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Divergent Effects of a Combined Hormonal Oral Contraceptive on Insulin Sensitivity in Lean versus Obese Women

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Abstract

Objective—To evaluate the effects of a commonly used combined hormonal oral contraceptive (OC) on carbohydrate metabolism in obese as compared with obese women.

Design—6-month prospective study.

Setting—Clinical Research Center at an academic medical center.

Patients—Premenopausal non-diabetic women with BMI < 25 kg/m^2 (n=15) or > 30 kg/m^2 (n=14).

Intervention—Ethinyl estradiol 35mcg and norgestimate 0.18/0.215/0.25 mg for 6 cycles.

Main Outcome Measures—Insulin sensitivity (Si) by frequent sampling intravenous glucose tolerance test; other indices of insulin sensitivity (ISI HOMA, Matsuda index); fasting lipid panel.

Results—Si changed from 6.62±3.69 min^{-1}/mu/L (baseline) to 8.23±3.30 min^{-1}/mu/L (6 months) in lean women, and from 4.36±2.32 to 3.82±2.32 min^{-1}/mu/L in obese women (p for interaction=0.0494). Divergent effects on insulin sensitivity were also observed with ISI HOMA (p=0.0128) and Matsuda index (p=0.0227). LDL increased by approximately 20 mg/dL in both groups (p<0.005 [lean]; p<0.01 [obese]).

Conclusions—Lean and obese women exhibit differential changes in insulin sensitivity when given 6 months of a commonly used OC. The mechanisms of these differences, and whether these divergent effects persist long-term, require further investigations.

Capsule—Lean and obese non-diabetic women exhibit differential changes in insulin sensitivity when given 6 months of a commonly used OC (ethinyl estradiol 35mcg and norgestimate 0.18/0.215/0.25 mg)

Keywords

Oral contraceptives; Obesity; Insulin resistance; Carbohydrate metabolism; Cholesterol

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Introduction

The combined hormonal oral contraceptive (OC) pill is the most commonly used contraceptive method due to its effectiveness and reversibility (1;2). OCs, especially those with high estrogen doses (≥ 50 μg ethinylestradiol), may be associated with alterations in carbohydrate metabolism (3;4). OCs with ethinylestradiol at lower doses probably have limited effects on carbohydrate metabolism in *normal weight women* (5). However, no information is available regarding the effects among obese women (5).

The prevalence of obesity and overweight is increasing worldwide. Obesity is associated with insulin resistance, impaired glucose tolerance, and increased risk of diabetes (6). Hence, even a small degree of worsening insulin sensitivity with OC use may be of clinical relevance for obese women.

In this report, we compared effects of a commonly used combined hormonal OC containing ethinylestradiol 35mcg and norgestimate 0.18/0.215/0.25 mg on carbohydrate metabolism in obese and lean women. We studied this particular OC because it is one of the most commonly used (2), and because the safety profile of the progestin, norgestimate, has been established, with previous reports suggesting no significant worsening of fasting insulin, glucose, or glycosylated hemoglobin in non-obese women (7). We hypothesized that combined hormonal OC will affect insulin sensitivity differently in lean versus obese women. In addition, we evaluated the effects of this OC on blood pressure and lipid profile in obese versus lean women.

Materials and Methods

Subjects

Premenopausal women 18 to 40 years of age were enrolled. Obese women had a BMI > 30 kg/m^2 and lean women had a BMI < 25 kg/m^2. Women with the following characteristics were excluded: (1) diabetes by fasting glucose or a 2-hour glucose tolerance test (OGTT); (2) contraindications to OC use (e.g. history of thromboembolism, coronary/ cerebrovascular events, prolonged immobilization, blood pressure ≥ 160/ 100 mmHg, age ≥ 35 years and smoker of ≥ 20 cigarettes/day, migraines, malignancies, hepatic diseases); (3) use of systemic hormonal contraceptives, insulin sensitizers, anti-hyperlipidemic drugs, antihypertensives, or glucocorticoids within 3 months; (4) pregnancy or lactation; (5) actively attempting weight loss (> 2 kg of weight loss in the previous month). All women were normal cycling.

Before study procedures, all participants provided signed, informed consent. The study was approved by Virginia Commonwealth University Institutional Review Board, and was registered at clinicaltrials.gov (NCT00205504). None of the authors had any conflict of interest.

Study Procedures

All evaluations were performed in the follicular phase, confirmed by a serum progesterone concentration < 2 ng/mL. Subjects were admitted to the General Clinical Research Center after a 12-hour fast. On day 1, blood pressure, anthropometric measurements, comprehensive metabolic panel, fasting lipid profile, serum fasting insulin and glucose concentrations were obtained. Absence of pregnancy was confirmed by a urine pregnancy test. Subjects underwent a 2-hour OGTT with 75g glucose, and blood samples were collected every 15 minutes for the determination of serum glucose and insulin concentrations.

On day 2, after a 12-hour fast, the participants underwent the modified frequent sampling intravenous glucose tolerance test (FSIVGTT)(8-10). At time 0, 300mg/kg dextrose was administered intravenously over 1 minute, and insulin at 0.03U/kg was administered similarly 20 minutes later. Serum glucose and insulin concentrations were obtained at 29 time points over 3 hours (10). Subjects received supplies of ethinylestradiol 35mcg and norgestimate 0.18/0.215/0.25 mg (Ortho Tri-Cyclen®, Ortho-McNeil Pharmaceuticals) and were instructed to start administering the OC that day. Proper use of the OC was explained. The women were instructed not to modify their dietary and physical activity habits from baseline during the study period.

During week 12 (third cycle of OC), subjects returned for testing between day 5 and 7 of the hormone-free week, to minimize the effect of progestins on insulin sensitivity. The assessments for this visit were the same as day 1. Medication compliance was verified by interview and pill counts.

During the last week of cycle 6 (6 months), subjects returned between day 5 and 7 of the hormone-free week, for repeat assessments as performed in day 1 and 2.

Laboratory Assays

See laboratory assays in Supplemental Materials.

Metabolic Syndrome Risk Factors

The number of metabolic syndrome risk factors at baseline in both lean and obese women were evaluated to serve as a general indicator of metabolic risk. The National Cholesterol Education Program definition of the metabolic syndrome was used (11).

Insulin sensitivity and Indices of Insulin-Glucose Dynamics

Glucose-insulin dynamics during FSIVGTT were analyzed using the Minimal Model Identification Software (MINIMOD, version 6.02, Los Angeles, CA) (12). The FSIVGTT yields quantitative determinations of 1) tissue insulin sensitivity (Si); 2) acute insulin response to glucose (AIRg), which addresses adequacy of insulin secretion; 3) disposition index (DI), or AIRg*Si, which is a composite measure of insulin secretion and action; and 4) glucose effectiveness (Sg), the capacity of glucose to mediate its own disposal independent of insulin (12).

We analyzed insulin and glucose incremental areas-under-the-curve (AUC) upon OGTT by the trapezoidal rule after subtracting baseline values. We assessed incremental AUCs because fasting baseline values of insulin and glucose were already separately presented, and incremental AUCs reflect changes in response to glycemic loads (13). The glucose and insulin values during OGTT were used to calculate the Matsuda insulin sensitivity index (14). The homeostatic model assessment insulin sensitivity index (ISI HOMA) (15) was calculated from fasting glucose and insulin concentrations.

Statistical Analysis

The primary outcome was the mean change in insulin sensitivity (Si from FSIVGTT) from baseline to 6 months among obese versus lean women. Secondary outcomes were incremental $AUC_{glucose}$, incremental $AUC_{insulin}$, fasting glucose and insulin concentrations, insulin sensitivity as measured by ISI HOMA and Matsuda indices, systolic and diastolic blood pressure, lipid and anthropometric parameters. Normal distributions were determined by normal probability plots. Continuous variables were presented as mean values ± standard deviations. Results not normally distributed were log-transformed for statistical analyses

and, after back-transformation, were reported in their original units as geometric means with 95% confidence intervals.

Baseline comparisons between obese and lean women were performed via students' *t* tests, and Welch ANOVA tests if unequal variances were observed. Proportions were compared by Pearson Chi-square tests. We evaluated the mean change with OC administration in each parameter within all women, and within the obese and lean groups separately, using a paired *t* test.

For the primary outcome of interest, change in Si upon 6 months of OC was compared between the obese and lean women using a repeated measures analysis, testing for interaction between Si time-trends and baseline obesity status. Changes in secondary outcomes of interest between the 2 groups were analyzed similarly.

Based on a previous cross-sectional study on $AUC_{glucose}$ among non-obese and obese women taking oral contraceptives (16), 14 women per group were needed to achieve a power of 80%. Statistical analysis was performed using JMP 8.0 (SAS Institute Inc., Cary, NC). P values <0.05 were considered statistically significant.

Results

Baseline Characteristics

A total of 48 lean and obese women provided informed consent for the study. Of these, 4 subjects did not meet inclusion criteria, 9 did not attend their first study appointment, 1 subject was lost to follow up after day 1, and 4 subjects withdrew from the protocol shortly after initial baseline studies (personal reasons [n=2], fear of venipuncture [n=1], dizziness after one dose of OC [n=1]). One obese participant was withdrawn by the investigator due to protocol violation (the participant began a weight loss program during the study). In all, 29 women (15 lean and 14 obese women) completed the study.

At baseline, lean and obese women were demographically similar (Table 1), but blood pressure, BMI, waist-to-hip ratio, and number of metabolic syndrome risk factors were all significantly higher in the obese group (Tables 1 and 2). As expected, the obese group was more insulin resistant at baseline (as assessed by Si, ISI HOMA, and Matsuda index) (Table 2). Obese women also exhibited significantly increased AIRg, possibly a compensation to reduced insulin sensitivity.

Effects of OC in All Women

When *all* women were analyzed together, OC use for 6 months did not affect any insulin sensitivity parameters (Si, ISI HOMA, and Matsuda index), nor had any significant effects on insulin or glucose homeostasis (incremental $AUC_{glucose}$ and $AUC_{insulin}$, AIRg, DI, and Sg) (Table 3). Systolic and diastolic blood pressure, BMI, waist circumference and waist-to-hip ratio after 6 months of the OC also were not significantly different from baseline (Table 3). However, the OC significantly increased total cholesterol, LDL, HDL and triglycerides (Table 3). In particular, LDL increased by 20% (from 90 to 108 mg/dL, p<0.001) over the 6 months of OC administration.

Effect of Baseline Obesity Status on Change in Insulin Sensitivity During OC Use

OC use for 6 months resulted in divergent effects on Si as measured by FSIVGTT in lean versus obese women (p=0.0494 for interaction between obesity status and Si time-trend, Figure 1 and Table 2). Other measures of insulin sensitivity, Matsuda index (p=0.0227) and ISI HOMA (p=0.0128) all showed the same divergent effects, suggesting these results were

internally consistent. There were no significant differences between lean and obese women in changes in AIRg, Sg or DI during 6 months of OC (Table 2). There were also no significant differences in changes in fasting glucose, fasting insulin, incremental $AUC_{insulin}$ or incremental $AUC_{glucose}$ between obese and lean women with OC administration (Table 2). Although the effect of OC on fructosamine was not significantly different between the lean and obese groups, when 6-month values were compared to baseline, fructosamine increased significantly only in obese women (from 270 to 320 μmol/L, p=0.0449), suggesting that average glucose levels in obese women increased during OC administration.

Effects of OC on Cardiovascular Risk Factors in Lean and Obese Groups

Use of OC did not change systolic and diastolic blood pressure, BMI, waist circumference, waist-to-hip ratio within either group (Table 2). However, OC significantly increased total cholesterol in both groups. LDL cholesterol increased in both lean (+19.5 ± 14.5 mg/dL, p=0.0002) and obese (+17.3 ± 19.9 mg/dL, p=0.0064) women. As expected, HDL cholesterol also increased in both groups (+7.5 ± 11.0 mg/dL [p=0.024] in lean women and +7.6 ± 4.8 mg/dL [p<0.0001] in obese women). Triglycerides increased significantly only in lean women (+34.2 ± 44.5 mg/dL, p=0.0129). There were no differential changes in any of the above parameters between lean and obese women.

Discussion

We sought to examine the effects of a commonly used combined hormonal OC on carbohydrate metabolism in obese versus lean women. OC use for 6 months appeared to have divergent effects on insulin sensitivity in lean women as compared with obese women. This significant divergence was seen with all measures of insulin sensitivity assessed (Si, Matsuda index, and ISI HOMA).

There have been decades of research on the effects of combined OCs on carbohydrate metabolism (5;17). The earliest studies evaluated combined OCs with a relatively high estrogen dose (3;4), or with progestins with higher androgenicity than those commonly used nowadays (18). Studies performed with lower-dose estrogen and less androgenic progestins have suggested little to no effect on carbohydrate metabolism (7). Using the same OC agent used in our study (ethinylestradiol 35mcg/ norgestimate 0.18/0.215/0.25 mg, or Ortho Tri-Cyclen®), Burkman et al reported no significant changes in fasting glucose or insulin levels, or glycosylated hemoglobin in a 2-year study conducted in 1783 healthy women (7). Similarly, monophasic formulation of this combined OC (35 mcg ethinylestradiol/ 0.25 mg norgestimate) in 42022 women (342,348 menstrual cycles) also suggested little effect on lipid metabolism and fasting glucose (19). However, neither of the of these latter studies directly evaluated insulin sensitivity. Moreover, studies in obese or overweight women, who are at higher risk of metabolic derangements, are lacking, as reported in the recent Cochrane analysis (5).

In this report we observed a differential effect on insulin sensitivity between obese and lean women when given a commonly used combined OC. Our finding is supported by previous evidence suggesting that baseline insulin sensitivity may affect changes in insulin sensitivity during OC administration. In women with and without prior gestational diabetes using OCs containing 30 mcg of ethinylestradiol and triphasic levonorgestrel, insulin sensitivity worsened more in women with a history of gestation diabetes (20). One cross-sectional study reported that obese women taking OCs had higher $AUC_{glucose}$ during OGTT as compared with lean women (16). Finally, ethinylestradiol-cyproterone acetate OC worsened $AUC_{insulin}$ in obese (21), but not lean (22) women with polycystic ovary syndrome. To our knowledge, the present report is the first prospective study describing differential changes in insulin sensitivity between lean and obese women during OC use.

Insulin resistance (ISI HOMA) seems to only worsen in obese women, but not in lean women. Obesity is associated with chronic inflammation (23), which in turn plays a role in insulin resistance (24). Hormone replacement therapy may increase inflammation, as suggested by C-reactive protein concentrations, in post-menopausal women (25). However, whether exogenous hormones in the form of OCs induce inflammation in premenopausal women, and whether obese women are particularly susceptible, are unknown.

We also observed an increase of LDL by almost 20 mg/dL (a 16-20% increase) in both lean and obese women after 6 months of OC. Most, but not all (26;27), studies evaluating cyproterone- (28;29) , desogestrel- (30), drospirenone-(31) , norethindrone- (32), or levonorgestrel-(33) containing OC did not report increases in LDL, even in women with disorders associated with insulin resistance, such as polycystic ovary syndrome, history of gestational diabetes, or diabetes. One study reported an increase in mid-cycle LDL by 2.2% and 5.7% with ethinylestradiol 35mcg and norgestimate over 12 and 24 month (7). The timing of LDL assessment may be important. Wiegratz et al. evaluated lipid profiles at day 2, 11 and 21 at baseline and after 12 cycles of triphasic norgestimate and gestodene OCs (34). At the 12^{th} cycle of OC, LDL concentrations were highest (36% above baseline) during the pill-free week, and then lowered as active pills commenced (10% above baseline). In our current study, because women were assessed during their pill-free week, elevations of LDL by OC may be magnified. However, elevations of LDL over baseline would be expected (34) even if LDL concentrations were to be evaluated at mid-cycle.

This study has several limitations. First, we have only evaluated metabolic parameters during OC administration for 6 months. Since contraception methods are most likely used for longer periods, future studies should evaluate the long-term effects of OCs in obese women. Secondly, we did not include a placebo group in the study, which would be logistically difficult to perform. However, significant changes in metabolic parameters not due to study medications would be unlikely during a relatively brief 6-month period. Lastly, a relatively small number of women were studied. Lack of a significant difference in some parameters, such as $AUC_{glucose}$, between lean and obese women could be due to a lack of power.

In conclusion, lean and obese women seem to exhibit differential changes in insulin sensitivity when given 6 months of a commonly used OC. Both the mechanisms of these differences, such as chronic inflammation, and whether these divergent effects persist long-term, require further investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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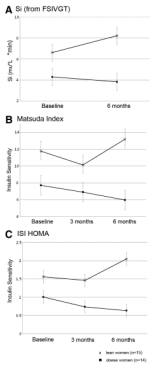

Figure 1. Insulin Sensitivity during 6 months OC administration in Lean and Obese Groups (Mean ± SE)

P-values were for comparisons of insulin sensitivity time trends between lean and obese groups in repeated measures analysis.

Insulin sensitivity assessments included (A) Si (insulin sensitivity) obtained from frequently sampled intravenous glucose tolerance test (FSIVGTT) at baseline and 6 months; (B) Matsuda index of insulin sensitivity obtained from oral glucose tolerance test at baseline, 3 and 6 months; (C) the insulin sensitivity index by homeostatic model assessment (ISI HOMA), using fasting glucose and insulin concentrations at baseline, 3 and 6 months. Lean and obese women exhibited statistically significantly different time trends in (A) Si (p=0.0494), (B) Matsuda index (p=0.0227), and (C) ISI HOMA (p=0.0128), during the 6 months of oral contraceptive use.

Table 1

Baseline Demographic and Clinical Characteristics of the Study Patients

Parameter	Lean Women (n=15)	Obese Women (n=14)	p-value
Age (yr)	21.4 ± 2.3	22.6 ± 5.4	0.4357
BMI (kg/m^2)	21.3 ±1.8	37.1 ±6.7	**<0.0001**
No. of metabolic syndrome risk factors[a]			**0.0017**
0	11	2	
1	4	5	
2	0	4	
3+	0	3	
Race			
Caucasian	10 (66.7)	7 (50)	0.1956
Non-Caucasian	5 (33.3)	7 (50)	

Values were mean ± SD for continuous variables, or number (%) for categorical variables.

[a] P-value was from Chi-square test comparing the number of participants with and without at least two metabolic syndrome risk factors present at baseline

Table 2

Effects of the Combined Oral Contraceptive Pill on Glucose Metabolism, Blood Pressure and Lipid Parameters in Lean and Obese Women

Parameter	Lean Women (n=15)		Obese Women (n=14)		P-value† (baseline comparisons between groups)	P-value‡ (comparisons of OC effects between groups)
	Baseline	6 Months	Baseline	6 Months		
Glucose Metabolism						
Fasting glucose (mg/dL)	81 ± 4.0	82 ± 5.2	85 ± 4.8	86 ± 5.1	**0.0249**	0.9837
Fasting insulin (μIU/mL)	3.6 ± 1.25	3.7 ± 3.40	7.3 ± 5.99	8.7 ± 3.28	**0.0369** *	0.4627
Incremental AUC insulin $_{0\text{-}120}$ (μIU/ml• min)§	3762 ±2453.1	3439 ± 2501.5	4274 ± 2370.0	4301 ± 2416.7	0.4889	0.5102
Incremental AUC glucose $_{0\text{-}120}$ (mg/dL• min)§	2917 ± 2274.3	4208 ± 2325.0	2686 ± 2197.1	2676 ± 2246.2	0.8090	0.2337
Fructosamine (μmol/L)	319 ± 79.7	302 ± 75.8	270 ± 94.0	320 ± 65.7[a]	0.1393	0.1284
Si (min^{-1}/mu/L)¶	6.62 ± 3.69	8.23 ± 3.30	4.36 ± 2.32	3.82 ± 3.12	0.0607	**0.0494**
AIRg (mu • L^{-1} • min) ¶	341.6 ± 209.85	313.5 ± 381.34	803.7 ± 411.82	801.4 ± 346.65	**0.0013** *	0.6878
Sg (1000 • min^{-1})ψ ¶	29.2 (22.6-37.8)	26.4 (18.8-36.9)	25.8 (19.6-33.9)	18.1 (13.1-25.1)	0.4638	0.3502
Disposition Index (AIRg • Si) ¶	2062 ± 1336.1	2080 ± 1657.1	3077 ± 1905.9	2591 ± 1558.9	0.1067	0.4288
ISI HOMA&	1.56 ± 0.501	2.05 ± 0.705	1.01 ± 0.574	0.63 ± 0.659[c]	**0.0088**	**0.0128**
Matsuda index§	11.8 ± 5.02	13.2 ± 4.79	7.7 ± 3.80	6.0 ± 4.54	**0.0188**	**0.0227**
Cardiovascular and Anthropometric Risk Factors						
Systolic blood pressure (mmHg)	105.7 ± 8.6	106.5 ± 12.2	122.1 ± 3.2	123.5 ± 11.7	**0.0010**	0.4826
Diastolic blood pressure (mmHg)	68.0 ± 3.7	66.5 ± 6.8	74.4 ± 1.8	73.4 ± 6.6	**0.0173**	0.4069
BMI (kg/m^2)	21.3 ± 1.8	21.4 ± 4.9	37.1 ± 6.7	37.6 ± 4.7	**<0.0001**	0.1932
Waist circ (cm)	70.2 ± 4.1	70.9 ± 10.7	100.0 ± 14.4	101.0 ± 10.5	**<0.0001**	0.5643
Waist-to-hip ratio	0.73 ± 0.027	0.73 ± 0.057	0.79 ± 0.059	0.81 ± 0.057	**0.0016**	0.8864
Total cholesterol (mg/dL)	155 ± 30.2	181 ± 29.1[d]	164 ± 23.3	194 ± 28.1[d]	0.3613	0.3857

Parameter	Lean Women (n=15)		Obese Women (n=14)		P-value† (baseline comparisons between groups)	P-value‡ (comparisons of OC effects between groups)
	Baseline	6 Months	Baseline	6 Months		
LDL (mg/dL)	84 ± 24.3	104 ± 26.1[c]	95 ± 18.4	113 ± 25.2[b]	0.1607	0.2121
Triglycerides (mg/dL)	72 ± 52.0	106 ± 52.9[b]	72 ± 50.3	83 ± 51.1	0.9711	0.1179
HDL (mg/dL)	53 ± 10.0	61 ± 12.8[a]	51 ± 10.7	58 ± 12.4[d]	0.5306	0.9563
Total/HDL cholesterol ratio	3.0 ± 0.57	3.1 ± 0.78	3.3 ± 0.71	3.5 ± 0.75	0.1281	0.1699

Values are mean ± SD, or geometric means (95% CI) when indicated by the symbol ψ

† Baseline comparisons between groups, performed by independent students' t tests, or

* Welch Anova test (as appropriate for unequal variances)

‡ Comparisons of OC effects between lean and obese groups, performed by repeated measures ANOVA (Time × obesity status)

[a] P<0.05 for comparison between baseline and 6 months within group, performed with paired t tests

[b] P<0.01 for comparison between baseline and 6 months within group, performed with paired t tests

[c] P<0.005 for comparison between baseline and 6 months within group, performed with paired t tests

[d] P≤0.001 for comparison between baseline and 6 months within group, performed with paired t tests

§ Area-under-the-curve (AUC) insulin and glucose, and Matsuda index of insulin sensitivity were obtained via oral glucose tolerance test

¶ Estimates of insulin sensitivity (Si), acute insulin response to glucose (AIRg), glucose effectiveness (Sg), and disposition index (product of AIRg and Si) were derived from frequently sampled IV glucose tolerance test.

& Insulin sensitivity assessed by the homeostatic model assessment (ISI HOMA) were derived from fasting glucose and insulin values.

Table 3

Effects of the Combined Oral Contraceptive Pill on Glucose Metabolism and Cardiovascular Parameters in All Women

	Baseline	24 Weeks	P-Value
Glucose Metabolism			
Fasting insulin (μIU/mL)	5.5 ± 4.7	6.3 ± 3.8	0.0833
Fasting glucose (mg/dL)	83 ± 4.8	83.7 ± 5.4	0.5335
Incremental AUC insulin $_{0\text{-}120}$ (μIU/ml• min)§	4070 ± 2428	3980 ± 1934	0.9912
Incremental AUC glucose $_{0\text{-}120}$ (mg/dL• min)§	2828 ± 2005	3506 ± 2344	0.1178
Fructosamine (μmol/L)	295 ± 88.9	312 ± 70.2	0.4693
Si (min^{-1}/mu/L) ¶	5.36 ± 3.18	5.98 ± 4.01	0.4198
AIRg (mu • L^{-1} • min) ¶	579 ± 394.5	572 ± 451.1	0.5278
β cell function¶	140 ±125.3	135 ± 99.5	0.8339
Sg (1000 • min^{-1}) ¶	32.0 ± 27.3	24.7 ± 10.1	0.2151
Disposition Index (AIRg • S_i)	2582 ± 1710	2401 ± 1518	0.2891
ISI HOMA&	1.25 ± 0.58	1.28 ±1.18	0.3142
Matsuda index§	9.6 ± 4.83	9.0 ± 6.38	0.3719
Cardiovascular and Anthropometric risk factors			
Systolic blood pressure (mmHg)	113 ± 13.9	116 ± 14.1	0.2552
Diastolic blood pressure (mmHg)	71 ± 7.2	70 ± 7.0	0.4490
BMI (kg/m^2)	28.8 ± 9.3	29.5 ± 9.5	0.1234
Waist circumference (cm)	83 ± 19.4	86 ± 18.4	0.2148
Waist-to-hip ratio	0.75 ± 0.08	0.77 ± 0.06	0.2270
Total cholesterol (mg/dL)	160 ± 27.4	188 ± 31.0	**<0.0001**
LDL (mg/dL)	90 ± 22.3	108 ± 27.6	**<0.0001**
Triglycerides (mg/dL)	73 ± 39.9	95 ± 47.6	**0.0049**
HDL (mg/dL)	52 ± 10.4	60 ± 15.0	**<0.0001**
Total/HDL cholesterol ratio	3.1 ± 0.67	3.3 ±0.87	0.0604

Values were Mean ± SD

§Area-under-the-curve (AUC) insulin and glucose, and Matsuda index of insulin sensitivity were obtained via oral glucose tolerance test

¶Estimates of insulin sensitivity (Si), acute insulin response to glucose (AIRg), glucose effectiveness (Sg), and disposition index (product of AIRg and Si) were derived from frequently sampled IV glucose tolerance test.

&Insulin sensitivity assessed by the homeostatic model assessment (ISI HOMA) were derived from fasting glucose and insulin values.