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Serum Insulin and Inflammatory Markers in Overweight Individuals with and without Dyslipidemia

Philip Barter, Y. Ruth McPherson, Kijoung Song, Y. Antero Kesäniemi, Robert Mahley, Gérard Waeber, Thomas Bersot, Vincent Mooser, Dawn Waterworth, and Scott M. Grundy

The Heart Research Institute (P.B.), Sydney, New South Wales 2050, Australia; University of Ottawa Heart Institute (Y.R.M.), Ottawa, Ontario, Canada K1Y 4W7; Genetics Research (K.S., V.M., D.W.), GlaxoSmithKline, Collegeville, Pennsylvania 19406; Department of Internal Medicine and Biocenter Oulu (Y.A.K.), University of Oulu, FIN-90014 Oulu, Finland; Gladstone Institute of Cardiovascular Disease (R.M., T.B.), University of California, San Francisco, San Francisco, California 94158; Department of Medicine (G.W.), Lausanne University Hospital, 1011 Lausanne, Switzerland; and Center for Human Nutrition (S.M.G.), University of Texas Southwestern Medical Center, Dallas, Texas 75235

Context: The worldwide epidemic of overweight and obesity is setting the scene for a new wave of premature cardiovascular disease.

Objective: The objective of this study was to define relationships between dyslipidemia and other metabolic abnormalities in overweight subjects.

Design: This study included comparison of overweight subjects with and without dyslipidemia.

Setting: The setting was an institutional practice.

Patients: Dyslipidemic subjects (n = 715) had plasma triglyceride greater than or equal to the 75th percentile in combination with high-density lipoprotein cholesterol (HDL-C) less than or equal to the 25th percentile. Unrelated, normolipidemic controls (n = 1073) had HDL-C higher than the median and triglyceride lower than the median. It was a requirement for the control subjects to have a body mass index (BMI) greater than 25 kg/m^2.

Main Outcome Measures: The main outcome measures included BMI, inflammatory markers, adipokines, blood pressure, and fasting plasma glucose and insulin.

Results: The mean BMI in the subjects and controls was 28.7 and 28.2 kg/m^2, respectively. Subjects had higher levels of plasma high-sensitivity C-reactive protein (3.0 *vs.* 2.0 mg/liter; $P < 0.001$), lower levels of adiponectin (4.7 *vs.* 6.6 mg/liter; $P < 0.001$), and, after adjustment for age, BMI, gender, smoking, statin, and β-blocker use, higher systolic ($P = 0.001$) and diastolic ($P = 0.05$) blood pressures. Fasting plasma glucose, insulin, and homeostasis model of assessment-insulin resistance were all significantly higher in subjects than controls ($P < 0.0001$).

Conclusions: Identification of people solely on the basis of an elevated plasma triglyceride and a low HDL-C uncovers an overweight group of people who have a generalized metabolic disorder. In contrast, overweight people with normal plasma lipids have normal glucose and insulin metabolism, low levels of inflammatory markers, and normal blood pressure. Such people may thus be at relatively low risk of developing diabetes and cardiovascular disease despite being overweight. **(*J Clin Endocrinol Metab* 92: 2041–2045, 2007)**

OVERWEIGHT AND OBESITY are increasing worldwide at an alarming rate and are setting the scene for a major epidemic of premature cardiovascular disease (CVD) (1–3). In large part, the increased CVD risk associated with being overweight or obese is secondary to a host of concomitant metabolic abnormalities (4). Being overweight increases the likelihood of developing type 2 diabetes (5–7) and CVD (8–10), although these relationships are complex with some apparent inconsistencies. For example, people with manifest CVD appear to have a reduced risk of dying if they have a moderately increased body mass index (BMI) (11). This suggests that being overweight *per se* is not the problem. Rather, it may be the metabolic abnormalities that often coexist with overweight and obesity. Overweight people without overt diabetes frequently have a cluster of abnormalities that include impaired fasting glucose, hyperinsulinemia, elevated blood pressure, a dyslipidemia characterized by a low level of high-density lipoprotein cholesterol (HDL-C) and high plasma triglyceride, and an increased level of inflammatory markers in their blood (12). A commonly used term for the clustering of abnormalities associated with being overweight is the metabolic syndrome (13, 14).

The Genetic Epidemiology of the Metabolic Syndrome (GEMS) study is a large multinational, family-based study designed to explore the genetic basis of the metabolic syndrome (15, 16). A simple lipid-based criterion was used to identify subjects who were required to have the combination of an elevated plasma triglyceride (upper 25th percentile) and a low HDL-C (lower 25th percentile). A previous analysis of the GEMS data indicated that people with this form of dyslipidemia had more hypertension, more obesity, and more hyperglycemia than was observed in unaffected controls (15). Overall, 86% of affected individuals in the GEMS study had a BMI greater than 25 kg/m^2, with 76% meeting the criteria for the metabolic syndrome as defined by the U.S. National Cholesterol Education Program. The question arises: do overweight people (BMI > 25 kg/m^2) whose plasma lipids are normal differ from their dyslipidemic counterparts

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; GEMS, Genetic Epidemiology of the Metabolic Syndrome; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

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in terms of the presence of the other components of the metabolic syndrome?

To address this question, the GEMS study also recruited control subjects who were required to have a BMI greater than 25 kg/m^2 but whose HDL-C was higher and plasma triglyceride was lower than median values adjusted for age, gender, and country. This design provided two distinct groups of overweight people: one group included people with low HDL-C and high triglyceride (dyslipidemic group), whereas the other included people with a higher than average HDL-C and a lower than average plasma triglyceride (normolipidemic group).

Subjects and Methods

Experimental subjects

Subjects were recruited from two centers in Europe (Oulu, Finland and Lausanne, Switzerland), one center in the United States (Dallas, TX), one center in Canada (Ottawa, Ontario), one in Turkey (Istanbul), and one in Australia (Adelaide, South Australia). Having found that the Turkish subjects differed genetically from the subjects from other countries, they were excluded from this analysis. This decision was made *a priori*. It should be noted that exclusion of Turkish subjects from the analysis had little impact on the results and did not in any way change the conclusions that have been drawn. Detailed information regarding the GEMS study design, sampling frame, and recruitment procedures has been reported previously (15, 16). Participants (ages 18–70 yr) were considered affected if they simultaneously had plasma triglyceride levels greater than or equal to the 75th percentile adjusted for age and gender and HDL-C levels less than or equal to the 25th percentile adjusted for age and gender. These lipid values were either current measurements (80%) or from medical history within the 3 yr before entry into the study (20%). All measurements were conducted in laboratories that used standardized methods. Because of variation in plasma lipid levels among different countries, cut points for triglyceride and HDL-C were defined by national databases for each study site as described previously (15). Affected subjects were excluded from analysis if they had a fasting blood glucose level greater than 6.9 mmol/liter, a BMI greater than or equal to 35 kg/m^2, were HIV positive, were a recipient of an organ transplant, were affected by familial hypercholesterolemia, or if they were heavy alcohol users (more than 8 U of alcohol per day). A total of 715 subjects met these criteria and were included as affected subjects in the analyses reported in this paper.

An additional 1073 unrelated, unaffected controls were recruited from the same centers. To qualify as a control, subjects had a plasma triglyceride in the lower 50th percentile and an HDL-C in the upper 50th percentile. It was also a requirement for the control subjects to have a BMI greater than 25 kg/m^2 to match the BMI of the affected subjects. Exclusion criteria for the controls were the same as those applied to the affected subjects.

The institutional review board at each participating site approved the protocol and the informed consent forms.

Materials and methods

A standardized questionnaire was administered to all participants. In addition to demographic data, it captured information on comorbid conditions and the use of medications, tobacco, and alcohol. Height, weight, waist circumference, and hip circumference, as well as three blood pressure measurements, were obtained for each participant. The average of the second and third systolic and diastolic blood pressure readings was used in the analyses.

Plasma and serum samples were collected after a 12-h fasting period. All assays were conducted by Pathway Diagnostics (Los Angeles, CA): plasma lipids and glucose were measured as described previously (15); adiponectin was measured using an ELISA (R & D Systems, Minneapolis, MN); high-sensitivity C-reactive protein (hs-CRP) and insulin were measured using chemiluminescent assays (Diagnostic Products, Los Angeles, CA); low-density lipoprotein (LDL) size was measured using a LipoPrint kit from Quantimetrix (Redondo Beach, CA); leptin was quantified using an ELISA (American Lab Products, Windham, NH); and apolipoprotein B was measured using an immunoturbidometric assay (Polymedco, Chicago, IL).

Several metabolic markers with skewed distributions were normalized before additional analysis using log transformation and cubic root transformation for adiponectin. Basic demographic variables were compared between subjects and controls using Pearson's χ^2 tests for categorical variables and general linear modeling for continuous variables. Variables were adjusted for age, gender, smoking, and statin and β-blocker usage, using a multivariate mixed model with age included as a nonparametric function (spline).

Results

Characteristics of the study population (Table 1)

The study included 715 (57% male) subjects and 1073 (54% male) unrelated controls. Subjects were younger than controls. Smoking was more prevalent in the subjects than controls, as was the consumption of β-blockers and statins. Subjects had a higher prevalence of coronary heart disease (CHD) in both men and women compared with controls, although there were a higher proportion of male subjects with CHD than female subjects.

TABLE 1. Characteristics of the study population

	Total group		Men		Women	
	Subjects	Controls	Subjects	Controls	Subjects	Controls
n	715	1073	410	580	305	493
Age (yr)	50.3 ± 8.6	55.1 ± 9.0[a,e]	49.9 ± 8.6	55.3 ± 9.1[a,e]	50.7 ± 8.7	54.7 ± 9.0[a,e]
Smoking	407 (59.9)	461 (44.8)[a,e]	252 (64.8)	298 (54.1)[a,d]	155 (53.5)	163 (34.0)[a,e]
β-Blocker[b]	151 (23.2)	43 (4.9)[a,e]	92 (23.8)	21 (4.3)[a,e]	59 (22.4)	22 (5.5)[a,e]
Diuretics	80 (12.8)	39 (4.5)[a,e]	32 (8.7)	12 (2.5)[a,e]	48 (18.5)	27 (6.9)[a,e]
Statin	300 (46.6)	16 (1.8)[a,e]	198 (50.6)	14 (2.9)[a,e]	102 (40.3)	2 (0.5)[a,e]
CHD	172 (24.1)	18 (1.7)[a,e]	122 (29.8)	12 (2.1)[a,e]	50 (16.5)	6 (1.2)[a,e]
Menopause					186 (61.2)	319 (64.8)[a,NS]
HRT					64 (25.4)	92 (21.9)[a,NS]
Oral contraceptive					15 (4.9)	5 (1.0)[a,c]

Data are presented as mean ± SD or number (percentage) for non-normally distributed variables. NS, No significance.
[a] *P* values of the difference between subjects and controls.
[b] Current and ex-smokers.
[c] $P < 0.05$.
[d] $P < 0.001$.
[e] $P < 0.0001$.

Adiposity, CRP, adiponectin, and leptin (Table 2)

The mean BMI in the subjects and controls was 28.7 and 28.2 kg/m^2, respectively. This small difference was statistically significant in the total group and in both men and women ($P < 0.001$). The waist circumference of the subjects was substantially and significantly greater in the subjects than in controls in the total population (97.7 *vs.* 94.6; $P < 0.0001$) and also in the male (100.9 *vs.* 99.2; $P < 0.001$) and female (93.4 *vs.* 89.3; $P < 0.0001$) participants (Table 2). The difference in waist circumference remained statistically significant ($P < 0.001$) when adjusted for BMI. There were no differences in the hip circumference between the subjects and controls (107.7 *vs.* 107.7; not significant), but the waist to hip ratio was significantly greater in the subjects than controls (0.91 *vs.* 0.088; $P < 0.0001$).

When considering the total population, plasma hs-CRP was significantly higher in subjects than controls (3.0 *vs.* 2.0 mg/liter; $P < 0.001$), whereas adiponectin was significantly lower in the subjects (4.7 *vs.* 6.6 mg/liter; $P < 0.0001$) (Table 2). These differences in both hs-CRP and adiponectin between subjects and controls were significant after adjustment for age, gender, smoking, BMI, and statin use. The unadjusted concentrations of leptin were similar between subjects and controls and were not significantly different when adjusted for age, BMI, gender, smoking, and statin usage.

The difference between hs-CRP levels in subjects and controls observed in the total population were highly significant in the female subgroup (4.4 *vs.* 2.5 mg/liter; $P < 0.0001$) but not in the males (2.4 *vs.* 2.1). Although adiponectin levels were somewhat higher in women than in men, they were significantly lower in both male and female subjects compared with their respective controls. Leptin levels were substantially higher in females than in males, but a significant difference between subjects and controls was found only in men.

Plasma lipids glucose and insulin (Table 3)

The plasma lipids in the subjects and controls differed in several respects, most of which were predictable. Apart from the prespecified differences in levels of HDL-C and plasma triglyceride, subjects had significantly higher levels of plasma total cholesterol ($P < 0.0001$), apolipoprotein B ($P < 0.001$), and non-HDL-C ($P < 0.001$) than controls. Subjects also had smaller LDL particles than controls ($P < 0.0001$). These differences between subjects and controls were all significant after adjustment for age, gender, smoking, BMI, and statin use. The concentration of LDL cholesterol, however, was only modestly different between subjects and controls ($P < 0.05$), a difference that appeared to originate from women rather than men.

The concentration of plasma glucose was significantly higher in subjects than controls after adjustment for age, waist circumference, gender, smoking, and statin usage ($P < 0.05$). Fasting insulin and homeostasis model of assessment-insulin resistance were also significantly higher in subjects than controls in both unadjusted and adjusted analyses ($P < 0.0001$). These differences in glucose and insulin between subjects and controls were apparent in both men and women.

The unadjusted systolic and diastolic blood pressures were not different between the subjects and controls, but, when adjusted for age, weight, gender, smoking, statin, and β-blocker use, both the systolic ($P < 0.001$) and diastolic ($P < 0.05$) blood pressures were higher in the subjects than controls (result not shown). This difference was mainly derived from the men and not from the women.

Discussion

This large-scale study compares two groups of individuals with comparable BMIs who were selected solely on the basis of whether or not they had an elevated plasma triglyceride and low HDL-C. The dyslipidemic group had significantly greater waist circumference, higher fasting levels of plasma glucose and insulin, higher levels of CRP, lower levels of adiponectin, and (after adjustment for age, gender, smoking, and β-blocker use) higher levels of systolic and diastolic blood pressure. The metabolic differences could not be explained entirely on the basis of greater waist circumferences in the subjects, because they generally persisted after adjustment of the data for this measure.

It should be noted that the two groups were not matched for a number of potentially confounding variables that may have introduced a bias that was not completely eliminated by statistical adjustment. However, the fact that the subjects were significantly younger than the controls and had a much

TABLE 2. Adiposity, CRP, adiponectin, and leptin

	Total group		Men		Women	
	Subjects	Controls	Subjects	Controls	Subjects	Controls
BMI (kg/m^2)	28.7 ± 3.5	28.2 ± 3.7^{a,f}	28.5 ± 3.3	27.9 ± 3.4^{a,f}	29.0 ± 3.8	28.6 ± 4.1^{a,e}
Waist (cm)	97.7 ± 10.5	94.6 ± 12.1^{a,f}	100.9 ± 9.3	99.2 ± 10.9^{a,e}	93.4 ± 10.3	89.3 ± 11.3^{a,f}
Hip (cm)	107.7 ± 7.9	107.7 ± 8.9$^{a,\mathrm{NS}}$	106.9 ± 7.1	106.8 ± 7.9$^{a,\mathrm{NS}}$	108.8 ± 8.7	108.7 ± 9.8$^{a,\mathrm{NS}}$
Waist/hip ratio	0.91 ± 0.07	0.88 ± 0.09^{a,f}	0.94 ± 0.06	0.93 ± 0.07^{a,f}	0.86 ± 0.06	0.82 ± 0.06^{a,f}
CRP (mg/dl)	3 (0.1–150)	2 (0.1–126)^{b,d}	2.4 (0.1–150)	2.1 (0.1–62.1)$^{c,\mathrm{NS}}$	4.4 (0.1–80)	2.5 (0.1–126)^{c,e}
Leptin (ng/ml)	43.0 (3.0–150.0)	40.0 (3.0–150.0)$^{b,\mathrm{NS}}$	27.0 (3.0–150.0)	22.0 (3.0–150.0)^{c,f}	77.0 (3.0–150.0)	72.0 (3.0–150.0)$^{c,\mathrm{NS}}$
Adiponectin (mg/liter)	4.7 (0.39–25.0)	6.6 (0.81–25.0)^{b,f}	4.2 (0.75–25.0)	5.6 (0.81–25.0)^{c,f}	5.5 (0.39–25.0)	7.7 (1.0–25.0)^{c,f}

Data are presented as mean ± SD or median (range) for non-normally distributed variables. NS, No significance.
[a] P values of the difference between subjects and controls.
[b] P values of the difference between subjects and controls adjusted for age, gender, smoking, waist, and statins.
[c] P values of the difference between subjects and controls adjusted for age, smoking, waist, and statins.
[d] $P < 0.05$.
[e] $P < 0.001$.
[f] $P < 0.0001$.

TABLE 3. Plasma lipids, glucose, and insulin

	Total group		Men		Women	
	Subjects	Controls	Subjects	Controls	Subjects	Controls
HDL-C (mmol/liter)	0.95 ± 0.16	1.63 ± 0.32[a,e]	0.89 ± 0.12	1.5 ± 0.29[b,e]	1.0 ± 0.18	1.8 ± 0.29[b,e]
TG (mmol/liter)	2.80 (1.2–17.4)	0.96 (0.30–1.8)[a,e]	3.0 (1.4–16.7)	1.0 (0.40–1.8)[b,e]	2.5 (1.2–17.4)	0.90 (0.30–1.6)[b,e]
Total cholesterol (mmol/liter)	5.7 ± 1.2	5.5 ± 0.90[a,e]	5.6 ± 1.2	5.4 ± 0.9[b,d]	5.8 ± 1.2	5.3 ± 0.94[b,e]
LDL-C (mmol/liter)	3.4 ± 1.07	3.4 ± 0.86[a,c]	3.3 ± 1.1	3.4 ± 0.84[b,NS]	3.5 ± 1.0	3.3 ± 0.88[b,e]
Non-HDL-C (mmol/liter)	4.8 ± 1.16	3.8 ± 0.89[a,e]	4.7 ± 1.2	3.8 ± 0.88[b,e]	4.8 ± 1.7	3.6 ± 0.90[b,e]
LDL size (nm)	26.8 (24.5–27.7)	27.4 (25.7–27.7)[a,e]	26. 7(24.5–27.7)	27.3 (25.7–27.7)[b,e]	26.9 (24.5–27.7)	27.4 (26.2–27.7)[b,e]
ApoB (mg/dl)	118.2 ± 31.2	104.5 ± 23.1[a,e]	115.6 ± 30.1	105.7 ± 23.3[b,e]	121.6 ± 32.3	103.1 ± 22.8[b,e]
Glucose(mmol/liter)	5.3 (3.8–6.9)	5.1 (3.4–6.8)[a,c]	5.3 (3.8–6.9)	5.2 (3.6–6.8)[b,NS]	5.3 (3.8–6.9)	5.0 (3.4–6.6)[b,c]
Insulin (mIU/ml)	10.4 (2.0–89.9)	6.4 (2.0–85.3)[a,e]	10.5 (2.0–89.9)	6.6 (2.0–54.8)[b,e]	10.4 (2.0–69.8)	6.4 (2.0–85.3)[b,e]
Homa-IR	2.4 (0.41–20.0)	1.4 (0.30–17.1)[a,e]	2.4 (0.42–20.0)	1.5 (0.35–11.2)[b,e]	2.3 (0.41–16.8)	1.4 (0.30–17.1)[b,e]

Data are presented as mean ± SD or median (range) for non-normally distributed variables. TG, Triglycerides; ApoB, apolipoprotein B; Homa-IR, homeostasis model of assessment-insulin resistance; NS, no significance.

[a] *P* values of the difference between subjects and controls adjusted for age, gender, smoking, waist, and statins.

[b] *P* values of the difference between subjects and controls adjusted for age, smoking, waist, and statins.

[c] $P < 0.05$.

[d] $P < 0.001$.

[e] $P < 0.0001$.

greater consumption of statins than the controls would most likely have resulted in an underestimation rather than an overestimation of the real differences between the two groups.

The results in the whole group were reflective of those in the male and female participants, although there were some interesting (but unexplained) gender differences. For example, the significant difference in CRP levels between subjects and controls in the total group was driven by a difference in the female group with the small difference in men being statistically nonsignificant. Conversely, a significant difference in leptin levels between subjects and controls was apparent in men but not women. Overall, however, conclusions drawn from analyses of the total group apply also to both genders.

Mechanisms underlying the observed association of dyslipidemia with the other metabolic derangements are uncertain. On the one hand, there is evidence that a low concentration of HDL-C is an independent risk factor for developing diabetes (17), possibly reflecting an ability of HDL particles to enhance β-cell function and survival (18). On the other hand, it is possible that whatever process is responsible for the elevated plasma triglyceride and low HDL-C seen in the subjects in this study also causes the other metabolic abnormalities. One possibility is a process that resides in the adipose tissue.

People with abdominal obesity (as measured by waist circumference) frequently also have dyslipidemia and other features of the metabolic syndrome (19). The mechanism underlying these associations is not entirely clear but may relate to the fact that waist circumference correlates with the amount of visceral fat (20) that is known to be metabolically different from the fat residing in a sc location (21, 22). However, in our study, the multiple metabolic abnormalities in the dyslipidemic subjects persisted even after adjustment for waist circumference, suggesting that either there are causes of the metabolic syndrome beyond a simple excess of visceral fat or waist circumference is at best an imprecise measure of visceral adipose stores. Indeed, waist circumference is most likely influenced by more than the amount of visceral fat, with the amount of sc fat in the abdomen, the degree of abdominal musculature, and the overall stature of an individual all potentially impacting on the waist circumference.

It is quite possible that the underlying metabolic defect in dyslipidemic subjects reflects an insulin-resistant state that extends beyond adipose tissue to involve both muscle and liver. Indeed, previous investigators have postulated a condition called the insulin resistance syndrome in which a primary (presumably genetic) insulin resistance is responsible for multiple metabolic disorders, including dyslipidemia (23). There is strong circumstantial evidence that abdominal obesity on a background of genetic susceptibility to metabolic abnormalities worsens the expression of the metabolic syndrome (24).

The results of this study have implications of potentially major clinical importance in the face of the worldwide epidemic of overweight and obesity and the associated increased risk of type 2 diabetes and CVD. This analysis of the GEMS study clearly indicates that not all overweight people are at the same risk, with a much higher risk group being identified by the simple measurement of plasma triglyceride and HDL-C. The finding that overweight people who are normolipidemic tend to have normal glucose and insulin metabolism, low levels of inflammatory markers, and normal blood pressure suggests that such people may be at relatively low risk of developing diabetes and CVD, despite being overweight. Thus, identification of people solely on the basis of an elevated plasma triglyceride and a low HDL-C uncovers a more generalized metabolic disorder that goes far beyond a simple abnormality of lipid and lipoprotein metabolism. These results have important ramifications in terms of diagnostic approaches to metabolic syndrome and suggest that elevated waist circumference and dyslipidemia should perhaps be considered as obligatory components of the disorder. The observation that the subjects had a high prevalence of CHD associated with elevated levels of triglyceride and non-HDL-C and low levels of HDL-C suggests that these people represent a high-risk but still relatively undertreated group that should be more clearly targeted for aggressive therapy in lipid management guidelines. Additional studies

are now indicated to identify genetic variations that may be responsible for this clustering of metabolic abnormalities.

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Address all correspondence and requests for reprints to: Prof. Philip Barter, The Heart Research Institute, 114 Pyrmont Bridge Road, Camperdown, New South Wales 2050, Australia. E-mail: barterp@hri.org.au.

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