Deterioration of the Metabolic Risk Profile in Women

Respective contributions of impaired glucose tolerance and visceral fat accumulation

AGNÉS PASCOT, MSC[1,2]
JEAN-PIERRE DESPRÉS, PHD[1,2,5]
ISABELLE LEMIEUX, MSC[1,2]
NATALIE ALMÉRAS, PHD[1,2]
JEAN BERGERON, MD, MSC[1]
ANDRÉ NADEAU, MD[3]
DENIS PRUD'HOMME, MD, MSC[1,4]
ANGELO TREMBLAY, PHD[4]
SIMONE LEMIEUX, PHD[1,5]

OBJECTIVE — To determine whether the impaired glucose tolerance (IGT) state contributes to the deterioration of the metabolic profile in women after taking into account the contribution of visceral adipose tissue (AT) accumulation, as measured by computed tomography.

RESEARCH DESIGN AND METHODS — We studied 203 women with normal glucose tolerance (NGT) and 46 women with IGT, defined as a glycemia between 7.8 and 11.1 mmol/l measured 2 h after a 75-g oral glucose load.

RESULTS — Women with IGT were characterized by a higher visceral AT accumulation and by higher concentrations of fasting plasma glucose, insulin, and C-peptide as well as by higher plasma concentrations of cholesterol, triglycerides, and apolipoprotein B (apoB) and by greater cholesterol–to–HDL-cholesterol ratio, reduced LDL peak particle size, lower HDL-cholesterol and HDL_2-cholesterol concentrations, and higher blood pressure ($P < 0.01$) than women with NGT. When we matched 27 pairs of women for visceral AT and fat mass as well as for menopausal status, differences previously found in LDL-cholesterol, LDL peak particle size, HDL-cholesterol, and HDL_2-cholesterol concentrations as well as in the cholesterol–to–HDL-cholesterol ratio and blood pressure were eliminated, whereas triglyceride concentrations remained significantly higher in women with IGT.

CONCLUSIONS — A high visceral AT accumulation is a major factor involved in the deterioration of many metabolic variables in women with IGT, with the notable exception of triglyceride concentrations, which remained significantly different between women with NGT and women with IGT after adjustment for visceral fat.

Diabetes Care 24:902–908, 2001

Longitudinal epidemiological studies have shown that the risk of cardiovascular disease (CVD) mortality in type 2 diabetic subjects is at least twofold greater than in the general population and that this relative risk is generally higher in women than in men (1,2). CVD mortality rates are also increased in impaired glucose tolerance (IGT) states (3). This latter finding confirms the hypothesis that hyperglycemia is associated with CVD but does not necessarily imply that glucose intolerance is causally involved in the etiology of CVD.

Subjects with IGT have been shown to be abdominally obese (4,5). Furthermore, the IGT state is also associated with alterations in plasma lipoprotein-lipid concentrations (5,6), including the presence of small dense LDL particles (7). Hypertension and high concentrations of PAI-1, free fatty acids, and fibrinogen had also been reported in subjects with IGT (8).

Obesity (especially abdominal obesity) is an important feature of the insulin resistance syndrome (9), which may lead to IGT and type 2 diabetes. Therefore, we wanted to determine whether the simultaneous presence of abdominal obesity and the IGT state had a greater impact on the metabolic risk profile compared with abdominal obesity without the presence of an IGT state. To reach this objective, we studied 203 women with normal glucose tolerance (NGT) aged (means ± SD) 45.7 ± 8.4 years and 46 women with IGT aged 47.4 ± 10.5 years.

RESEARCH DESIGN AND METHODS

— A total of 249 women were recruited by solicitation through the media from the Québec City metropolitan area between 1987 and 1998. Subjects were between 31 and 74 years of age. All subjects were healthy nonsmoking volunteers and were not under treatment for coronary heart disease, diabetes, dyslipidemia, or endocrine disorders. IGT was determined as a plasma glucose level between 7.8 and 11.1 mmol/l 2 h after a 75-g glucose load, as recommended by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (10). Menopause was determined as the absence of menstruation for at least 1 year, and 44% of menopausal women were on hormone replacement therapy (HRT). All participants signed an informed consent document approved by

From the [1]Lipid Research Center, CHUQ Research Center; the [2]Quebec Heart Institute, Hospital Laval Research Center; the [3]Diabetes Research Unit, CHUQ Research Center; the [4]Division of Kinesiology, Department of Preventive and Social Medicine; and the [5]Department of Food Science and Nutrition, Laval University, Ste-Foy, Québec, Canada.

Address correspondence and reprint requests to Simone Lemieux, PhD, Department of Food Science and Nutrition, Laval University, Paul-Comtois Pavilion, Sainte-Foy (Québec), CANADA G1K 7P4. E-mail: simone.lemieux@aln.ulaval.ca.

Received for publication 19 October 2000 and accepted in revised form 6 February 2001.

Abbreviations: apo, apolipoprotein; AT, adipose tissue; CVD, cardiovascular disease; HRT, hormone replacement therapy; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SHBG, sex hormone–binding globulin.

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

Table 1—*Characteristics of women with NGT and women with IGT*

	Women with NGT	Women with IGT	% Difference
n	203	46	
Physical characteristics			
Age (years)	45.7 ± 8.4	47.4 ± 10.5	3.7
Menopausal (%)	61 (30)	21 (46)*	
Use of HRT† (%)	27 (44)	9 (43)	
BMI (kg/m^2)	27.2 ± 6.5	32.6 ± 8.2‡	19.9
Body fat mass (kg)	26.7 ± 12.6	36.6 ± 15.0‡	37.1
Waist circumference (cm)	82.5 ± 14.0	94.9 ± 15.9‡	15.0
Waist-to-hip ratio	0.79 ± 0.07	0.84 ± 0.07‡	6.3
Computed tomography abdominal AT areas (cm^2)			
Total	443 ± 211	605 ± 224‡	36.6
Visceral	103 ± 51	151 ± 51‡	46.6
Subcutaneous	340 ± 170	454 ± 192‡	33.5
Lipoprotein profile			
Cholesterol (mmol/l)			
Total	5.09 ± 0.89	5.63 ± 0.97§	10.6
VLDL‖	0.41 ± 0.28	0.65 ± 0.33‡	58.5
LDL	3.36 ± 0.81	3.76 ± 0.87¶	11.9
HDL	1.30 ± 0.33	1.20 ± 0.25#	–7.7
HDL_2‖	0.52 ± 0.22	0.45 ± 0.16¶	–13.5
HDL_3‖	0.74 ± 0.15	0.75 ± 0.15	1.4
Cholesterol/HDL-cholesterol	4.13 ± 1.16	4.87 ± 1.30‡	17.9
HDL_2/HDL_3‖	0.71 ± 0.28	0.61 ± 0.21¶	–14.1
Triglycerides (mmol/l)	1.27 ± 0.61	2.03 ± 0.82‡	59.8
Apo B (g/l)‖	0.95 ± 0.22	1.12 ± 0.26‡	17.9
Apo A-I (g/l)‖	1.28 ± 0.20	1.31 ± 0.20	2.3
LDL peak particle size (Å)**	254.7 ± 4.2	253.1 ± 3.2#	–0.6
Insulin-glucose homeostatis			
Fasting glucose (mmol/l)	4.97 ± 0.41	5.44 ± 0.54‡	9.5
Fasting insulin (pmol/l)	57.1 ± 40.6	106.3 ± 72.2‡	86.2
Fasting C-peptide (pmol/l)	693.2 ± 300.5	995.2 ± 404.3‡	43.6
Glucose area (× 10^{-3} mmol/l)	1.09 ± 0.16	1.53 ± 0.18‡	40.4
Insulin area (× 10^{-3} pmol/l)	69.0 ± 37.6	133.7 ± 98.9‡	93.8
C-peptide area (× 10^{-3} pmol/l)	479.4 ± 185.4	664.1 ± 251.9‡	38.5
2-h post-OGTT glucose (mmol/l)	5.70 ± 1.06	8.98 ± 0.96‡	57.5
Blood pressure (mmHg)			
Systolic‖	115 ± 13	123 ± 21#	10.0
Diastolic‖	74 ± 9	77 ± 10#	4.1

Data are means ± SD unless otherwise indicated. *$P < 0.05$; †expressed as a percentage of menopausal women; ‡significantly different between women with NGT versus women with IGT, $P < 0.0001$; §$P < 0.001$; ‖$n = 174$ in women with NGT and $n = 41$ in women with IGT; ¶$P < 0.01$; #$P < 0.05$; **$n = 113$ in women with NGT and $n = 29$ in women with IGT.

the Laval University Medical Ethics Committee.

Anthropometry

The hydrostatic weighing technique was used to measure body density, which was obtained from the mean of six measurements (11). The percentage of body fat was derived from body density using the equation of Siri (12). Height, body weight, and waist and hip circumferences were measured according to the procedures recommended at the Airlie Conference (13), and the waist-to-hip ratio was calculated accordingly. Abdominal adipose tissue (AT) areas were measured by computed tomography with a Siemens Somatom DHR scanner (Erlangen, Germany), as previously described (14). Blood pressures were obtained using a sphygmomanometer and a stethoscope according to the recommendations of the American Heart Association (15).

Plasma lipoprotein-lipid

Blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA after a 12-h overnight fast. Cholesterol and triglyceride concentrations were determined in plasma and lipoprotein fractions using an analyzer Technicon RA-500 (Bayer Corporation, Tarrytown, NY), and enzymatic reagents were obtained from Randox (Randox Laboratories, Crumlin, U.K.). Plasma lipoprotein fractions (VLDL, LDL, and HDL) were isolated using procedures that have been previously described (5). Plasma apolipoprotein B (apoB) and apoA-I concentrations were measured by the rocket immunoelectrophoretic method of Laurell (16). LDL peak particle size was

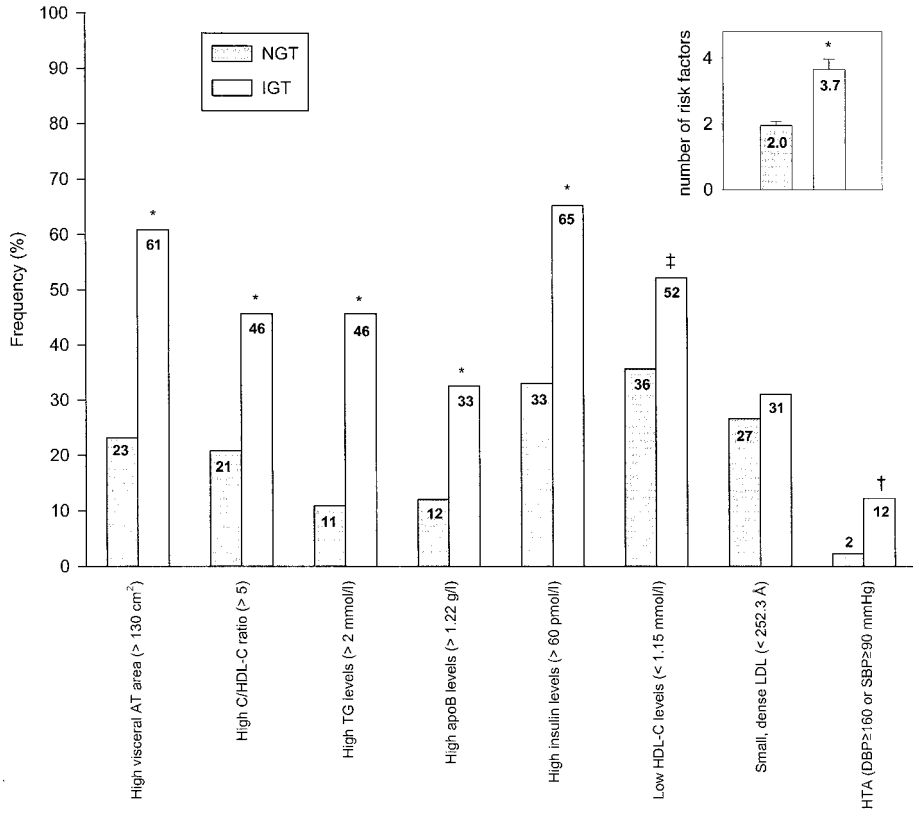

Figure 1—*Prevalence of deteriorated metabolic parameters predictive of CVD risk among 203 women with NGT and 46 women with IGT. C, cholesterol; TG, triglycerides; HTA, hypertension; DBP, diastolic blood pressure; SBP systolic blood pressure. Significant differences between the two groups:* *P < *0.002;* †P < *0.004;* ‡P < *0.04.*

assessed by nondenaturating 2–16% polyacrylamide gel electrophoresis of whole plasma, as previously reported (17).

Oral glucose tolerance test

A 75-g oral glucose tolerance test (OGTT) was performed in the morning after an overnight fast. For measurements of plasma glucose, insulin, and C-peptide concentrations, blood samples were collected at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min in EDTA-containing tubes through a venous catheter placed in an antecubital vein. The method used was described in detail in a previous publication (5).

Cutoff points for metabolic risk factors

The presence of components of the metabolic syndrome was assessed using the following referenced cutoff points: triglycerides >2 mmol/l (18), HDL-cholesterol <1.15 mmol/l (19), cholesterol–to–HDL-cholesterol ratio >5 (20), visceral AT area >130 cm^2 (21), fasting insulin >60 pmol/l (22), apoB >1.22 g/l (23), and blood pressure >160/90 mmHg (24). The cutoff point for LDL peak particle size was determined using the 25th percentile value of nonobese women (BMI <25 kg/m^2) with NGT.

Statistical analyses

Normality of the distribution for each variable was verified, and when variables were not normally distributed, log-transformed values were used for subsequent analyses. An unpaired Student's *t* test was performed to compare women with NGT and women with IGT. A χ^2 test was used to compare the prevalence of metabolic disturbances among women with NGT and IGT. Women with NGT and with IGT were paired on the basis of visceral AT area (±10 cm^2), fat mass (±1 kg), and menopausal status, and they were then compared using an unpaired Student's *t* test. Pearson or Spearman correlation coefficients were calculated (depending on the normality of the distribution) to quantify the univariate associations among variables. Stepwise multiple regression analyses were computed to sort out the independent contributions of visceral AT accumulation, fat mass, glucose tolerance, and menopausal status to the variation of metabolic variables. Analyses were performed on the SAS statistical package (SAS Institute, Cary, NC).

RESULTS — Table 1 shows that women with IGT were characterized by increased adiposity because they had higher values for BMI, body fat mass, waist circumference, and waist-to-hip ratio as well as higher total abdominal and visceral AT areas than women characterized by NGT ($P < 0.0001$). Furthermore, 46% of the women with IGT had entered menopause compared with 30% of the women characterized by NGT ($P < 0.05$). Fasting plasma concentrations of cholesterol (total, VLDL, and LDL), triglycerides, and apoB as well as the cholesterol–to–HDL-cholesterol ratio were significantly higher in women with IGT ($P < 0.01$), whereas HDL-cholesterol and HDL_2-cholesterol concentrations and the HDL_2-cholesterol–to–HDL_3-cholesterol ratio were significantly lower in women with IGT compared with women characterized by NGT ($P < 0.05$). Furthermore, LDL peak particle sizes were measured in a subgroup of subjects, and women with IGT were characterized by a reduced LDL peak particle size ($P < 0.04$) compared with women with NGT. In addition (and as expected), women with IGT were characterized by higher levels of glucose, insulin, and C-peptide in the fasting state and after an oral glucose load. Finally, systolic and diastolic blood pressures were slightly but significantly higher in women with IGT compared with women characterized by NGT ($P < 0.05$).

Because there was a greater prevalence of postmenopausal women in the group of women with IGT, we performed an analysis of covariance for menopause status, and similar results were found for all physical and metabolic variables studied (results not shown).

We also compared the prevalence of deteriorated metabolic parameters among the two groups of women by χ^2 analyses (Fig. 1). Except for the small dense LDL phenotype, a significantly higher proportion of women with IGT were characterized by a deterioration in all the variables

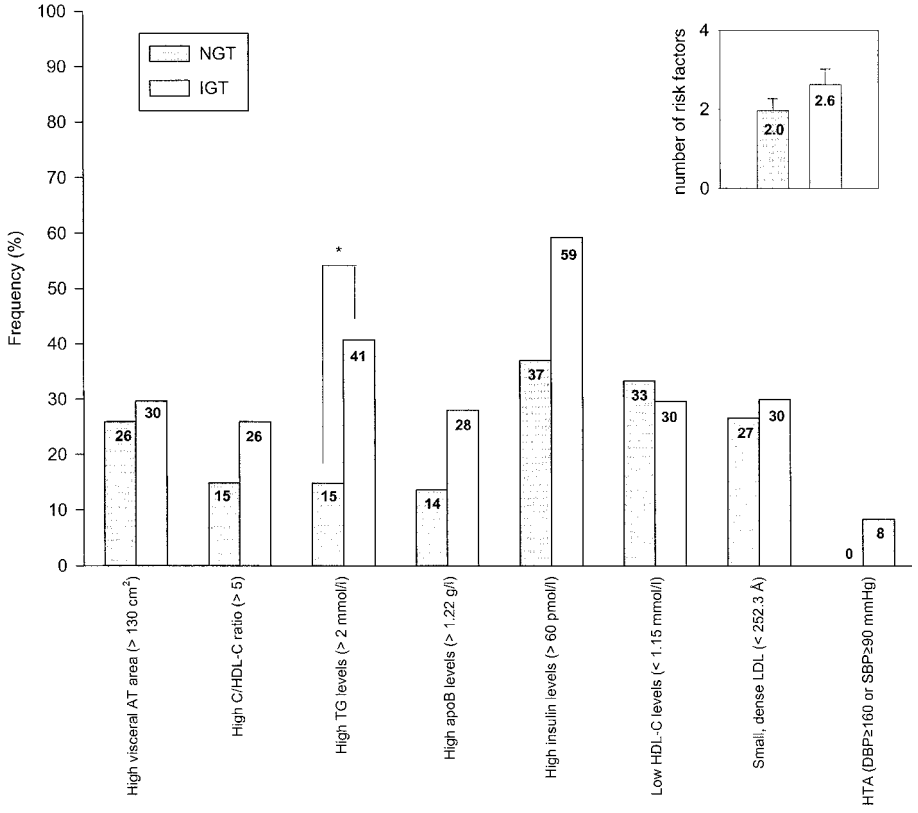

Figure 2—*Prevalence of deteriorated metabolic parameters predictive of CVD risk among 27 women with NGT and 27 women with IGT matched on the basis of fat mass, visceral adipose tissue, and menopausal status. C, cholesterol; TG, triglycerides; HTA, hypertension; DBP, diastolic blood pressure; SBP systolic blood pressure.* *P = *0.03.*

studied compared with women with NGT. We also calculated the number of risk factors found in every subject, and we found that women with IGT had a larger number of deteriorated metabolic parameters compared with women with NGT (3.7 vs. 2.0 risk factors, $P < 0.0001$).

To investigate the contribution of visceral AT area and fat mass to the differences between the IGT and NGT groups with regard to the lipoprotein-lipid variables, we matched 27 women characterized by NGT with 27 women with IGT. They were matched according to their amount of fat mass and visceral AT area as well as by their menopausal status. Women with NGT and IGT were obviously characterized by similar amounts of fat mass and visceral AT because they were matched on the basis of these variables (Table 2). Differences previously found in fasting plasma concentrations of glucose and C-peptide were eliminated, although women with IGT still displayed higher insulinemic-glycemic responses to an oral glucose load after this pairing procedure. Furthermore, also eliminated were differences initially found in plasma VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, HDL_2-cholesterol, total cholesterol–to–HDL-cholesterol ratio, and LDL peak particle size as well as in systolic and diastolic blood pressures (Table 2). On the other hand, significant differences remained with regard to concentrations of triglycerides, apoB, and total cholesterol.

We also compared the prevalence of deteriorated metabolic parameters between the two groups of women matched for body fat mass, visceral AT area, and menopausal status. We found that only the difference in the prevalence of triglyceride concentrations ≥2 mmol/l remained significantly different ($P < 0.03$); 41% of women with IGT were characterized by hypertriglyceridemia compared with only 15% of women with NGT (Fig. 2). When women with NGT were compared with those with IGT and similar body fat mass, visceral AT accumulation, and menopausal status, it was found that the total number of risk factors was not significantly different between the two groups (2.6 vs. 2.0 risk factors, NS).

Furthermore, despite a positive correlation between visceral fat and triglyceride concentrations in women with NGT ($r = 0.52$, $P < 0.0001$), no relationship between these two variables was observed in women with IGT ($r = 0.18$, NS). When we divided the two groups of women into low (<130 cm^2) vs. high (≥130 cm^2) levels of visceral AT, we found that women with NGT and low visceral AT had significantly lower triglyceride concentrations than women with NGT and high visceral AT accumulations (1.09 ± 0.38 vs. 1.86 ± 0.82 mmol/l; $P < 0.0001$). However, women with IGT and either low or high levels of visceral AT showed similar concentrations of triglycerides (1.87 ± 0.79 vs. 2.13 ± 0.83 mmol/l; NS). Finally, women with IGT and low levels of visceral AT had similar triglyceride concentrations compared with those with NGT and high visceral AT accumulations (1.87 ± 0.79 vs. 1.86 ± 0.82 mmol/l; NS).

CONCLUSIONS — It is well recognized that type 2 diabetes is associated with CVD. This relationship may be explained at least to some extent by the concomitant abnormalities in lipid and lipoprotein metabolism found in diabetic patients (25). Furthermore, type 2 diabetes is a heterogeneous condition from a metabolic standpoint and is invariably preceded by IGT (26). In that sense, IGT may also be a marker of CVD risk (27). Although a dyslipidemic state is frequently found in type 2 diabetic patients and in subjects characterized by IGT, it is also typically found in patients with visceral obesity who may nevertheless display NGT (28); it has been reported that individuals with a high accumulation of visceral AT are characterized by numerous alterations in their plasma lipoprotein-lipid profile (4,29). In this regard, we have recently reported that the higher visceral AT accumulation observed in men with IGT was an important factor involved in the deterioration of their CVD risk profile. In fact, we found that controlling for the variation in visceral AT accumulation eliminated the differences initially found between the two groups of men (NGT versus IGT) in their lipoprotein-lipid profiles, despite remaining differences in their indexes of plasma insulin–glucose homeostasis (5).

Table 2—*Characteristics of women with NGT and women with IGT paired on the basis of menopausal status, visceral AT area, and fat mass*

	Women with NGT	Women with IGT	% Difference
n	27	27	
Age (years)	46.2 ± 11.1	45.4 ± 14.1	–1.7
Menopausal (%)	13 (48)	13 (48)	
Use of HRT* (%)	5 (38)	7 (54)	
Body fat mass (kg)	27.5 ± 8.8	27.6 ± 9.3	0.4
Visceral AT area (cm^2)	115 ± 40	115 ± 38	0
Lipoprotein profile			
Cholesterol (mmol/l)			
Total	5.03 ± 0.71	5.49 ± 0.84†	9.1
VLDL	0.45 ± 0.32	0.60 ± 0.29	33.3
LDL	3.29 ± 0.59	3.59 ± 0.79	9.1
HDL	1.28 ± 0.34	1.29 ± 0.27	0.8
HDL_2	0.52 ± 0.25	0.48 ± 0.18	–7.7
HDL_3	0.72 ± 0.13	0.81 ± 0.16†	12.5
Cholesterol/HDL-cholesterol	4.12 ± 1.01	4.42 ± 1.16	7.3
HDL_2/HDL_3	0.71 ± 0.29	0.61 ± 0.24	–14.1
Triglycerides (mmol/l)	1.26 ± 0.65	1.96 ± 0.80‡	47.6
ApoB (g/l)	0.96 ± 0.18	1.09 ± 0.22†	13.5
ApoA-I (g/l)	1.30 ± 0.16	1.39 ± 0.19	6.9
LDL peak particle size (Å)	253.9 ± 4.3	253.1 ± 3.5	–0.3
Insulin-glucose homeostasis			
Fasting glucose (mmol/l)	4.92 ± 0.44	5.12 ± 0.42	4.1
Fasting insulin (pmol/l)	58.2 ± 31.7	81.9 ± 45.0†	40.7
Fasting C-peptide (pmol/l)	754.3 ± 298.5	854.8 ± 296.5	13.3
Glucose area ($\times 10^{-3}$ mmol/l)	1.15 ± 0.14	1.48 ± 0.15§	28.7
Insulin area ($\times 10^{-3}$ pmol/l)	68.3 ± 28.5	102.7 ± 51.6‡	50.4
C-peptide area ($\times 10^{-3}$ pmol/l)	533.8 ± 164.9	626.2 ± 192.1	17.3
2-h post-OGTT glucose (mmol/l)	6.05 ± 0.85	8.76 ± 0.91§	44.8
Blood pressure (mmHg)			
Systolic‖	115 ± 12	120 ± 20	4.3
Diastolic¶	74 ± 7	75 ± 9	1.4

Data are means ± SD. *Expressed as a percentage of menopausal women; †significantly different between women with NGT versus women with IGT, $P < 0.05$; ‡$P < 0.005$; §$P < 0.0001$; ‖$n = 22$ in women with NGT and $n = 24$ in women with IGT.

In the present study, women with IGT were also characterized by greater adiposity, including increased visceral fat accumulation compared with women with NGT, in accordance with previous observations (4,5). Increased risk for CVD in IGT may be partly attributable to elevated plasma glucose concentrations but may also be due to a greater prevalence of other CVD risk factors. Undoubtedly, there is an association between IGT and CVD. However, we have to bear in mind that in most cases, subjects with blood glucose in the upper normal range are also characterized by a cluster of several other unfavorable CVD risk parameters, such as elevated blood pressure and increased plasma lipids (30). In the present study, women with IGT were more frequently carriers of an important cluster of deteriorated metabolic parameters than women with NGT (3.7 vs. 2.0 risk factors).

The objective of the present study was to verify whether the increased visceral AT accumulation found in IGT could explain the altered lipid-lipoprotein profile associated with IGT. When we matched 27 women with NGT with 27 women characterized by IGT according to their body fat mass, visceral AT area, and menopausal status, most of the differences noted in the plasma lipoprotein-lipid profile were eliminated, despite major remaining differences in their plasma insulin-glucose homeostasis. However, differences in plasma triglyceride, apoB, and total cholesterol concentrations remained significant between the two matched groups. These results suggest that visceral AT accumulation contributes to the deterioration of the lipoprotein-lipid profile observed in women with IGT. However, alterations in insulin-glucose homeostasis that are typical of the IGT state may also play a role in the deterioration of the metabolic risk profile, especially for the regulation of circulating triglycerides. Therefore, present results indicate that high visceral AT accumulation ($\geq$130 cm^2) has a major impact on triglyceride concentrations in the NGT state. However, in the IGT state, the impact of visceral AT appears to be attenuated. The factors that may explain why women with IGT show high triglyceride concentrations even in the presence of low visceral AT accumulation remain unclear. It is also important to note that the independent effect of IGT per se on triglyceride concentration was not observed in our study performed in men (5). This may suggest that mechanisms that are regulating triglyceride concentrations are, to some extent, sex-specific. Accordingly, it is also interesting to note that the CVD risk associated with high triglyceride levels may also be sex-specific, because the evidence suggesting that hypertriglyceridemia is an independent CVD risk factor appears to be stronger in women than in men (31).

It is well known that diabetes is a significant and powerful risk factor for CVD. However, the relative CVD risk associated with type 2 diabetes appears to be greater in women than in men (2). It has been suggested that this diabetes-related increased CVD risk in women could be explained by the fact that diabetes has more adverse effects on CVD risk factors in women than in men. Mechanisms underlying the stronger relationship between lipids and glycemia in women than in men are not fully understood. Sex hormones may have a possible impact on this relationship. Indeed, lower sex hormone–binding globulin (SHBG) levels were found in postmenopausal women with IGT compared with those with NGT. These women also have higher androgen activity (as reflected by the testosterone-to-SHBG ratio) than postmenopausal women with NGT (32). Because insulin inhibits SHBG secretion in the liver (33), the hyperinsulinemic state of women with IGT may be associated with a dyslipidemic profile through alterations in SHBG and the estrogen/androgen balance (34).

Although normalization of blood glu-

cose in type 2 diabetes may be cost-effective, strong experimental evidence shows that treatment of other risk factors, particularly hypertension and hyperlipidemia, reduces cardiovascular mortality even among persons with diagnosed type 2 diabetes (35). Therefore, clinical interventions to reduce metabolic risk should focus on obesity, hypertension, and the sedentary lifestyle, which promote insulin resistance. Thus, because lipoprotein disorders are not innocent bystanders of the abnormalities that lead to type 2 diabetes (36), we believe that it is important to identify not only individuals with IGT but also those characterized by abdominal obesity, physical inactivity, and lipid disorders to prevent further aggravation of their hyperglycemia and dyslipidemia.

In summary, the deterioration in the lipoprotein-lipid profile observed in women with IGT is largely related to the increased visceral AT depot found in these women, and it is partly related to alterations in glucose-insulin homeostasis, especially the modulation of plasma triglyceride concentrations, that are typical of the IGT state.

Acknowledgments— This study was supported by the Canadian Diabetes Association and by the Canadian Institutes of Health Research (MT-14014 and MGC-15187). I.L. is a recipient of a studentship from the Heart and Stroke Foundation of Canada; J.B. is a clinical research scholar from the Fonds de la Recherche en Santé du Québec; and S.L. is a research scholar from the Canadian Institutes of Health Research.

The authors express their gratitude to the subjects for their excellent collaboration and to the staff of the Lipid Research Center, the Physical Activity Sciences Laboratory, and the Diabetes Research Unit for their contribution to this study. We especially thank L. Allard, S. Brulotte, L. Bargone, G. Fournier, H. Bessette, and C. Leblanc for their help in the collection and analysis of the data.

References

1. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. *JAMA* 241:2035–2038, 1979
2. Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 123:504–516, 1986
3. Jarrett RJ, McCartney P, Keen H: The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 22:79–84, 1982
4. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 36:54–59, 1987
5. Pascot A, Després JP, Lemieux I, Bergeron J, Nadeau A, Prud'homme D, Tremblay A, Lemieux S: Contribution of visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. *Diabetologia* 43:1126–1135, 2000
6. Laakso M, Barrett-Connor E: Asymptomatic hyperglycemia is associated with lipid and lipoprotein changes favoring atherosclerosis. *Arteriosclerosis* 9:665–672, 1989
7. Selby JV, Austin MA, Newman B, Zhang D, Quesenberry CP Jr, Mayer EJ, Krauss RM: LDL subclass phenotypes and the insulin resistance syndrome in women. *Circulation* 88:381–387, 1993
8. Temelkova-Kurktschiev T, Henkel E, Schaper F, Koehler C, Siegert G, Hanefeld M: Prevalence and atherosclerosis risk in different types of non-diabetic hyperglycemia: is mild hyperglycemia an underestimated evil? *Exp Clin Endocrinol Diabetes* 108:93–99, 2000
9. Després JP: Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 9:452–459, 1993
10. 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* 20:1183–1197, 1997
11. Meneely GR, Kaltreider NL: Volume of the lung determined by helium dilution. *J Clin Invest* 28:129–139, 1949
12. Siri WE: The gross composition of the body. *Adv Biol Med Phys* 4:239–280, 1956
13. The Airlie (VA) consensus conference: In *Standardization of anthropometric measurements*. Lohman T, Roche A, Martorel R, Eds. Champaign, IL, Human Kinetics 1988, p. 39–80
14. Ferland M, Després JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, Lupien PJ, Thériault G, Bouchard C: Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. *Br J Nutr* 61: 139–148, 1989
15. Kirkendall WM, Burton AC, Epstein FH, Freis ED: Recommendations for human blood pressure determination by sphygmomanometers. *Circulation* 36:980–988, 1967
16. Laurell CB: Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Anal Biochem* 15: 45–52, 1966
17. Tchernof A, Lamarche B, Prud'Homme D, Nadeau A, Moorjani S, Labrie F, Lupien PJ, Després JP: The dense LDL phenotype: association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. *Diabetes Care* 19:629–637, 1996
18. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR: Recommendations for the management and treatment of dyslipidemia: report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 162:1441–1447, 2000
19. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 41: 715–722, 1992
20. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 269:3015–3023, 1993
21. Després 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
22. Scarsella C, Alméras N, Mauriège P, Blanchet C, Dewailly E, Després JP, Bergeron J: Determination of reference values for fasting insulin levels in a representative sample of the adult Québec population (Abstract). *Atherosclerosis* 151:101, 2000
23. Connelly PW, Poapst M, Davignon J, Lussier-Cacan S, Reeder B, Lessard R, Hegele RA, Csima A: Reference values of plasma apolipoproteins A-I and B, and association with nonlipid risk factors in the populations of two Canadian provinces: Quebec and Saskatchewan: Canadian Heart Health Surveys Research Group. *Can J Cardiol* 15: 409–18, 1999
24. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
25. Syvanne M, Taskinen MR: Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus (Review). *Lancet* 350 (Suppl. 1):SI20–SI23, 1997
26. Walker M, Berrish TS, Stewart MW, Humphriss DB, Barriocanal L, Alberti KG: Metabolic heterogeneity in impaired glu-

cose tolerance. *Metabolism* 46:914–917, 1997
27. Laakso M, Lehto S: Epidemiology of risk factors for cardiovascular disease in diabetes and impaired glucose tolerance. *Atherosclerosis* 137 (Suppl.):S65–S73, 1998
28. Després JP: The insulin resistance-dyslipidemic syndrome of visceral obesity: effect on patients' risk (Review). *Obes Res* 6 (Suppl. 1):8S–17S, 1998
29. Després JP: Visceral obesity, insulin resistance, and related dyslipoproteinemias. *Diabetes 1991*. Rifkin H, Colwell JA, Taylor SI, Eds. Amsterdam, The Netherlands, Elsevier Science Publishers, 95–99, 1991
30. Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E: Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care* 22:45–49, 1999
31. Castelli WP: Epidemiology of triglycerides: a view from Framingham. *Am J Cardiol* 70:3H–9H, 1992
32. Larsson H, Ahren B: Androgen activity as a risk factor for impaired glucose tolerance in postmenopausal women. *Diabetes Care* 19:1399–403, 1996
33. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN, Blackard WG: A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 72:83–89, 1991
34. Tchernof A, Toth MJ, Poehlman ET: Sex hormone-binding globulin levels in middle-aged premenopausal women: associations with visceral obesity and metabolic profile. *Diabetes Care* 22:1875–1881, 1999
35. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410–418, 1999
36. Fagot-Campagna A, Narayan KM, Hanson RL, Imperatore G, Howard BV, Nelson RG, Pettitt DJ, Knowler WC: Plasma lipoproteins and incidence of non-insulin-dependent diabetes mellitus in Pima Indians: protective effect of HDL cholesterol in women. *Atherosclerosis* 128:113–119, 1997