# Metformin Reduces Weight, Centripetal Obesity, Insulin, Leptin, and Low-Density Lipoprotein Cholesterol in Nondiabetic, Morbidly Obese Subjects With Body Mass Index Greater Than 30

C.J. Glueck, R.N. Fontaine, Ping Wang, M.T.R. Subbiah, K. Weber, E. Illig, P. Streicher, Luann Sieve-Smith, T.M. Tracy, J.E. Lang, and P. McCullough

**We studied 31 nondiabetic, habitually (≥5 years) morbidly obese subjects (mean ± SD body mass index [BMI] 43 ± 8.7, median 43). Our specific aim was to determine whether metformin (2.55 g/d for 28 weeks) would ameliorate morbid obesity and reduce centripetal obesity; lipid and lipoprotein cholesterol, insulin, and leptin levels; and plasminogen activator inhibitor activity (PAI-Fx), risk factors for coronary heart disease (CHD). The patients were instructed to continue their prestudy dietary and exercise regimens without change. After 2 baseline visits 1 week apart, the 27 women and 4 men began receiving metformin, 2.55 g/d, which was continued for 28 weeks with follow-up visits at study weeks 5, 13, 21, and 29. Daily food intake was recorded by patients for 7 days before visits then reviewed with a dietitian. Kilocalories per day and per week were calculated. At each visit, fasting blood was obtained for measurement of lipid profile, insulin, leptin, and PAI-Fx. The mean ± SD kilocalories consumed per day, 1,951 ± 661 at entry, fell by week 29 to 1,719 ± 493 ($P$ = .014) but did not differ at weeks 5, 13, and 21 from that at week 29 ($P$ > .2). Weight fell from 258 ± 62 pounds at entry to 245 ± 54 pounds at week 29 ($P$ = .0001). Girth was reduced from 51.8 ± 6.2 to 49.2 ± 4.5 inches ($P$ = .0001). Waist circumference fell from 44.0 ± 6.4 inches to 41.3 ± 5.9 ($P$ = .0001). The waist/hip ratio fell from 0.85 ± 0.09 to 0.84 ± 0.09 ($P$ = .04). Fasting serum insulin, 28 ± 15 $\mu$U/mL at entry, fell to 21 ± 11 $\mu$U/mL at week 29 ($P$ = .0001), and leptin fell from 79 ± 33 ng/mL to 55 ± 27 ng/mL ($P$ = .0001). On metformin, there were linear trends in decrements in weight, girth, waist circumference, waist/hip ratio, insulin, and leptin throughout the study period ($P$ < .007). Low-density lipoprotein (LDL) cholesterol, 126 ± 34 mg/dL at study entry, fell to 112 ± 43 mg/dL at week 29 ($P$ = .001), with a linear trend toward decreasing levels throughout ($P$ = .036). By stepwise linear regression, the higher the entry weight, the larger the reduction in weight on metformin therapy (partial $R^2$ = 31%, $P$ = .001). The greater the reduction in kilocalories consumed per day, the greater the decrease in weight on meformin therapy (partial $R^2$ = 15%, $P$ = .011). The higher the waist/hip ratio at entry, the greater its reduction on metformin therapy (partial $R^2$ = 11%, $P$ = .004). The higher the entry serum leptin, the greater its reduction on metformin therapy (partial $R^2$ =29%, $P$ = .002). The geater the reduction in insulin on metformin, the greater the reduction in leptin (partial $R^2$ = 8%, $P$ = .03). The higher the entry PAI-Fx, the greater the reduction in PAI-Fx on metformin (partial $R^2$ = 43%, $P$ = .0001). Metformin safely and effectively reduces CHD risk factors (weight, fasting insulin, leptin, LDL cholesterol, centripetal obesity) in morbidly obese, nondiabetic subjects with BMI > 30, probably by virtue of its insulin-sensitizing action.**


THE INSULIN-SENSITIZING AGENT metformin induces weight loss in type 2 diabetic subjects[1,2] and in predominantly nondiabetic women with polycystic ovary syndrome.[3,4] Metformin-induced weight loss appears to be mediated by reduction of insulin resistance, with consequent reduction of fasting serum insulin levels.[1-4] Metformin can be given safely to euglycemic subjects because it reduces serum insulin but not glucose levels and does not induce hypoglycemia.[3]

Morbid obesity is closely associated with insulin resistance and hyperinsulinemia.[5,6] Heritable insulin resistance with consequent hyperinsulinemia may lead to weight gain, with subsequent superposition of acquired hyperinsulinemia on inherited hyperinsulinemia.[6] Excess caloric intake with subsequent hyperinsulinemia also contributes to the association of hyperinsulinemia and morbid obesity.[7]

Hyperinsulinemia is a significant independent risk factor for coronary heart disease (CHD) and carotid artery atherosclerosis.[8-11] Insulin resistance with concurrent hyperinsulinemia is associated with the atherogenic insulin resistance syndrome that commonly includes hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, centripetal obesity, type 2 diabetes, high levels of the hypofibrinolytic plasminogen activator inhibitor activity (PAI-Fx),[3] and often hypertension.[11-14]

In the recent UK Prospective Diabetes Study, metformin significantly reduced macrovascular and microvascular disease.[15,16] It was speculated that the reduction in macrovascular disease by metformin reflects a reduction in the atherogenic effects of hyperinsulinemia or a reduction of the insulin-stimulated high PAI-Fx levels.[16]

Leptin, a hormone secreted by adipose cells, is an integral component of the homeostatic loop of body weight regulation.[17] Leptin acts to control food intake and energy expenditure via neuropeptidergic effector molecules within the hypothalamus that suppress food intake.[17] Leptin concentrations increase with obesity and tend to decrease with weight loss, but there is a large variation in the response of leptin levels to decrements in body weight.[18] Leptin correlates with insulin resistance, particularly in women.[19] Hyperleptinemia, alone or acting synergistically with hyperinsulinemia, may play a central role in the genesis of cardiovascular risk factors that constitute the insulin resistance syndrome.[20]

In the current study, our specific aim in 31 nondiabetic,[21]

---

*From the Cholesterol Center, Jewish Hospital, and Molecular Diagnostics Laboratories, Cincinnati, OH.*
*Submitted November 10, 2000; accepted December 22, 2000.*
*Address reprint requests to C.J. Glueck, MD, The Cholesterol Center, Jewish Hospital, ABC Building, 3200 Burnet Ave, Cincinnati, OH 45229.*

*0026-0495/01/5007-0003$35.00/0*
*doi:10.1053/meta.2001.24192*

morbidly obese subjects (27 women, 4 men, median BMI 43) was to determine, in the absence of directed caloric or exercise change, whether metformin therapy (2.55 g/d) for 28 weeks would ameliorate morbid obesity and reduce CHD risk factors, and by what putative mechanisms.

## MATERIALS AND METHODS

### *Study Design*

The study followed a protocol approved by the Jewish Hospital institutional review board, with signed informed consent.

To enter the study, subjects were required to be habitually (for ≥5 antecedent years) morbidly obese (BMI > 30); nonsmokers; nondiabetic[21]; not pregnant or planning pregnancy during the study period; not using estrogens, progestins, oral contraceptives, corticosteroids, or thyroid replacement therapy; and with no endocrine (hypothyroidism, hypercorticism) or pharmacologic (exogenous corticosteroids, androgens, valproic acid) causes for morbid obesity. The diagnosis of type 2 diabetes mellitus was eliminated[21] by fasting plasma glucose < 110 mg/dL (30 subjects) or, in 1 subject with a glucose level of 115 mg/dL, by glucose <140 mg/dL 2 hours after a 75-g oral glucose load. Subjects were also required to have normal renal and liver function. Subjects using pharmacologic or over-the-counter regimens designed to facilitate weight loss were not eligible.

Study eligibility was established by history; physical examination; normal thyroxine, thyroid-stimulating hormone, cortisol, blood urea nitrogen, creatinine, and glucose levels; and normal liver function test tests. Fasting plasma glucose levels were quantitated using a glucose hexokinase method (glucose/HK; Boehringer Mannheim [now Roche Laboratories, Nutley, NJ]).

After 2 baseline visits 1 week apart, subjects started receiving metformin, 850 mg, 3 times per day with meals. Follow-up visits were made at study weeks 5, 13, 21, and 29. The patients were instructed to maintain their prestudy dietary and exercise regimens without change because we wished to determine whether the insulin-sensitizing action of metformin was responsible for weight loss in the absence of systematic, dietitian-guided caloric restriction or increase in energy expenditure. Daily food intake was recorded by patients for 7 days before each visit and reviewed in detail by a registered dietitian at each outpatient visit. Caloric intake was calculated using the Food Processor Program by ESHA research.[22] Habitual exercise levels were recorded at each visit.

At study entry and at each visit, after a ≥12 hour fast, blood was obtained in the morning for measurement of lipid profile, insulin, leptin, and PAI-Fx using previously published methods.[3,11,23] Plasma leptin levels were measured by radioimmunoassay using a DSL-53100 Human Leptin radioimmunoassay kit from Diagnostic System Laboratory Inc (Webster, TX). The assay had a minimum detection limit of 0.2 ng/mL. Samples with extremely high leptin levels were diluted before reassay, and the results were corrected accordingly.

Adherence to metformin therapy was assessed by subjects' use of enough precounted metformin tablets to cover the time between visits.

### *Patients*

Thirty-one nondiabetic[21] morbidly obese patients (BMI > 30), 4 men, 27 women, were newly referred from midwestern states as outpatients to the Jewish Hospital Cholesterol Center for the diagnosis and treatment of morbid obesity.

### *Statistical Analyses*

Repeated-measures analysis[24] was used to compare the mean of the 2 baseline visits before metformin therapy with the 4 subsequent visits on metformin therapy at study weeks 5, 13, 21, and 29 (Tables 1 through 4). Paired Wilcoxon tests[24] were also carried out, comparing baseline levels with levels at week 29. Because the *P* values for the paired Wilcoxon tests were virtually identical to those for repeated-measures analysis, only the latter *P* values are shown in Tables 1

**Table 1. Changes in Weight, Girth, and Waist Circumference in 31 Patients Receiving Metformin, 2.55 g/d, for 28 Weeks**

| Visit | | Weight (lb) | | | |
|---|---|---|---|---|---|
| | | Mean ± SD | Median | *P* (*v* visit 5) | *P* (*v* visit 1) |
| 1 | Pre-Rx* | 258 ± 62 | 254 | .0001 | |
| 2 | On-Rx, 4 weeks | 257 ± 60 | 252 | .0001 | .2 |
| 3 | On-Rx, 12 weeks | 251 ± 58 | 244 | .02 | .0001 |
| 4 | On-Rx, 20 weeks | 247 ± 55 | 236 | .3 | .0001 |
| 5 | On-Rx, 28 weeks | 245 ± 54 | 241 | | .0001 |
| | Linear trend | Decreasing, *P* = .0001 | | | |
| | | Girth (in) | | | |
| 1 | Pre-Rx* | 51.8 ± 6.2 | 50.6 | .0001 | |
| 2 | On-Rx, 4 weeks | 50.9 ± 4.7 | 51.3 | .0001 | .2 |
| 3 | On-Rx, 12 weeks | 50.8 ± 6.0 | 49.5 | .01 | .0001 |
| 4 | On-Rx, 20 weeks | 50.5 ± 5.7 | 50.0 | .07 | .0001 |
| 5 | On-Rx, 28 weeks | 49.2 ± 4.5 | 49.5 | | .0001 |
| | Linear trend | Decreasing, *P* = .0001 | | | |
| | | Waist Circumference (in) | | | |
| 1 | Pre-Rx* | 44.0 ± 6.4 | 43.3 | .0001 | |
| 2 | On-Rx, 4 weeks | 43.2 ± 5.9 | 43.0 | .0001 | .2 |
| 3 | On-Rx, 12 weeks | 42.8 ± 6.5 | 42.3 | .0002 | .0001 |
| 4 | On-Rx, 20 weeks | 42.3 ± 6.3 | 41.0 | .15 | .0001 |
| 5 | On-Rx, 28 weeks | 41.3 ± 5.9 | 40.0 | | .0001 |
| | Linear trend | Decreasing, *P* = .0001 | | | |

* Mean of 2 baseline visits, 1 week apart, before metformin administration.

**Table 2. Changes in Waist Circumference/Girth Ratio and Caloric Intake in 31 Patients Receiving Metformin, 2.55 g/d, for 28 Weeks**

| Visit | | Waist Circumference/Girth | | | |
|---|---|---|---|---|---|
| | | Mean ± SD | Median | $P$ ($v$ visit 5) | $P$ ($v$ visit 1) |
| 1 | Pre-Rx* | 0.850 ± .091 | 0.842 | .039 | |
| 2 | On-Rx, 4 weeks | 0.848 ± .085 | 0.842 | .12 | .60 |
| 3 | On-Rx, 12 weeks | 0.843 ± .083 | 0.843 | .11 | .65 |
| 4 | On-Rx, 20 weeks | 0.838 ± .081 | 0.824 | .87 | .020 |
| 5 | On-Rx, 28 weeks | 0.838 ± .086 | 0.833 | | .039 |
| | Linear trend | Decreasing, $P$ = .0074 | | | |
| | | Kilocalories Consumed per Day | | | |
| 1 | Pre-Rx* | 1,951 ± 661 | 2,057 | .01 | |
| 2 | On-Rx, 4 weeks | 1,844 ± 579 | 1,759 | .2 | .2 |
| 3 | On-Rx, 12 weeks | 1,703 ± 518 | 1,590 | .4 | .001 |
| 4 | On-Rx, 20 weeks | 1,699 ± 524 | 1,521 | .5 | .002 |
| 5 | On-Rx, 28 weeks | 1,719 ± 493 | 1,640 | | .01 |
| | Linear trend | Decreasing, $P$ = .002 | | | |
| | | Kilocalories Consumed per Week | | | |
| 1 | Pre-Rx* | 13,626 ± 4,679 | 14,399 | .017 | |
| 2 | On-Rx, 4 weeks | 12,907 ± 4,053 | 12,316 | .2 | .2 |
| 3 | On-Rx, 12 weeks | 11,918 ± 3,622 | 11,129 | .4 | .001 |
| 4 | On-Rx, 20 weeks | 11,895 ± 3,673 | 10,643 | .5 | .002 |
| 5 | On-Rx, 28 weeks | 12,033 ± 3,453 | 11,481 | | .017 |
| | Linear trend | Decreasing, $P$ = .0026 | | | |

* Mean of 2 baseline visits, 1 week apart, before metformin administration.

through 4. Linear trends in changes in variables on metformin therapy were tested (SAS PROC Mixed).[24]

Correlations between variables at baseline and between changes in variables on metformin therapy were calculated using Spearman's methods.[24]

Stepwise regression[24] was carried out to assess significant independent determinants of changes (Δ) in weight, waist/hip ratio, insulin, leptin, and PAI-Fx on metformin therapy, with the following pretreatment (baseline) explanatory variables: weight, waist/hip ratio, insulin, leptin, PAI-Fx, and glucose. Additional explanatory variables included

**Table 3. Changes in LDL Cholesterol, Fasting Serum Insulin, and Leptin in 31 Patients Receiving Metformin, 2.55 g/d, for 28 Weeks**

| Visit | | LDL Cholesterol (mg/dL) | | | |
|---|---|---|---|---|---|
| | | Mean ± SD | Median | $P$ ($v$ visit 5) | $P$ ($v$ visit 1) |
| 1 | Pre-Rx* | 126 ± 34 | 124 | .001 | |
| 2 | On-Rx, 4 weeks | 109 ± 30 | 103 | .4 | .0001 |
| 3 | On-Rx, 12 weeks | 113 ± 34 | 105 | .8 | .003 |
| 4 | On-Rx, 20 weeks | 116 ± 33 | 112 | .4 | .01 |
| 5 | On-Rx, 28 weeks | 112 ± 43 | 108 | | .001 |
| | Linear trend | Decreasing, $P$ = .036 | | | |
| | | Insulin (μU/mL) | | | |
| 1 | Pre-Rx* | 28 ± 15 | 28 | .0001 | |
| 2 | On-Rx, 4 weeks | 25 ± 16 | 21 | .02 | .04 |
| 3 | On-Rx, 12 weeks | 23 ± 12 | 20 | .6 | .0001 |
| 4 | On-Rx, 20 weeks | 23 ± 12 | 21 | .4 | .0003 |
| 5 | On-Rx, 28 weeks | 21 ± 11 | 17 | | .0001 |
| | Linear trend | Decreasing, $P$ = .0001 | | | |
| | | Leptin (ng/mL) | | | |
| 1 | Pre-Rx* | 79 ± 33 | 72 | .0001 | |
| 2 | On-Rx, 4 weeks | 71 ± 28 | 64 | .0001 | .011 |
| 3 | On-Rx, 12 weeks | 64 ± 28 | 60 | .013 | .0001 |
| 4 | On-Rx, 20 weeks | 61 ± 27 | 56 | .27 | .0001 |
| 5 | On-Rx, 28 weeks | 55 ± 27 | 52 | | .0001 |
| | Linear trend | Decreasing, $P$ = .0001 | | | |

* Mean of 2 baseline visits, 1 week apart, before metformin administration.

**Table 4. Changes in PAI-Fx in 31 Patients Receiving Metformin, 2.55 g/d for 28 Weeks**

| | | PAI-Fx (U/mL) | | | |
|---|---|---|---|---|---|
| Visit | | Mean ± SD | Median | P (v visit 5) | P (v visit 1) |
| 1 | Pre-Rx* | 23.5 ± 19.2 | 16.9 | .3 | |
| 2 | On-Rx, 4 weeks | 16.2 ± 9.7 | 15.6 | .04 | .002 |
| 3 | On-Rx, 12 weeks | 20.7 ± 10.9 | 17.8 | .8 | .2 |
| 4 | On-Rx, 20 weeks | 21.6 ± 14.1 | 20.1 | 1.0 | .3 |
| 5 | On-Rx, 28 weeks | 21.0 ± 14.8 | 16.5 | | .3 |
| | Linear trend | | Not significant | | |

* Mean of 2 baseline visits, 1 week apart, before metformin administration.

the following changes on metformin therapy, excluding overlap in each regression model of dependent and explanatory variables: Δweight, Δwaist/hip ratio, Δinsulin, Δleptin, ΔPAI-Fx, Δkilocalories consumed per day, Δkilocalories consumed per week, Δcholesterol, Δtriglyceride, and ΔHDL cholesterol. Additional explanatory variables included age and sex.

### *Study Limitations*

The major limitation of the current study is the absence of a placebo group. However, the subjects all had been morbidly obese (BMI > 30) for 5 years or more before study entry, and previous weight loss programs had failed in all cases. Moreover, to carry out power and sample size calculations for a planned future placebo-controlled, double-blind study, we needed data on mean and SD of changes in weight, caloric intake, insulin, and leptin on metformin therapy, none of which were available for the very morbidly obese before the current study.

## RESULTS

### *Patients*

The 27 women and 4 men, ages 20 to 67 , median 37 years, were all white. By selection, each subject had a BMI > 30 at study entry. Fasting plasma glucose levels were normal[21] (<110 mg/dL) in 30 of the 31 subjects; 1 subject had a level of 115 mg/dL and a normal level (132 mg/dL) 2 hours after glucose load. Mean ± SD fasting plasma glucose was 94 ± 10 mg/dL (median, 95 mg/dL). Of the 31 subjects, 21 (68%) had high fasting serum insulin levels (≥20 μU/mL) at entry before metformin therapy, and 14 (45%) had high PAI-Fx (>18.2 U/L). Leptin levels at entry were high (≥15 ng/mL) in all 31 subjects (100%).

### *Weight, Girth, Waist, Lipid Profile, Insulin, Leptin, and PAI-Fx*

Tables 1 through 4 show mean ± SD and median levels for the major measured variables at study entry (visit 1 = mean of visits 0 and 1, before metformin therapy). Mean ± SD weight fell from 258 ± 62 pounds at entry to 245 ± 54 at week 29 (*P* = .0001; Table 1). Girth decreased from 51.8 ± 6.2 to 49.2 ± 4.5 inches (*P* = .0001; Table 1). Waist circumference decreased from 44.0 ± 6.4 to 41.3 ± 5.9 inches (*P* = .0001; Table 1). On metformin therapy, there were linear trends over time for decrements in weight, girth, and waist circumference (*P* = .0001 for all). The ratio of waist circumference to girth decreased from 0.85 ± 0.09 to 0.84 ± 0.09 (*P* = .04; Table 2). On metformin therapy, there was a linear trend toward a decreasing waist/hip ratio (*P* = .007; Table 2).

Mean ± SD kilocalories consumed per day, 1,951 ± 661 at study entry, decreased by week 29 to 1,719 ± 493 (*P* = .014), but values at weeks 5, 13, and 21 did not differ from those at week 29 (*P* > .2; Table 2). Kilocalories consumed per week, 13,626 ± 4,679 at entry, decreased by week 29 to 12,033 ± 3,453 (*P* = .017), but values at weeks 5, 13, and 21 did not differ from those at week 29 (Table 2). There were no changes in habitual physical activity during the study.

Insulin, 28 ± 15 μU/mL at entry, decreased to 21 ± 11 at week 29 (*P* = .0001; Table 3). Leptin, 79 ± 33 ng/mL (median, 72 ng/mL) at entry, decreased on metformin therapy to 55 ± 27 ng/mL (median, 52 ng/mL; *P* = .0001; Table 3). On metformin therapy, there were linear trends over time for decrements in insulin and leptin (*P* = .0001; Table 3).

Low-density lipoprotein (LDL) cholesterol, 126 ± 34 mg/dL at study entry, fell to 112 ± 43 at week 29 (*P* = .001), with a linear trend toward decreasing levels throughout (*P* = .036; Table 3).

Total plasma cholesterol fell from 201 ± 34 mg/dL at entry to 186 ± 42 mg/dL on metformin therapy (*P* = .0005). There were no changes (*P* > .05) in triglyceride or HDL cholesterol levels. Although PAI-Fx decreased after 4 weeks on metformin therapy, this reduction was not sustained throughout the study (Table 4).

### *Correlates of Weight, Insulin, Leptin, and PAI-Fx and Their Changes on Metformin*

At study entry, weight was correlated positively with fasting serum insulin (*r* = .43, *P* = .015). Waist circumference was inversely correlated with HDL cholesterol (*r* = −.35, *P* = .053), and was positively correlated with LDL cholesterol (*r* = .43, *P* = .017), insulin (*r* = .52, *P* = .003), and PAI-Fx (*r* = .53, *P* = .002). The waist/hip ratio was positively correlated with triglycerides (*r* = .40, *P* = .026), insulin (*r* = .53, *P* = .002), the insulin/glucose ratio (*r* = .53, *P* = .002), and PAI-Fx (*r* = .68, *P* = .0001) and was inversely correlated with HDL cholesterol (*r* = −.40, *P* = .028). Fasting serum insulin was positively correlated with PAI-Fx (*r* = .60, *P* = .0003). Fasting serum leptin was positively correlated with girth (*r* = .45, *P* = .01).

At study entry, kilocalories consumed per week did not correlate (*P* > .10) with any of the other measured variables, including weight (*r* = .16, *P* = .40), girth (*r* = .22, *P* = .23), and waist circumference (*r* = .10, *P* = .58).

By stepwise linear regression, the higher the entry weight, the larger the reduction in weight on metformin therapy (partial $R^2$ = 31%, *P* = .001), and the greater the reduction in calories, the greater the decrease in weight on meformin therapy (partial $R^2$ = 15%, *P* = 0.011). The higher the waist/hip ratio at entry, the larger the reduction in waist/hip ratio on metformin therapy

($R^2$ = 11%, $P$ = .004). When entry insulin level was high, there was a lesser decrease in the waist/hip ratio on metformin therapy (partial $R^2$ = 16%, $P$ = .02). The higher the pretreatment insulin, the greater the reduction in insulin on metformin therapy (partial $R^2$ = 43%, $P$ = .0001).

The higher the entry serum leptin level, the greater the reduction in serum leptin on metformin therapy (partial $R^2$ = 29%, $P$ = .002). The greater the reduction in insulin, the greater the reduction in leptin on metformin therapy (partial $R^2$ = 8%, $P$ = .03).

The higher the entry PAI-Fx, the greater the reduction in PAI-Fx on metformin therapy (partial $R^2$ = 43%, $P$ = .0001). The higher the entry insulin level, the smaller the reduction in PAI-Fx on metformin therapy (partial $R^2$ = 15%, $P$ = .005).

## DISCUSSION

Morbid obesity in the current study was closely associated with multiple CHD risk factors that represent the atherogenic insulin resistance syndrome[11-14]: hyperinsulinemia, hyperleptinemia, low HDL cholesterol, high triglycerides, high LDL cholesterol, and high PAI-Fx. Hence, as in the current report, safe and effective approaches to amelioration of obesity should reduce CHD risk. In the current study, without any directed caloric restriction or increase in habitual exercise, metformin safely and effectively reduced weight, waist circumference, girth, waist/hip ratio, fasting serum insulin, leptin, and LDL cholesterol in morbidly obese, nondiabetic subjects with BMI $>$ 30, in part by virtue of its insulin-sensitizing action. However, despite a mean weight reduction of 13 pounds, the subjects remained obese after 28 weeks on metformin therapy.

In the current study, only 15% of weight loss and none of the change in the waist/hip ratio could be attributed to self-directed reductions in caloric intake during metformin treatment. The relatively low caloric intake at entry and on metformin therapy reported by these morbidly obese subjects probably reflects systematic underreporting of caloric intake, as previously described.[25] However, we speculate that underreporting of caloric intake should be internally consistent before and during metformin therapy.

Hyperinsulinemia probably augments CHD risk directly, as well as through its inverse effects on HDL cholesterol level and positive associations with type 2 diabetes, obesity, triglycerides, PAI-Fx, leptin, and hypertension.[8-16,20,26,27] Metformin, by improving insulin sensitivity and decreasing serum insulin levels compared with to sulphonylureas and exogenous insulin, reduces macrovascular events in type 2 diabetes.[15,16] The insulin-sensitizing drug metformin might have promise in primary and secondary CHD prevention not only in patients with type 2 diabetes,[15,16] but also in euglycemic, hyperinsulinemic subjects.[11,19,20,26]

We recognize that fasting serum insulin is not the gold standard for assessment of insulin sensitivity, as represented by the glucose clamp technique.[28] Fasting serum insulin level has been used as a crude, simple, and practical surrogate index of insulin sensitivity[11,29-31] but explains only 30% to 40% of the variance in glucose clamp–determined insulin sensitivity.[32] The progression from impaired glucose tolerance to type 2 diabetes is thought to reflect a decrease in insulin secretion rather than an increase in insulin resistance.[33]

Plasma leptin correlates with insulin resistance.[19] Hyperleptinemia, alone or in conjunction with hyperinsulinemia, contributes to the cluster of cardiovascular risk factors that make up the insulin resistance syndrome.[20] In the current report, mean leptin decreased 30% on metformin therapy, and reductions in insulin were independently associated with reductions in leptin. These findings were similar to those of Pasquali et al[34] in obese women with polycystic ovary syndrome, in which metformin decreased both leptin and fasting serum insulin. Morin-Papunen et al,[35] in 26 obese women with polycystic ovary syndrome, also showed that metformin decreased serum leptin concentrations. In obese subjects with high serum leptin levels, treatment with exogenous leptin may produce weight loss, presumably by overcoming leptin insensitivity.[36] The interaction between central and peripheral signals for the control of food intake is caused by leptin, which can modulate the activity of neuropeptide Y and other peptides in the hypothalamus that are known to affect eating behavior.[37] Feedback between leptin and neuropeptide Y may be disturbed in obesity and in polycystic ovary syndrome.[37]

Metformin, probably by virtue of its insulin-sensitizing action, appears to have promise in euglycemic, morbidly obese subjects as a safe and effective weight loss agent[3,26,35] that reduces centripetal obesity, with an added bonus of reduction of the CHD risk factors hyperinsulinemia, hyperleptinemia, and high LDL cholesterol levels.

## REFERENCES

1. Hauner H: The impact of pharmacotherapy on weight management in Type 2 diabetes. Int J Obes Relat Metab Disord 23:S12-S17, 1999 (suppl 7)

2. Lee A, Morley JE: Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. Obes Res 6:47-53, 1998

3. Glueck CJ, Wang P, Fontaine R, et al: Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome. Metabolism 48:511-519, 1999

4. Kolodziejczyk B, Duleba AJ, Spaczynski RZ, et al: Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril 73:1149-1154, 2000

5. Tounian P, Frelut ML, Parlier G, et al: Weight loss and changes in energy metabolism in massively obese adolescents. Int J Obes Relat Metab Disord 23:830-837, 1999

6. Gerich JE: The genetic basis of type 2 diabetes mellitus: Impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev 19: 491-503, 1998

7. Wannamethee SG, Shaper AG: Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 22:1266-1272, 1999

8. Folsom AR, Szklo M, Stevens J, et al: A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 209:935-942, 1997

9. Burchfiel CM, Sharp DS, Curb JD, et al: Hyperinsulinemia and cardiovascular disease in elderly men: The Honolulu Heart Program. Arterioscler Thromb Vasc Biol 18:450-457, 1998

10. Bonora E, Willeit J, Kicchl S, et al: Relationship between insulin and carotid atherosclerosis in the general population. The Bruneck Study. Stroke 28:1147-1152, 1997

11. Glueck CJ, Lang JE, Tracy T, et al: Contribution of fasting

hyperinsulinemia to prediction of atherosclerotic cardiovascular disease status in 293 hyperlipidemic patients. Metabolism 11:1437-1444, 1999

12. Bao W, Srinivasan SR, Berenson GS: Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults. The Bogalusa Heart Study. Circulation 93:54-59, 1996

13. Jeppesen J, Facchini FS, Reaven GM: Individuals with high total cholesterol/HDL cholesterol ratios are insulin resistant. J Intern Med 243:293-8, 1998

14. Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998

15. UK Prospective Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with Type 2 diabetes (UKPDS 34). Lancet 352:854-865, 1998

16. UK Prospective Study Group: UK Prospective Diabetes Study 24: Relative efficacy of sulfonylurea, insulin, and metformin therapy in newly diagnosed non-insulin dependent diabetes with primary diet diet failure followed for six years. Ann Intern Med 128:165-175, 1998

17. Inui A: Cancer anorexia-cachexia syndrome: Are neuropeptides the key? Cancer Res 59:4493-4501, 1999

18. von Rossum EF, Nicklas BJ, Dennis KE, et al: Leptin responses to weight loss in postmenopausal women: relationship to sex-hormone binding globulin and visceral obesity. Obes Res 8:29-35, 2000

19. Panarotto D, Ardilouze JL, Tessier D, et al: The degree of hyperinsulinemia and impaired glucose tolerance predicts plasma leptin concentrations in women only: A new exploratory paradigm. Metabolism 49:1055-62, 2000

20. Zimmet P, Boyko EJ, Collier GR, et al: Etiology of the metabolic syndrome: Potential role of insulin resistance, leptin resistance, and other players. Ann NY Acad Sci 892:25-44, 1999

21. American Diabetes Association: Screening for type 2 diabetes. Diabetes Care 20:1183-1197, 1997 (suppl 1)

22. Food Processor for Windows. Nutrition Analysis and Fitness Software, version 7.4. Salem, OR, ESHA Research, 1999

23. Glueck CJ, Glueck HI, Tracy T, et al: Relationship between Lp(a), lipids, apolipoproteins, basal and stimulated fibrinolytic regulators, and D-dimer. Metabolism 42:236-246, 1993

24. SAS/STAT Software: Changes and Enhancements Through Release 6.12. Cary, NC, SAS Institute, February 1997

25. Goris AH, Westerterp-Plantenga MS, Westerterp KR: Undereating and underrecording of habitual food intake in obese men: Selective underreporting of fat intake. Am J Clin Nutr 71:130-134, 2000

26. Velazquez E, Mendoza SG, Wang P, et al: Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein (a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 46:454-457, 1997

27. Bavenholm P, de Faire U, Landou C, et al: Progression of coronary artery disease in young male post-infarction patients is linked to disturbances of carbohydrate and lipoprotein metabolism and to impaired fibrinolytic function. Eur Heart J 19:402-410, 1998

28. DeFronzo RA, Tobin JD, Andres R: The glucose clamp technique: a method for the quantification of beta cell sensitivity to glucose and of tissue sensitivity to insulin. Am J Physiol 237:E214-E223, 1979

29. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance test. N Engl J Med 320:703-706, 1989

30. Fontbonne A, Charles MA, Thibult N, et al: Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: The Paris Prospective Study, 15 year follow-up. Diabetologia 34:356-361, 1991

31. Haffner SM, Valdez RA, Hazuda HH, et al: Prospective analysis of the insulin resistance syndrome (syndrome X). Diabetes 41:715-722, 1992

32. Laakso M: How good a marker is insulin level for insulin resistance? Am J Epidemiol 137:959-965, 1993

33. Saad MF, Knowler WC, Pettitt DJ, et al: The natural history of impaired glucose tolerance in the Pima Indians. N Engl J Med 319: 1500-1507, 1988

34. Pasquali R, Gambineri A, Biscotti D, et al: Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 85:2767-2774, 2000

35. Morin-Papunen LC, Koivunen RM, Tomas C, et al: Decreased serum leptin concentrations during Metformin therapy in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 83:2566-2568, 1998

36. Heymsfield SB, Greenberg AS, Fujioka K, et al: Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. JAMA 282:1568-1575, 1999

37. Baranowska B, Radzikowska M, Wasilewska-Dziubinska E, et al: Neuropeptide Y, leptin, galanin and insulin in women with polycystic ovary syndrome. Gynecol Endocrinol 13:344-351, 1999