired insulin sensitivity. We would suggest that PAEE probably influences insulin sensitivity and other CVD risk factors primarily through its effects on energy balance and body composition (39). That is, lower levels of PAEE found in the MONW group may favor a positive energy balance, especially because total daily energy intake was similar between the groups. Thus, low levels of PAEE may favor a greater increase in total and central adiposity in susceptible individuals (40).

Despite differences in other phenotypic characteristics between the MONW and normal groups, no differences were found in the total–to–HDL cholesterol ratio, fasting triglycerides, and LDL cholesterol. The cardioprotective effects of estrogen on plasma lipids has been well documented (41). Thus, it is possible that the presence of estrogen in these young women may exert a stronger influence on plasma lipids than differences in physical activity and adiposity.

Our results have clinical implications for the detection and treatment of susceptible individuals for type 2 diabetes and CVD. The phenotypic features associated with impaired insulin sensitivity (increased body adiposity and low levels of physical activity) are generally responsive to lifestyle modifications such as dietary restriction and aerobic exercise training (39,42). Therefore, identification and early treatment of these individuals, particularly at younger ages before metabolic diseases become overt and established, would have a substantial public health value. It needs to be emphasized, however, that our cross-sectional study cannot establish a causative relationship. Further studies using exercise, dietary, or pharmacological interventions are needed to evaluate whether the metabolic profile of MONW individuals can be normalized.

In conclusion, we found that despite a normal body weight, a subset of young, apparently healthy women displayed a cluster of risky phenotypic characteristics that may eventually predispose them to type 2 diabetes and CVD.

ACKNOWLEDGMENTS

This work was supported by the GCRC (RR-00109) from the University of Vermont; a fellowship from the American Heart Association, Maine/New Hampshire/Vermont Affiliate (to R.V.D.); grant no. R01-AG15114 (to P.A.A.); and a grant from the Department of Defense (DE 950226) (to E.T.P.).

We would like to extend our gratitude to all participants in this study. Furthermore, the expert technical help of the staff at the GCRC is greatly appreciated. We would also like to thank Denise DeFalco-McGeein, RNC, NP, for help with physical examinations of patients. Appreciation is also extended to Ethan A.H. Sims, MD, for thoughtful discussions on this topic.

REFERENCES

1. Ruderman NB, Schneider SH, Berchtold P: The "metabolically-obese," normal-weight individual. *Am J Clin Nutr* 34:1617–1621, 1981
2. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S: The metabolically obese, normal-weight individual revisited. *Diabetes* 47:699–713, 1998
3. Hollenbeck C, Reaven GM: Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *J Clin Endocrinol Metab* 64:1169–1173, 1987
4. Dvorak RV, Poehlman ET: Appendicular skeletal muscle mass, physical activity, and cognitive status in patients with Alzheimer's disease. *Neurology* 51:1386–1390, 1998
5. Sjostrom L, Kvist H, Cederblad A, Tylen U: Determination of total adipose tis-

sue and body fat in women by computed tomography, 40K, and tritium. *Am J Physiol* 250:E736–E745, 1986
6. Garcia-Rubi E, Starling RD, Tchernof A, Matthews DE, Walston JD, Shuldiner AR, Silver K, Poehlman ET, Calles-Escandon J: $Trp^{64}Arg$ variant of the β_3-adrenoceptor and insulin resistance in obese postmenopausal women. *J Clin Endocrinol Metab* 83:4002–4006, 1999
7. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET: Examination of data normalization procedures for expressing peak VO_2 data. *J Appl Physiol* 93:2288–2292, 1993
8. Schoeller DA, van Santen E: Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol* 53:955–959, 1982
9. Poehlman ET, Toth MJ, Goran MI, Carpenter WH, Newhouse P, Rosen CJ: Daily energy expenditure in free-living non-institutionalized Alzheimer's patients: a doubly labeled water study. *Neurology* 48:997–1002, 1997
10. Wong WW, Lee LS, Klein PD: Deuterium and oxygen-18 measurement on microliter samples of urine, plasma, saliva, and human milk. *Am J Clin Nutr* 45:905–913, 1987
11. Speakman JR, Nair KS, Goran MI: Revised equation for calculating CO_2 production from doubly labeled water in humans. *Am J Physiol* 264:E912–E917, 1993
12. Racette SB, Schoeller DA, Luke AH, Shay K, Hnilicka J, Kushner RF: Relative dilution spaces of ^2H to O_{18} labeled water in humans. *Am J Physiol* 267:E585–E590, 1994
13. Black AE, Prentice AM, Coward WA: Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. *Hum Nutr Clin Nutr* 40:381–391, 1986
14. Weir JB: New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol Lond* 109:1–9, 1949
15. Donaldson KE, Carpenter WH, Toth MJ, Goran MI, Newhouse P, Poehlman ET: No evidence for a higher resting metabolic rate in noninstitutionalized Alzheimer's disease patients. *J Am Ger Soc* 44:1232–1234, 1996
16. Poehlman ET, Melby CL, Badylak SF: Relation of age and physical exercise status on metabolic rate in younger and older healthy men. *J Geront* 46:B54–B58, 1991
17. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E233, 1979
18. DeFronzo RA: Glucose intolerance and aging: evidence for tissue insensitivity to insulin. *Diabetes* 28:1095–1101, 1979
19. Poehlman ET, Viers HF, Detzer M: Influence of physical activity and dietary restraint on resting energy expenditure in young nonobese females. *Can J Physiol Pharmacol* 69:320–326, 1991
20. Webb GD, Toth MJ, Poehlman ET: Influence of physiological factors on the age-related increase in blood pressure in healthy men. *Exp Gerontol* 31:341–350, 1996
21. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
22. Beck-Nielsen H, Groop LC: Metabolic and genetic characterization of prediabetic states: sequence of events leading to non-insulin-dependent diabetes mellitus. *J Clin Invest* 94:1714–1721, 1994
23. Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno, Bonati PA, Bergonzani M, Gnudi L, Passeri M: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 320:702–706, 1989
24. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334:374–381, 1996
25. Satterthwaite FW: An approximate distribution of estimates of variance components. *Biometrics Bulletin* 2:110–114, 1946
26. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 272:205–211, 1994
27. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 22:S5–S19, 1999
28. Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E, Pyorala K: 5-year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin-dependent diabetic and nondiabetic subjects. *Circulation* 82:27–36, 1990
29. Seidell JC, Bouchard C: Visceral fat in relation to health: is it a major culprit of simply an innocent bystander? *Int J Obes* 21:626–631, 1997
30. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE: Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46:1579–1585, 1997
31. Bonora E, Del Prato S, Bonadonna RC, Gulli G, Solini A, Shank ML, Ghiatas AA, Lancaster JL, Kilcoyne RF, Alyassin AM: Total body fat content and fat topography are associated differently with in vivo glucose metabolism in nonobese and obese nondiabetic women. *Diabetes* 41:1151–1159, 1992
32. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ: Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 45:633–638, 1996
33. Ross R, Fortier L, Hudson R: Separate associations between visceral and subcutaneous adipose tissue distribution, insulin and glucose levels in obese women. *Diabetes Care* 96:1404–1411, 1996
34. Despres JP, Lamarche B: Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. *Nutr Res Rev* 6:137–159, 1993
35. American Diabetes Association: Screening for type 2 diabetes (Position Statement). *Diabetes Care* 22 (Suppl. 1):S20–S23, 1999
36. Nyholm B, Mengel A, Nielsen S, Skjaerbaek C, Moller N, Alberti KG, Schmitz O: Insulin resistance in relatives of NIDDM patients: the role of physical fitness and muscle metabolism. *Diabetologia* 39:813–822, 1996
37. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
38. Starling RD, Matthews DE, Ades PA, Poehlman ET: Assessment of physical activity in older individuals: a doubly labeled water study. *J Appl Physiol* 86:2090–2096, 1999
39. Katzel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, Goldberg AP: Effects of weight loss vs aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men: a randomized controlled trial. *JAMA* 274:1915–1921, 1995
40. Poehlman ET, Toth MJ, Bunyard LB, Gardner AW, Donaldson KE, Colman E, Fonong T, Ades PA: Physiological predictors of increasing total and central adiposity in aging men and women. *Arch Intern Med* 155:2443–2448, 1995
41. Mendelsohn ME, Karas RH: The protective effect of estrogen on the cardiovascular system. *N Engl J Med* 340:1801–1811, 1999
42. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EA: Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes* 33:311–318, 1984