Metformin and Carbohydrate-Modified Diet: A Novel Obesity Treatment Protocol

Preliminary Findings From a Case Series of Nondiabetic Women With Midlife Weight Gain and Hyperinsulinemia

Harriette R. Mogul, MD, MPH, Stephen J. Peterson, MD,† Bernard I. Weinstein, PhD,‡ Shaochun Zhang, MD, MS,* and A. Louis Southren, MD**

The authors conducted a retrospective analysis of a new obesity treatment protocol, metformin and hypocaloric, carbohydrate-modified diet, in high-risk, nondiabetic hyperinsulinemic women with progressive midlife weight gain (refractory to diet and exercise). Thirty consecutive nondiabetic women with glucose-mediated area-under-the-curve (AUC) insulin elevations (≥100μU/mL) in two body mass index (BMI) categories (group I: 25 to 32.9 kg/m^2 and group II: 33 to 41.7 kg/m^2) participated in a 1-year treatment program of metformin (mean daily doses of 1,500 mg/day [group I] and 2,000 mg/day [group II]) and carbohydrate-modified dietary regimens. Follow-up body weight (at 3, 6, and 12 months), percentage of patients meeting goal weight attainment (10% reduction in body weight or BMI normalization), and fasting insulin levels (as available) are reported in 26 women (18/18 in group I and 8/12 in group II) who returned for one or more follow-up visits. Significant weight loss was observed at 3, 6, and 12 months in both group I (3.47 [SE 0.68], 6.41 [0.72], and 8.06 [0.96] kg, $P < 0.0001$) and group II (4.4 [0.8], 9.7 [2.3], 15.1 [3.3], $P = 0.001$, 0.004, 0.011). Twenty-five of 26 (96%) patients lost ≥5% of their body weight at 6 months and 21/26 (81%) patients lost ≥10% of their body weight at 12 months. Posttreatment fasting insulin decrement (−35.5 [8.2]%) was the most significant predictor of 1-year weight loss (R^2=0.656, regression coefficient = 0.810, $P = 0.005$). Following completion of the 1-year intervention study, weight stabilization (within 1 kg) was observed at a 6-month surveillance in 8/9 patients who attained goal weight and continued metformin without additional nutritional counseling, in contrast to weight gain (≥4 kg or 50% of lost weight) in 5/6 patients who discontinued metformin. The authors concluded that metformin and carbohydrate-modified hypocaloric diet could be an effective novel treatment for long-term weight management in nondiabetic, hyperinsulinemic women. **Key words:** Obesity—Insulin resistance—Menopause—Hyperinsulinemia—Weight gain.

The increasing prevalence and adverse health consequences of obesity are widely recognized, and its treatment has been designated an important public health priority. The emerging perception of obesity as a chronic medical condition[1] and the increasing acceptability of medication as an adjunct to diet and exercise in lifelong obesity management[2–4] has stimulated an intense search for effective new therapeutic agents. No medications are currently US Food and Drug Administration–approved for more than 1 year of treatment. The development of new antiobesity drugs and demonstration of their long-term safety, critical to chronic administration, will require considerable time. A number of available, long-used medications, however, produce weight loss when used for other indications and may be an alternative source of pharmacotherapies. Evaluation of such drugs—especially those with well-established long-term safety profiles—could generate novel and, most impor-

Heart Disease 2001;3:285–292
Copyright © 2001 Lippincott Williams & Wilkins, Inc.
*From the *Divisions of Endocrinology and †General Internal Medicine, ‡Department of Medicine and Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, New York.*

Address correspondence to Dr. Harriette R. Mogul, Munger Pavilion, Room 409, Valhalla, NY 10595; E-mail: hrmogul@nymc.edu

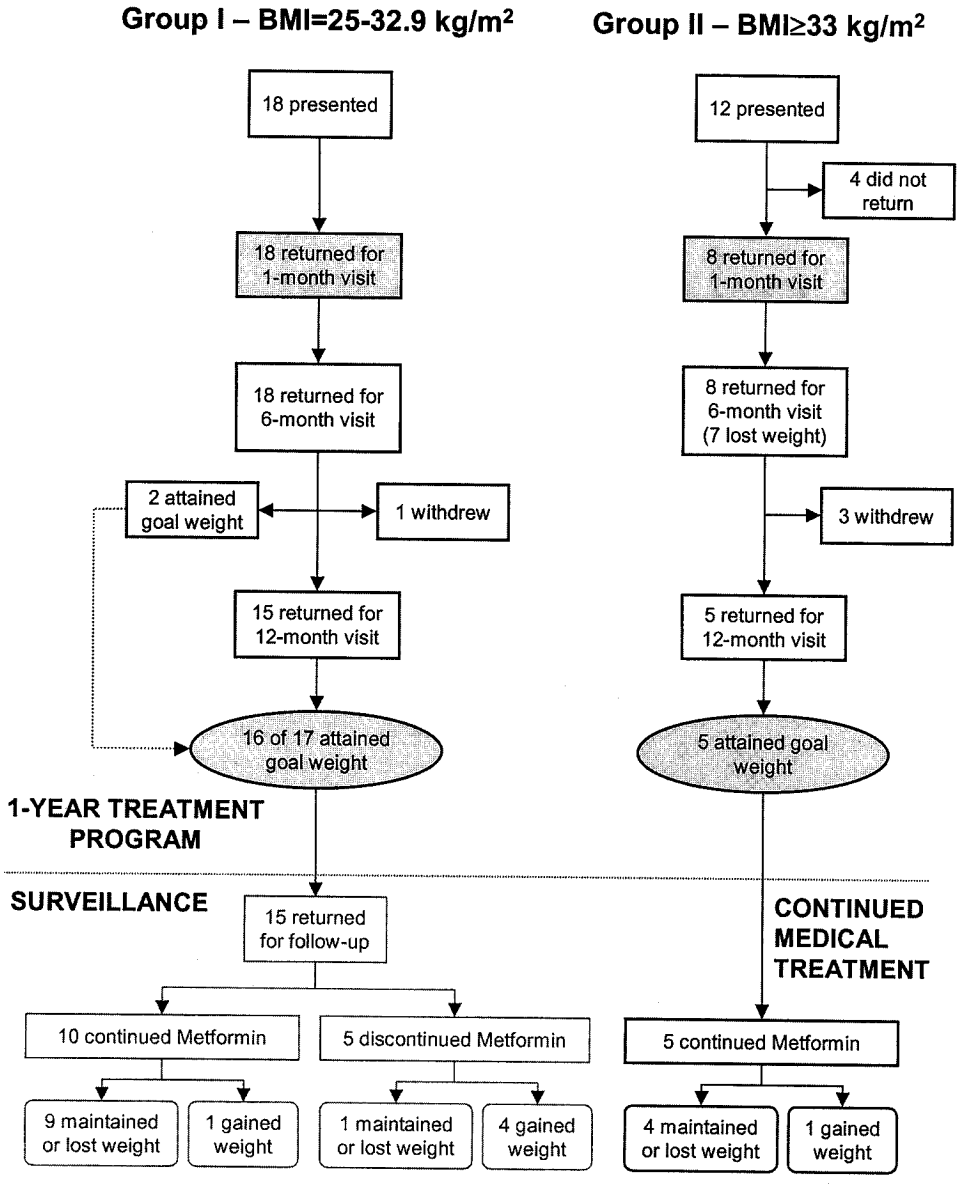

Figure 1. Patient flow diagram. BMI = body mass index.

tantly, immediately accessible antiobesity treatments, to address the alarming, escalating adiposity of Americans.

Metformin has been widely used and well tolerated in the treatment of patients with type 2 diabetes for several decades. Its use has been associated with weight loss in placebo-controlled, randomized clinical trials[5] and prospective studies of diabetic subjects,[6] nondiabetic Europeans with central fat distribution,[7] and in insulin-resistant women with polycystic ovarian syndrome,[8–11] and men with human immunodeficiency virus (HIV)-related lipodystrophy.[12] Short-term studies have demonstrated that metformin reduces total caloric intake.[13,14] This collective research suggests that metformin could be a useful therapeutic agent for long-term weight management. Metformin has not been previously evaluated in the United States as an adjunct to dietary intervention in the primary treatment of obesity or hyperinsulinemia in nondiabetic subjects.

The goals of this report are 1) to evaluate a potential new and effective strategy for weight reduction—metformin plus carbohydrate modification and moderate caloric restriction—in a distinct population of nondiabetic, hyperinsulinemic women with midlife weight gain and other risk factors for the development of diabetes and cardiovascular disease; and 2) to evaluate preliminary data on the efficacy of this regimen in patients followed in a clinical setting, as a prelude to contemplating scientifically rigorous, broad-scale, clinical treatment trials in other, comparably insulin resistant, patient populations. The treatment protocol was designed to evaluate our hypotheses that in specific subpopulations—patients with glucose-mediated hyperinsulinemia—weight gain is a consequence of insulin overproduction, and pharmacologic and dietary strategies that target hyperinsulinemia will promote weight loss.

METHODS

Patients

A retrospective analysis was conducted on 30 consecutive hyperinsulinemic women (glucose-mediated area-un-

TABLE 1
Baseline clinical characteristics of two study groups by weight range category

Characteristics	Group I (BMI: 25–32.9 kg/m^2) n = 18		Group II (BMI: >33 kg/m^2) n = 8		*P* value
	Mean	SE	Mean	SE	
Age, y	53.6	1.5	47.3	1.6	0.020*
Weight, kg/lbs	74.0/162.9	1.9/4.1	99.4/219.0	4.5/9.9	0.000*
Body mass index, kg/m^2	29.3	1.3	38.9	5.6	0.001*
AUC insulin, μU/mL	150.4	15.1	138.5	22.6	0.661
Fasting glucose, mg/dL	97.2	3.2	93.0	4.1	0.447
2-Hour glucose, mg/dL	126.2	16.5	114.8	9.0	0.660
Fasting insulin, μU/mL	12.6	1.3	13.4	1.2	0.700
2-Hour insulin, μU/mL	73.7	10.4	68.8	10.6	0.772
Systolic BP, mmHg	128.9	3.8	132.5	5.3	0.598
Diastolic BP, mmHg	80.4	2.5	77.3	3.0	0.456
Total cholesterol, (mmolL)/(mg/dL	5.8/225.9	0.2/8.3	6.2/240.0	0.6/24.8	0.496
HDL cholesterol, (mmolL)/(mg/dL)	1.4/53.7	0.1/3.3	1.4/54.5	0.1/4.0	0.905
LDL cholesterol, (mmolL)/(mg/dL)	3.7/143.5	0.2/7.3	3.7/144.3	0.7/26.8	0.969
Triglycerides, (mmolL)/(mg/dL)	1.7/152.9	0.3/30.5	2.2/197.3	0.4/34.9	0.488

To convert glucose from mg/dL, multiply by 0.05551. To convert insulin from μU/mL to pmol/L, multiply by 7.175.
BMI = body mass index; AUC = area under the curve; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

der-the-curve [AUC] insulin levels >100 μU/mL) who presented to an Endocrine Faculty Practice–based weight management program at an academic medical center and participated in a 1-year obesity treatment plan. All patients had been referred for medically supervised weight management because of the presence of documented cardiovascular risk factors and failure to lose weight with conventional medical care—caloric restriction plus participation in regular exercise (at a minimum level of three moderate-intensity 30-minute sessions per week) conforming to current public health guidelines.[15] All patients initially complained of midlife weight gain (defined as an increment of 20 pounds or more since the 20s); all had documented hyperinsulinemia following the performance of standard (75-gram) oral glucose tolerance tests, undertaken as part of a formal cardiovascular risk assessment at either our affiliated Menopausal Health Program or General Internal Medicine Practice Group. The final data set represents all women in two body mass index (BMI) categories seen consecutively over an 18-month period who returned for at least one follow-up treatment visit, independent of outcome (n = 26). Group I consisted of 18 (of a total of 18 women initially presenting) patients who were overweight to mildly obese (BMI in the 25 to 32.9 kg/m^2 range, a defined risk category for women[16]) and group II consisted of eight obese (BMI 33 to 41.7 kg/m^2) women (from a total of 12 who initially presented).

Assessment and Treatment

As part of their initial evaluation in The Weight Management Program, patients completed a 400-item health history questionnaire. The survey included demographic variables, family history, medical systems review, lifetime weight and dietary history, assessment of appetite, eating behaviors and exercise patterns, and validated psychometric instruments, such as the Center for Epidemiologic Studies for Depression (CES-D) and CAGE (Cut down, Annoyed, Guilty, and Eye opener) instruments. All patients gave written permission for record review. Eligibility for the metformin/dietary treatment protocol required 1) self-reported or physician-documented progressive weight gain in the prior year, despite regular exercise (at a minimum level of three 30-minute intervals/week) and attempted adherence to weight-reduction diet for a minimum of 6 months; 2) evidence of glucose-mediated hyperinsulinemia, based on an AUC insulin response to a standard 75-g oral glucose tolerance test ≥100 μU/mL; and 3) presence of at least one concomitant risk factor for the development of diabetes or cardiovascular disease, or both, such as hypertension, dyslipidemia, or truncal adiposity, as traditionally defined.

Patients were treated with metformin in combination with a carbohydrate-modified, hypocaloric diet. Metformin was administered, in gradually escalating doses, with suppression of food cravings and appetite as a clinical end point. Treatment was initiated with 500 mg at dinner time and increased by 500 mg after the first week. Dosage was adjusted at the 1- and 3-month visits and subsequently increased to mean daily doses of 1,500 mg/day (range 1,000 to 2,850 mg) in group I and 2,000 mg/day (range 1,500 to 2,850 mg) in group II. The nutritional intervention consisted of a flexible food plan, using a variant of the American Diabetes/American Dietetic Association exchange system, with a recommended 600-kcal/day deficit and total caloric intake in the range of 1,200 to 1,800 calories/day. The dietary composition approximated 40 to 45% of calories from carbohydrates, 30 to 35% from protein, and 20 to 25% from fat. The cornerstone of the dietary regimen was the elimination of all added simple (free) sugars, with reduction of both complex carbohydrates and fat exchanges to a maximum of three to four each per day. Patients were encouraged to increase their intake of vegetables and low-fat protein, to limit fruits and other carbohydrates to high-fiber/low-glycemic-index selections, and

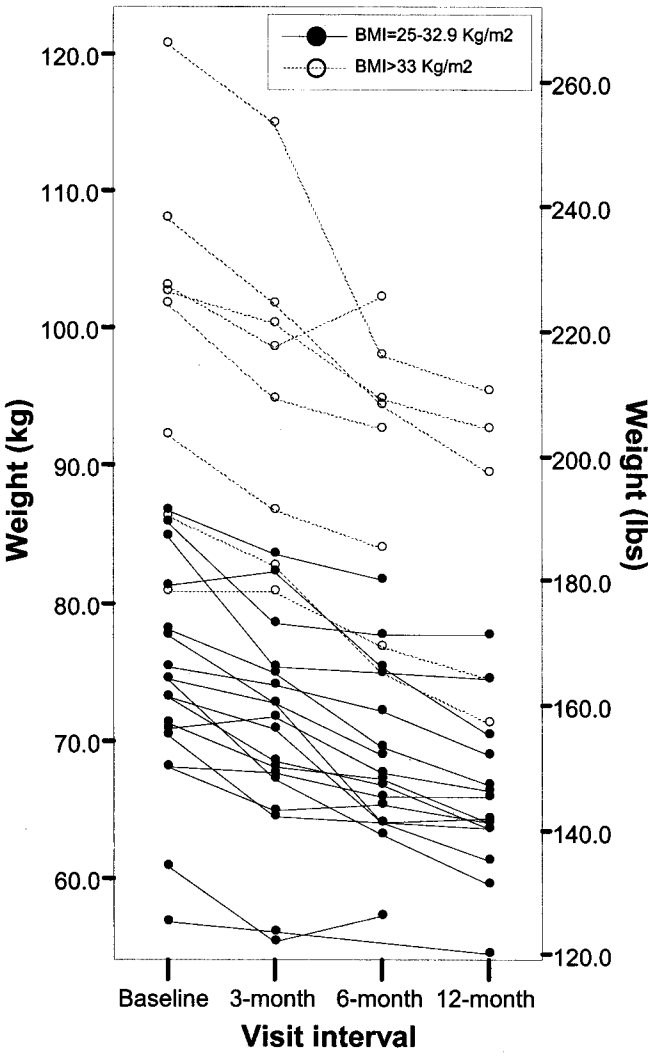

Figure 2. Body weight at specified treatment intervals following initiation of metformin and dietary intervention in 26 patients. BMI = body mass index. (Note: Overlapping values account for decreased number of data points at 12 months.)

to avoid densely caloric fat- and sugar-laden foods. Sample menus were created to incorporate specific individual food preferences to promote long-term dietary compliance. Clinical care consisted exclusively of 30-minute encounters with a treating physician to record body weight and blood pressure; review medication side effects; evaluate changes in appetite, food cravings, and food intake patterns; and provide additional nutritional counseling and behavior modification as indicated. Patients in group I were seen typically at 1, 3, 6, and 12 months after the initiation of metformin for a mean number of five treatment visits; patients in group II had a mean number of seven treatment visits with additional visits, typically, at 2 and 9 months.

Patients enrolling in the Weight Management Program were advised that the focus of the program was adoption of long-term health-enhancing dietary changes and lifestyle modification with modest (5 to 15% 1-year) weight reduction. A 1-year treatment goal of a 10% reduction in body weight (or normalization of BMI <25 kg/m^2]) and realistic long-term treatment objectives (individualized by initial weight and personal long-range expectations) were outlined at the onset of the program. Patients were advised that treatment goals would be reassessed at the completion of the 1-year intervention program. At that time, they could elect to continue the medically supervised hypocaloric diet and behavior modification for additional weight reduction or receive a weight maintenance diet, with or without metformin as desired, and return at 6-month intervals for surveillance or medication renewal. Group I participants in the lower BMI range were also advised that they could withdraw from the active program if they attained goal weight at an earlier interval.

Statistical Analyses

Analysis of variance (ANOVA) was used to compare the baseline characteristics of the two BMI groups. Paired *t*-tests and linear regression analyses were used to evaluate absolute and relative changes in weight and fasting insulin at 3-, 6-, and 12-month treatment intervals. An intention-to-treat analysis, based on all patients who returned for one posttreatment visit, was used to calculate the percentage of patients achieving 5 and 10% reductions in body weight at the indicated time points. Maximum-likelihood estimator-based logistic regression was used to evaluate predictors of goal weight attainment. The Statistical Package for the Social Sciences (SPSS, version 10.0) was used to conduct the analyses and to generate graphics. All *t*-tests were two-sided with *P* values reported as exact. The group means are reported with standard error (SE). All reported figures represent SPSS computer-generated outputs. (SPSS outputs do not allow the symbol ≥. Therefore, computer-generated graphics do not denote BMI category as ≥33 kg/m^3.)

RESULTS

The final data set consisted of 26 women who returned for at least one posttreatment visit (Fig 1). Twenty-five women were white and one Asian American; the mean age was 51.7 (SE 1.30) years. At baseline, all subjects engaged in moderate-intensity exercise (three or more 30-minute sessions/week); none of the women were smokers. Twenty-one women were postmenopausal, 18 of whom were on transdermal estrogen replacement treatment (ERT) and one of whom was taking oral ERT. Other baseline clinical characteristics of the two patient groups are outlined in Table 1. With the exception of weight (74.0 [1.9] versus 99.4 [4.5] kg) and BMI (29.3 [1.3] versus 38.9 [5.6] kg/m^2), as expected, and age (53.6 [1.5] versus 47.3 [1.6] years, $P = 0.020$), there were no significant group mean differences between groups I and II. In contrast to fasting and 2-hour glucose measures, which were completely within normal range in both groups, fasting, 2-hour, and glucose-mediated AUC insulin levels were elevated in groups I and II, respectively, 12.6 (1.3), 73.7 (10.4), and 150.4 (15.1) μU/mL and 13.4 (1.2), 68.8 (10.6), and 138.5 (22.6) μU/mL. Other abnormalities included elevated total and low-density lipoprotein (LDL) cholesterol and triglyceride levels.

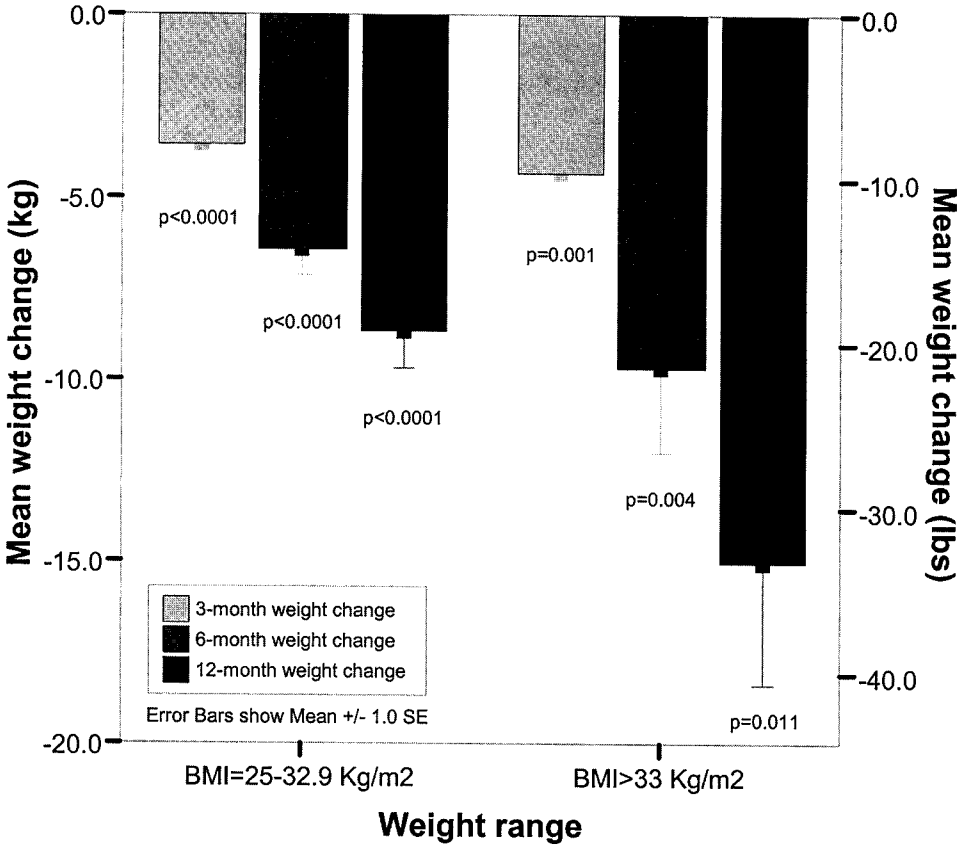

Figure 3. Mean weight changes from baseline at 3-month, 6-month, and 12-month in group I and group II patients. Data are expressed as the mean ± standard error (SE). BMI = body mass index.

Body weight declined over time (Fig. 2). Paired *t*-tests (Fig. 3) demonstrated significant weight loss at 3 months, 6 months, and 1 year in groups I and II, respectively 3.47 (0.68), 6.41 (0.72), and 8.06 (0.96) kg ($P = 0.000$) and 4.4 (0.8), 9.7 (2.3), 15.1 (3.3) kg, ($P = 0.001$, 0.004, 0.011) with mean percentage weight reductions 4.61 (0.88), 8.45 (0.90), 10.72 (1.20)%, and 4.27 (0.78), 9.48 (1.93), 14.65 (2.50)%. Using an intention-to-treat (ITT) analysis, summarized in Figure 1, 16 of 18 (88%) of the patients in Group I and 5 of 8 (63%) in Group II, a total of 21/26 (81%), met the 1-year goal of 10% reduction in body weight (or normalization of BMI [<25 kg/m^2] for 1 patient). Six-month weight loss ≥5% was observed in 25/26 (96%) of the patients. Significant weight loss was noted between the 6- and 12-month visits in each group, respectively 1.93 kg (0.40) (4.62 [0.95]%), $P = 0.001$, and 3.18 kg (0.52) (8.72 [3.05]%), $P = 0.004$.

Follow-up fasting insulin (available in 20 patients) declined significantly in the two groups, respectively 5.31 (1.44) and 4.02 (0.063) μU/mL ($P = 0.003$ and 0.001) (Figs. 4 and 5). Multiple linear regression analyses demonstrated that of all study covariates (including age, hormone use, and baseline BMI), the percentage change in fasting insulin at 3- to 6-month follow-up (−35.5 [8.2]%) was the most significant predictor of 12-month weight loss ($R^2 = 0.656$, regression coefficient = 0.810, $P = 0.005$).

Metformin, at gradually escalating doses to mean final daily doses of 1,500 mg (group I) and 2,000 mg/day (group II), was well tolerated. Serum electrolytes, serum creatinine, and liver enzymes, measured in all patients at 1-month posttreatment and monitored at regular treatment intervals, remained entirely within normal levels throughout treatment, except for a transient borderline elevation in alanine aminotransferase (ALT) in one patient. No patients reported significant diarrhea, other gastrointestinal symptoms, or adverse clinical complications, and none discontinued metformin before reaching their goal weight. All patients reported "detectable" reductions in appetite and food cravings at the 1-month visit (in response to the query: "Have you noticed any change in appetite or food cravings?") with elimination of cravings at the 3-month visit. As previously noted, appetite reduction and elimination of food cravings were used to determine the final dosage and timing of metformin administration.

Surveillance data following completion of the 1-year intervention program was available for 15/18 patients in group I. Goal weight maintenance in the absence of medical supervision (≤1-year weight) was observed at 3 to 6 months in 8/9 patients who continued metformin with weight gain (>4 kg or 50% of lost weight) at the 3-month surveillance visit in 5/6 patients who discontinued metformin (data not shown).

DISCUSSION

Findings from this clinical case series suggest that metformin might be an effective therapeutic adjunct to dietary interventions and other lifestyle modifications in promoting long-term weight management in hyperinsulinemic women. Metformin has not been previously evaluated as a primary treatment for weight reduction in hyperinsulinemic subjects in the United States. Metformin-induced

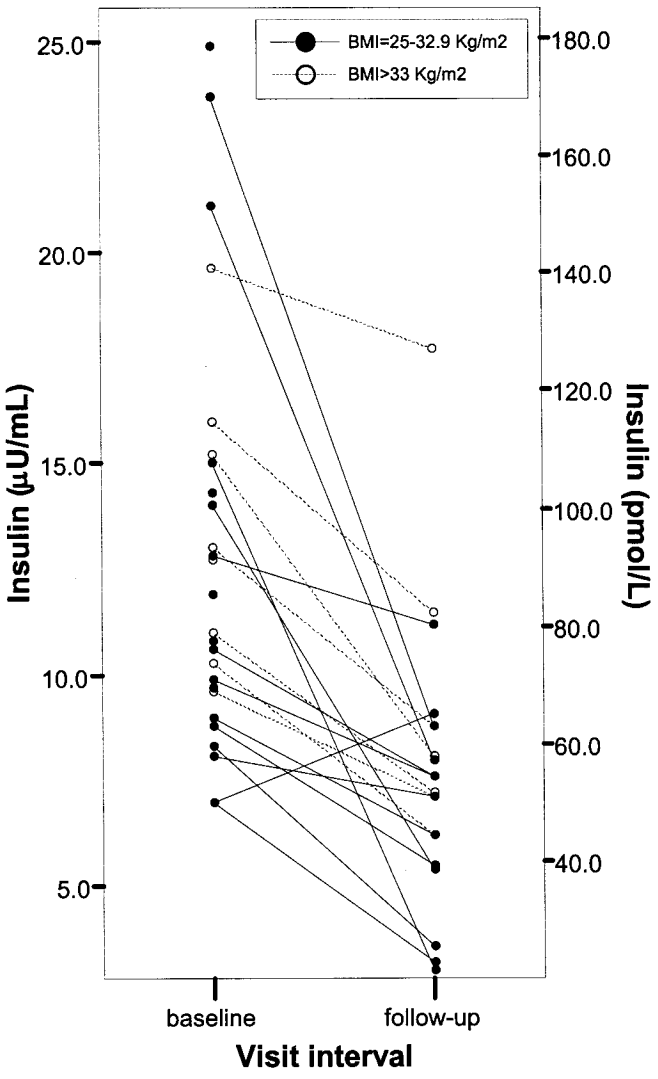

Figure 4. Fasting insulin at baseline and follow-up in 26 patients. BMI = body mass index.

weight reduction is consistent with data from studies of diabetic populations[5] and nondiabetic populations with hyperinsulinemia,[7,17] including subjects with HIV-related lipodystrophy,[12] impaired glucose tolerance, and most,[8,9,18] but not all[10,11] studies of women with polycystic ovarian syndrome. Many of these studies did not incorporate a formal weight reduction program or evaluate weight loss as a primary outcome variable.

Although clearly not directly comparable to clinical trial data, these findings might be evaluated in the context of reported studies of orlistat (120 mg three times per day) and sibutramine (10 mg once daily), which employed dietary regimens similar in total caloric content (though different in dietary composition). Our 6-month and 1-year weight losses of 7.5 kg (8.7%) and 10.7 kg (12.3%) for the combined groups compare favorably with 1-year weight losses observed in the treatment arms of such studies (7.9 kg,[19] 8.76 kg,[20] 10.3 kg,[21] and 9.7%[22]), in which subjects received more intensive treatment (i.e., biweekly or monthly weight monitoring and nutritional counseling) compared with the total five and seven visits/year-1 in our two patient groups. The percentage of patients with ≥5% 6-month weight loss and ≥10% 1-year weight loss in our combined patient cohort, respectively 96% and 81%, exceed the highest ranges reported in the treatment arms of these trials, in which the percentage with 5% 1-year weight loss was 50.5%,[19] 35%,[23] 54.2%,[24] and 69.6%,[25] and the percentage with 10% 1-year weight loss was 28%[23] and 42.1%.[25]

Two features of our case series data are notable. Progressive weight loss after 6 months of treatment contrasts with findings from other obesity treatment studies (even those employing a comprehensive multidisciplinary approach and medication[3]) that, typically, produce a maximum weight loss of 10 to 15% after 4 to 6 months of intensive treatment, followed by a weight plateau and weight gain in the majority of patients.[3] Weight stabilization following the completion of the intervention (as observed at the 6-month surveillance visit) in 8/9 (88%) of the patients who continued medication, without weight monitoring or nutritional counseling, is also unique. This observation suggests that metformin may promote long-term weight maintenance among select patients.

The success of the treatment effect might be the result of matching the clinical intervention to the metabolic characteristics of the patients. A robust decline of insulin after treatment was observed and insulin decrement was the single best predictor of final weight in the regression analyses. These findings are consistent with insulin's well-defined actions on nutrient flux, lipid partitioning, and fat deposition; the association of exogenous and endogenous insulin levels with weight gain demonstrated in large multicenter studies;[26,27] and findings from longitudinal studies of prepubertal Pima Indian children[28] and young adults,[29] in which high endogenous insulin was a significant independent predictor of future weight gain, suggesting that hyperinsulinemia is a metabolic antecedent or cause, rather than a consequence of obesity, with "an important primary role in the pathogenesis of obesity."[28]

To our knowledge, our data are the first to support a possible cause-and-effect relationship between insulin reduction and weight loss. These findings support hypotheses underlying the design of the intervention, namely: 1) hyperinsulinemia may contribute to weight gain in unique subpopulations; and conversely, 2) strategies that reduce hyperinsulinemia could be associated with long-term weight maintenance in these subpopulations. Thus, combined dietary and pharmacologic strategies, believed to diminish insulin overproduction, may have had a positive synergistic metabolic effect in this distinct subpopulation of women with glucose-mediated hyperinsulinemia that, as hypothesized, promoted and sustained weight stabilization.

Dose-dependent reductions in appetite and food cravings, "detectable" within days of treatment initiation and "virtually eliminated" by the 3-month visit in all patients, suggests that a central anorexiant action of metformin may have contributed to the weight reduction. This observation is consistent with prior reports of metformin in decreasing food intake.[13,14] Thus, in addition to its other metabolic

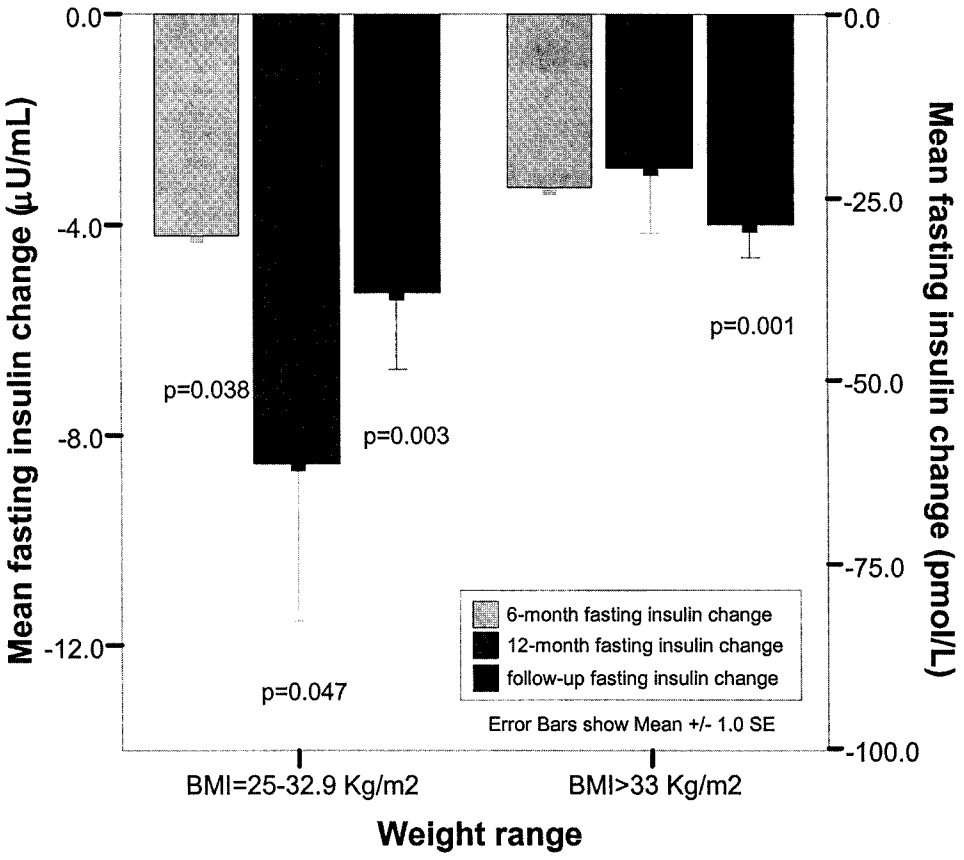

Figure 5. Mean absolute and percent changes from baseline in fasting insulin levels at 6-month, 12-month, and post-treatment (follow-up visit) in group I and group II patients. Data are expressed as the mean ± standard error (SE). BMI = body mass index.

properties (including decreased hepatic glucose output and reduction of free fatty acids) that ultimately diminish compensatory hyperinsulinemia, metformin may have novel pharmacologic actions that could enhance its efficacy as an antiobesity agent. The long-term safety profile of metformin and its association with cardiovascular risk reduction, observed in many prospective studies,[7,30–32] suggest that metformin may be a uniquely suitable therapeutic agent for weight management, especially in patients with hyperinsulinemia.

The dietary component could not be independently evaluated in our treatment protocol. However, the dietary regimen was readily adopted and was associated with long-term changes in energy balance and weight stabilization. The prescribed dietary strategy allowed for a wide range of food choices that promoted reduction in overall caloric intake consistent with the program's focus on promoting long-term dietary change, rather than short-term weight reduction. The structured meal plan conforms to recent obesity treatment recommendations[33] and rigorous research findings.[34] The specific hypocaloric diet, with elimination of all simple sugars and reduction of total and high glycemic-index carbohydrates and fat exchanges, has not been previously assessed in adult patients.

The optimal dietary regimen for weight management remains a subject of ongoing debate,[35–37] although low-carbohydrate diets[38,39] and the substitution of high-fiber for high-glycemic-index carbohydrates are increasingly advocated,[40,41] especially as preventive interventions in insulin-resistant patients, comparable with our patients. Weight data from the intervention and surveillance phases demonstrates a high degree of acceptability and adherence and suggests that comparable programs should be further evaluated.

The highly motivated and health-conscious recipients of our treatment protocol may not be representative of the population at large. However, the current $33 billion expenditure for the weight reduction industry in the United States provides evidence of the weight reduction efforts of multitudes of Americans. Few physician-based weight management programs are currently available for obese Americans. The minimal level of care (five visits for group I and 7 visits in group II) and the high compliance rate of our treatment protocol suggest that similar integrated dietary–pharmacologic programs could be contemplated to expand care options for other, comparably hyperinsulinemic obese patient populations.

Findings from this clinical case series are highly preliminary and are not intended to replace a full-fledged intervention trial employing standard, clearly defined, rigorous study design methods. Eligibility for the treatment protocol required evidence of weight gain refractory to conventional medical therapy documented by physician referral. Although inclusion of a concurrent comparison treatment group was not possible in this case series, patients served as their own historical control subjects. Methodologic limitations are clearly inherent in the retrospective analysis of data from a clinical case series such as ours. However, we suggest that the magnitude and duration of the treatment effect and the potential implications of this novel regimen for the

burgeoning obesity epidemic are sufficiently compelling to stimulate additional rigorous clinical research.

CONCLUSION

A 1-year treatment protocol of metformin, in combination with carbohydrate modification, produced progressive weight reduction in a case series of high-risk, nondiabetic, hyperinsulinemic women, with midlife weight gain and obesity (refractory to diet and exercise). Following completion of the 1-year intervention program, weight stabilization was observed at a 6-month surveillance visit in 8 of 9 patients (88%) who attained goal weight and continued medication without nutritional counseling, in contrast to weight gain in 5/6 (83%) of women who discontinued metformin. These preliminary findings suggest that metformin might be a useful adjunct to dietary interventions and other lifestyle modifications in promoting long-range weight maintenance in relevant subpopulations. The established long-term safety profile of metformin and the efficacy, acceptability, and relative ease of implementation of this regimen suggest that broad-based, placebo-controlled, randomized clinical trials may be warranted to confirm these findings and elucidate potential underlying mechanisms.

Acknowledgment: The authors thank Judith Wylie-Rossett, EdD, Wei Nchih Lee, MD, MPH, Doug Mogul, MPH, and Fred Mogul for their thoughtful comments on the research and their assistance with the manuscript.

REFERENCES

1. Aronne LJ. Obesity. *Med Clin North Am* 1998;82:161–181.
2. Stunkard AJ. Current views on obesity. *Am J Med* 1996;100:230–236.
3. Manson JE, Faich GA. Pharmacotherapy for obesity: do the benefits outweigh the risks [editorial]? *N Engl J Med* 1996;335:659–660.
4. Bray GA. Evaluation of drugs for treating obesity. *Obes Res* 1995;3(Suppl 4): 425S–434S.
5. Campbell IW, Menzies DG, Chalmers J, et al. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. *Diabetes Metab* 1994;20: 394–400.
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published erratum appears in *Lancet* 1998;352:1557]. *Lancet* 1998;1998:352: 854–865.
7. Fontbonne A, Charles MA, Juhan V, I, et al. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 1996;19:920–926.
8. Crave JC, Fimbel S, Lejeune H, et al. Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. *J Clin Endocrinol Metab* 1995;80:2057–2062.
9. Casimirri F, Biscotti M, Gambineri A. Metformin improves insulin, body fat distribution, and androgens in obese women with and without the polycystic ovary syndrome [abstract]. *Int J Obes* 1997;S61.
10. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996;335:617–623.
11. Moghetti P, Castello R, Negri C, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double -blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000; 85:139–146.
12. Hadigan C, Corcoran C, Basgoz N, et al. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. *JAMA* 2000;284:472–477.
13. Paolisso G, Amato L, Eccellente R, et al. Effect of metformin on food intake in obese subjects. *Eur J Clin Invest* 1998;28:441–446.
14. 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* 1998;6:47–53.
15. National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: NIH Publication No. 98-4083; 1998.
16. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med* 1995;333:677–685.
17. Munro JF, MacCuish AC, Marshall A, et al. Weight-reducing effect of diguanides in obese non-diabetic women. *BMJ* 1969;2:13–15.
18. 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* 1999;48:511–519.
19. Hauptman J, Lucas C, Boldrin MN, et al. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000;9:160–167.
20. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;281:235–242.
21. Sjostrom L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;352:167–172.
22. Rossner S, Sjostrom L, Noack R, et al. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res* 2000;8:49–61.
23. Finer N, James WP, Kopelman PG, et al. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord* 2000;24:306–313.
24. Lindgarde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med* 2000;248:245–254.
25. Zavoral JH. Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens* 1998;16:2013–2017.
26. Purnell JQ, Hokanson JE, Marcovina SM, et al. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. *JAMA* 1998;280:140–146.
27. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281:2005–2012.
28. Odeleye OE, de-Courten M, Pettitt DJ, et al. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes* 1997;46:1341–1345.
29. Folsom AR, Vitelli LL, Lewis CE, et al. Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts. *Int J Obes Relat Metab Disord* 1998;22:48–54.
30. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997;102:99–110.
31. Giugliano D, De-Rosa N, Di-Maro G, et al. Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive, obese women. *Diabetes Care* 1993;16:1387–1390.
32. Charles MA, Morange P, Eschwege E, et al. Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 study. Biguanides and the Prevention of the Risk of Obesity. *Diabetes Care* 1998;21:1967–1972.
33. Epstein LH, Myers MD, Raynor HA, et al. Treatment of Pediatric Obesity. *Pediatrics* 1998;101:554–572.
34. Wing RR, Jeffery RW, Burton LR, et al. Food provision vs structured meal plans in the behavioral treatment of obesity. *Int J Obes Relat Metab Disord* 1996;20:56–62.
35. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998;68:1157–1173.
36. Taubes G. Nutrition. The soft science of dietary fat. *Science* 2001;291:2536–2545.
37. Willett WC. Dietary fat and obesity: an unconvincing relation [editorial]. *Am J Clin Nutr* 1998;68:1149–1150.
38. Baba NH, Sawaya S, Torbay N, et al. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. *Int J Obes* 1999;23:1202–1205.
39. Skov AR, Toubro S, Ronn B, et al. Randomized trial on protein vs carbohydrate in ad libitun fat reduced diet for the treatment of obesity. *Int J Obes* 1999;23: 529–536.
40. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA* 1999;282:1539–1546.
41. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000;71:1455–1461.