Long-Term (2–4 Year) Weight Reduction With Metformin Plus Carbohydrate-Modified Diet in Euglycemic, Hyperinsulinemic, Midlife Women (Syndrome W)

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Abstract: Long-term weight reduction remains the ultimate objective and challenge of obesity management. Few long-term dietary or pharmacointervention studies have been conducted and there is a critical need for long-range treatment strategies that are effective, safe, and acceptable. The authors conducted a retrospective cohort analysis of 21 euglycemic, hyperinsulinemic women with progressive, refractory, midlife weight gain (Syndrome W) who had previously lost weight (≥10% reduction from baseline) with a comprehensive 1-year treatment program that included metformin and a hypocaloric, carbohydrate-modified (low-glycemic index) diet, as well as, other lifestyle modifications. The goal of the analysis was to determine long-term efficacy of the composite intervention using NHLBI criteria for weight stabilization, weight regain ≤3 kg (6.6 lb) in 2 years. Of a total of 26 consecutive women with Syndrome W who achieved goal weight during a 3-year period (1998–2001), 21 women (mean [standard error] age, 55.2 [2.4] years; mean body mass index, 34.2 [1.3] kg/m²) continued metformin and returned for annual follow-up visits. Weight maintenance was observed at the final (2–4 year) follow-up visit in 19/21 (90.5%) of women. Mean final follow-up weight (77.5 [2.8] kg) correlated highly with mean weight at 1-year protocol completion (77.2 [2.7] kg), (correlation coefficients rₓᵧ = 0.96, P = 0.000), demonstrating long-term weight reduction in the surveillance phase. Significant and robust decrements in fasting insulin (-28.4% [8.1%] to -43.4% [3.7%]) were observed at all follow-up visits (P ≤ 0.002). This preliminary case series suggests that metformin may be an effective long-term adjunct to dietary and other interventions in the treatment of obesity in hyperinsulinemic patients. A randomized clinical trial of the dual regimen should be considered in nondiabetic women with midlife weight gain and hyperinsulinemia (Syndrome W) and, quite possibly, in additional euglycemic overweight and obese subjects with documented hyperinsulinemia and other portentous features of the Metabolic Syndrome.

Key Words: Metabolic Syndrome, women, obesity, menopause, hyperinsulinemia, weight loss

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Long-term weight reduction remains the ultimate objective and challenge of obesity management. Few long-term studies of dietary regimens or pharmacotherapy have been conducted, and there is a discernible paucity of long-term treatment strategies that are effective, safe, and acceptable. It is well acknowledged that most of the patients who successfully lose weight in traditional dietary programs regain this weight within 2–4 years. Therefore, pharmacotherapies are increasingly advocated as an adjunct to lifestyle intervention in the management of obesity. No medications are currently approved for long-term (greater than 1 year) usage. The longest medication follow-up studies of FDA-approved "long-term" medications—2 year trials of orlistat and sibutramine—demonstrate diminished weight regain in subjects receiving medication compared with placebo. Long-term safety concerns and/or side effects have limited their acceptability for long-term use. Clinicians have few options for evidence-based treatment models for patients seeking medically supervised weight reduction, which may account for the low rate of obese patients who are advised to lose weight during routine physician check-ups. Therapeutic regimens that can be implemented in an office setting—especially those with demonstrable long-term efficacy and safety—are critically needed to address the escalating obesity epidemic in the United States and other industrialized nations.

We previously reported a case series in which metformin was combined with a carbohydrate-modified, hypocaloric, low-glycemic-index diet as a primary treatment of obesity and insulin modulation in euglycemic, midlife
women with Syndrome W, an early variant of the Metabolic Syndrome characterized by progressive, refractory, midlife weight gain, appetite dysregulation, and abnormal glucose-mediated insulin response curves (area-under-the-curve [AUC]-insulin ≥ 100 μU/mL). Significant weight loss was observed in women stratified into 2 body mass index (BMI) categories (group 1: 25–32.9 kg/m² and group 2: 33–41.7 kg/m²) at the completion of the active 1-year protocol, respectively, 8.06 [0.96] and 15.1 [3.3] kg (P < 0.0001, 0.011) and 10.7% [1.2%] and 14.65% [2.5%]. Using an intention-to-treat (ITT) analysis of all women who initially presented and returned for ≥1 follow-up visit, (18/18 in group 1 and 12/18 in group 2), body weight reduction ≥10% was observed at 12-months in 21 out of 26 participants (81%). With the exception of mean ages (53.6 [1.5] in group 1 and 47.3 [1.6] in group 2) and weight, there were no statistically significant differences in baseline clinical and laboratory characteristics (including blood pressure, glucose and insulin parameters, and lipid profiles) between the 2 groups. Surveillance data, available in 15 of the 17 patients in group 1 and in all 5 patients in group 2 who attained goal weight, demonstrated weight maintenance (within 1 kg) in 9 out of 10 group 1 patients who continued metformin, with weight gain (≥4 kg or 50% of lost weight) in 5 of the 6 group 1 patients who discontinued metformin; 4 of the 5 group 2 patients who continued metformin also maintained or lost additional weight. Thus, at the 6 month surveillance visit, out of 15 patients who continued metformin, a total of 13 patients (9 from group 1 and 4 from group 2) who continued metformin had demonstrable evidence of effective weight management.

The current analysis was undertaken to assess long term efficacy of the regimen in patients from the initial report who continued metformin (group A) and a second cohort (group B), representing all additional women with Syndrome W (ie, group B), maintaining metformin

**FIGURE 1.** Study flow chart and derivation of the dataset

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with progressive midlife weight gain, normal glucose tolerance curves, elevated glucose-mediated AUC-insulin values, abdominal adiposity, and self-reported appetite changes\textsuperscript{12} who had attained goal weight in the subsequent 2-year period, 1999–2001 (Fig. 1). We asked the following specific research question: “Could the continued use of metformin sustain weight reduction in women with Syndrome W who had previously lost $\geq 10\%$ of their body weight after participating in an office-based, 1-year comprehensive program of metformin, carbohydrate modified diet, and other intensive lifestyle interventions?” The primary outcome of interest was the percentage of women with weight stabilization, defined by current consensus guidelines: weight regain $\leq 3$ kg (6.6 lb) in 2 years,\textsuperscript{4} as recorded at annual surveillance visits.

**MATERIALS AND METHODS**

We conducted a retrospective analysis of all consecutive Syndrome W patients ($n = 21$) who attained 1-year goal weight loss (defined as $\geq 10\%$ or BMI normalization ($\leq 25$ kg/m\textsuperscript{2}) between 1998–2001 and returned for medication renewal and surveillance visits after implementing the stated obesity treatment protocol. The 21 study subjects included 11 (out of the total of 13 women who continued metformin, from the initial study publication),\textsuperscript{12} plus 10 additional consecutive euglycemic, hyperinsulinemic subjects with a wider age and body weight distribution than women in the initial cohort. The dataset represented 80.5% of all women—21 out of a total of 26 women aged 40–70 years—with glucose and insulin curves that conformed to the definition of Syndrome W, who achieved 1-year goal weight loss at our weight management program in the referenced time period (Fig. 1). SPSS-based paired $t$ tests and logistic regression were used to compare weight, fasting insulin, and relevant covariates at baseline, treatment completion, and 1-year intervals in the subjects. All patients gave written permission for chart review. No patients who continued metformin and returned for surveillance visits were excluded because of failure to provide written permission for chart review. (Three group B patients did not return for recording of surveillance data, but continued metformin under the care of other physicians.)

Detailed description of the baseline assessment and eligibility requirements for participation in the metformin/dietary treatment protocol have been previously reported.\textsuperscript{13} The latter included (1) history of progressive, refractory midlife weight gain (greater than 20 pounds “since the 20s”; (2) AUC insulin response $\geq 100$ $\mu$U/mL to a standard 75-g oral glucose tolerance test; and (3) the presence of at least one additional risk factor for the Metabolic Syndrome.

**Description of the Treatment Model**

High-risk euglycemic women were treated with a comprehensive, integrated weight reduction program that included health education, nutritional and behavioral counsel-

ing and a treatment protocol geared to attenuate glucose-mediated hyperinsulinemia documented in the patients; i.e., metformin (Glucophage\textsuperscript{®}) (1,500–2000 mg/d) with carbohydrate-modified diet, as previously described.\textsuperscript{13} Metformin was administered to all patients in gradually escalating doses with suppression of food cravings and appetite as a clinical end point. Treatment was initiated at 500 mg twice daily, and increased at weekly intervals, as tolerated, after the third week. Mean final daily dose was 2000 mg/d (range 1,500–2,500 mg).

The dietary component consisted of a flexible food plan approximating a total daily caloric intake of 1200–1800 kcal (with a planned 600-kcal/d deficit) and a dietary composition of 45–50% carbohydrates, 30–35% protein and 15–20% fat. The focus of the dietary intervention was the promotion of long-term dietary change through an increased intake of vegetables and low-fat protein, a liberal intake of high fiber/low-glycemic index carbohydrate selections, restriction of added refined sugars, and avoidance of densely caloric fat-and sugar-laden foods as summarized in the Appendix. Reduction of refined and other starches (except low-glycemic-index fruits) at breakfast and lunch was an additional feature of the dietary component. (Lifestyle intervention did not include exercise, since all participants reported baseline exercise levels that already conformed to or exceeded advocated public health guidelines—minimum 3 times per week).

At treatment initiation, patients received an assessment of goal weight objectives, life circumstances, and social support structure, and intensive health counseling, including written health education materials. The health education module outlined the implications and health risks of hyperinsulinemia and insulin resistance; and the relevance of the macronutrient composition of the diet, carbohydrate load, and insulin sensitizing medication as potential mechanisms for their attenuation. Patients were seen for dietary, behavioral, and health counseling and assessment of metformin tolerability and efficacy for a mean number of 6 physician office visits in the first (active) year of treatment. They were then advised to continue metformin and the dietary intervention and return for 6-month surveillance visits in year 2, and annually thereafter, to renew medication, review dietary compliance, and monitor body weight, waist circumference, blood pressure, serum glucose, insulin, and chemistry, and lipid profiles.

**RESULTS**

**Baseline Characteristics**

Baseline characteristics of the study population included mean [standard error] age of 55.2[2.4] years, BMI of 34.2 [1.3] kg/m\textsuperscript{2}, fasting glucose of 95.1 [2.6] mg/dL, glucose-mediated AUC-insulin of 161.6 [31.2] $\mu$U/mL, and waist circumference of 41.1 [1.5] in (Table 1). All patients
TABLE 1. Baseline Clinical Characteristics of the Study Source Population

<table>
<thead>
<tr>
<th>Study Covariate</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Weight (kg/lb)</td>
<td>89.3/196.9</td>
<td>3.6/7.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>34.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Waist circumference (inches)</td>
<td>41.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>95.1</td>
<td>2.6</td>
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<tr>
<td>2-hour glucose (mg/dL)</td>
<td>113.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)</td>
<td>13.5</td>
<td>1.3</td>
</tr>
<tr>
<td>2-hour insulin (μU/mL)</td>
<td>66.3</td>
<td>7.1</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<td>Diastolic BP (mm Hg)</td>
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<td>2.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
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<td>15.8</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>57.9</td>
<td>4.8</td>
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<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>141.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>153.2</td>
<td>27.3</td>
</tr>
<tr>
<td>AUC insulin (μU/mL)</td>
<td>161.6</td>
<td>28.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; AUC, area under the curve; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

To convert glucose from mg/dL to mmol/L, multiply by 0.05551. To convert insulin from μU/mL to pmol/L, multiply by 7.175.

were white nonsmokers who engaged in “moderate” intensity exercise (≥3 sessions/week). Seven women received l-thyroxin (for coexisting hypothyroidism) and 10 women received transdermal estrogen replacement.

The majority of women (18 of 21 patients, 85.6%) did not meet NCEP criteria for the Metabolic Syndrome14 (Table 2). The mean number of NCEP-defined risk factors for the Metabolic Syndrome was 1.52 [23]. Waist circumference ≥35 in was the most prevalent Metabolic Syndrome component, observed in 20 of the 21 women. Hypertension was present in 6 women, including 5 with blood pressures recordings ≥130/≥85 mm Hg (and an additional woman on antihypertensive medication at baseline with a normal blood pressure reading). Seven women had an HDL <50 mg/dL, 4 of whom also had a triglyceride level ≥150 mg/dL.

Follow-up Data

Mean body weight decreased significantly (P’s ≤ 0.002) from baseline weight, 89.3 [3.6] kg, at all surveillance visits (Fig. 2). Both parametric and nonparametric analyses indicated highly statistically significant correlations between the final (2–4 year) treatment weight, 77.5 [2.8] kg (-12.7% [1.4%]) and mean weight at 1-year protocol completion, 77.2 [2.7] kg (-13.2% [1.1%]), with a Pearson correlation coefficient (rxy) of 0.961 (P = 0.000) and Spearman rho of 0.960 (P = 0.000). Nineteen of 21 (90.5%) women regained ≤3 kg at final follow-up (3–4 years in 11 from the original cohort and 1–2 years in the 10 additional subjects).

Mean baseline waist circumference decreased significantly at all visits (P = 0.000–0.005), with additional decline between the treatment completion (37.4 [3.67] in) and the final follow-up visit (36.1 [1.04] in) (-8.7% [1.29%] and -9.6% [1.33%] compared with baseline; Fig. 3). Mean fasting insulin at baseline, protocol completion, and final (2–4 year) follow-up visit were, respectively, 13.5 [1.2], 7.8 [1.0], and 8.7 [0.8] μU/mL with significant decrements (P ≤ 0.002) observed at all follow-up visit intervals (range, -28.4% [8.1%] to -43.4% [3.7%]; Fig. 3).

Metformin, in the gradually escalating dosage regimen (mean final daily dose 2000 mg/d), was well tolerated, without reported side effects or electrolyte imbalance. None of the patients in the cohort discontinued metformin, other than for brief intervals in accordance with package insert instructions (ie, when undergoing general anesthesia or receiving contrast medium during the performance of diagnostic testing; 2 patients).

TABLE 2B. Number of Metabolic Syndrome Components in Study Subjects at Baseline

<table>
<thead>
<tr>
<th>No. of Components</th>
<th>No. of Patients</th>
<th>Percent</th>
<th>Cumulative Percent</th>
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<tr>
<td>0</td>
<td>3</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>38.1</td>
<td>52.4</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>33.3</td>
<td>85.7</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>9.5</td>
<td>95.2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>4.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2A. Characteristics and Components of the Metabolic Syndrome in the Study Population

<table>
<thead>
<tr>
<th>Waist circumference ≥35 in</th>
<th>Blood pressure ≥130/≥85 mm Hg</th>
<th>HDL cholesterol ≤50 mg/dL</th>
<th>Triglycerides ≥150 mg/dL</th>
<th>Fasting Blood Glucose ≥126 mg/dL</th>
<th>Three or more Metabolic Syndrome Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20 (95.2%)</td>
<td>6 (25.6%)</td>
<td>7 (33.3%)</td>
<td>5 (23.8%)</td>
<td>9 (0%)</td>
</tr>
<tr>
<td>No</td>
<td>1 (4.8%)</td>
<td>15 (71.4%)</td>
<td>14 (66.7%)</td>
<td>15 (71.4%)</td>
<td>21 (100%)</td>
</tr>
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DISCUSSION

The data suggest that metformin promoted long-term (2–4 year) weight stabilization in a high percentage (90.5%) of nondiabetic hyperinsulinemic women with midlife weight gain (Syndrome W) who had previously lost weight in a comprehensive treatment program of carbohydrate-modified, hypocaloric diet, behavioral and nutritional counseling, health education, and continuation of their customary exercise program. Even with an ITT analysis based on all patients who continued metformin after weight loss (ie, in which patients lost to follow-up are categorized as treatment failures), 19 out of 26 patients (73.1%) maintained or lost additional weight.

We believe this is the first publication of sustained long-term weight reduction levels (-12.7% weight decrement at 2–4 year follow-up) in a significant percentage of medically treated patients. Clearly, these preliminary findings are not directly comparable to those of randomized clinical trials. They nonetheless suggest that, as increasingly advocated, medication can serve as an important adjunct to comprehensive behavioral and dietary lifestyle interventions in the treatment of obesity and that the beneficial treatment effects can be maintained beyond the active treatment phase.

The magnitude and duration of weight stabilization contrast with available long-term data from most other obesity studies with high rates of recidivism (eg, 61–86% at
2.5–3.5 years), as summarized in several excellent recent reviews. Since many of these studies had low follow-up rates (e.g., 50%) that are believed to overrepresent the true weight stabilization rate, the differences between the study findings and other studies may be even greater than indicated. The relatively high follow-up rate—80.1% (21/26) of all women with Syndrome W who attained goal weight in the referenced time period—is an apparent strength of our clinical series. Maximal retention of participants is particularly important in weight-reduction studies, where participants who drop out are likely to represent lack of adherence to treatment assignment. The high follow-up rate may possibly reflect the ease of implementation and long-range potential of the treatment protocol. The clinical setting and/or the program’s orientation to long-term dietary change and lifestyle modification in contrast to short-term weight reduction may have contributed to the high subject retention rate.

We believe the identification of hyperinsulinemia in overweight women, the majority of whom (81%) did not meet current NCEP consensus criteria for the Metabolic Syndrome, is an important element of our treatment algorithm. Most obesity studies do not assess insulin levels or obtain glucose-mediated insulin response curves as part of the baseline evaluation of study candidates. Although there is increasing recognition of the adverse health consequences of the Metabolic Syndrome, clinicians have not focused on the implications of hyperinsulinemia in midlife subjects whose composite glucose levels, blood pressure, and lipid profiles do not (yet) qualify them for this diagnostic entity. Determination of insulin status in a subset of overweight or obese midlife women with a constellation of symptoms (midlife weight gain, “waist gain,” and appetite dysregulation) that fulfilled criteria for Syndrome W was an important prerequisite to treatment with insulin-sensitizing medication and carbohydrate modification.

The robust and significant ($P \leq 0.002$) decline in mean fasting insulin (-27.5–43.8%) and its apparent normalization (range, 7.8 [1.0] µU/mL to 8.7 [0.8] µU/mL) at all post-treatment surveillance intervals suggest that long-term attenuation of hyperinsulinemia is associated with long-term weight loss in women with initial insulin response-curve elevations. The magnitude and duration of the insulin decrement (43.8% at 1 year) support the study hypotheses implicating insulin as an antecedent to weight gain in specific populations, as previously proposed.12,13,19 This suggests that the specificity and synergism of the regimen—the targeting of treatment modalities to the metabolic characteristics of the study population—may have contributed to treatment outcome.

The observed weight stabilization during the surveillance period suggests relative long-term dietary adherence to the nutritional regimen implemented in the active treatment, although the dual intervention does not allow an independent assessment of the dietary component of the program. This
composite dietary approach—with its focus on quality and timing, in addition to quantity of carbohydrate load—has not been previously evaluated as a therapeutic modality. However, it integrates dietary principles that have been the subject of rigorous clinical20 and epidemiologic research, including the relationship of high-glycemic-index foods to caloric consumption and obesity, cardiovascular disease and diabetes,21-26 and the role of dietary protein in enhancing satiety and weight-reduction as suggested in several recent short-term dietary studies.27-29

The optimal macronutrient composition for safe and effective weight reduction has been a subject of ongoing controversy and recent intensified debate. The efficacy of conventional high-carbohydrate, low-fat, low-protein, hypocaloric diets has been challenged by the emergence of well-designed, short-term dietary comparison studies at 3 academic centers in the past year.27-29 These have demonstrated that, compared with conventional high-carbohydrate (50-55%), low-fat diets, increased dietary protein (~45%) or increased fat consumption (50%) produced significantly greater 6-month weight loss. Low-carbohydrate diets and the relative merits of the 2 dietary extremes have also been the subject of several systematic reviews30 and commentaries.31,32 These conclude that there is insufficient evidence for or against the recommendation for high-fat, low-carbohydrate diets30 and indicate that large, long-term studies will be necessary to ascertain the appropriate dietary carbohydrate, protein, and fat content for weight reduction, as well as long-term efficacy and safety.31,32

The avoidance of both low-fat (intrinsically high-carbohydrate) and low-carbohydrate (intrinsically high-fat) dietary extremes is a unique feature of our dietary approach. The carbohydrate modification, which is the cornerstone of our flexible food plan, embodies the same reduction of free sugars and refined starches as high-fat, low-carbohydrate (20-60 g/d) regimens, but the dietary composition—45-50% carbohydrates, 30-35% protein and 15-20% fat—and the advocated increase in vegetables, low-fat protein, low-glycemic-index fruits, and whole grains contrast notably with the typically defined30 “very-low-carbohydrate, high-protein diet.” Avoidance of the excess fat consumption that accompanies most carbohydrate-restricted diets conforms to established public health guidelines, based on extensive long-term data supporting a causal association of high fat diets with cardiovascular disease, insulin resistance, and cancer.33 Thus, the carbohydrate-modified diet replicates the recommended “heart healthiness of a balanced diet consisting of a wide variety of foods,”32 producing desirable rates of weight reduction with what may well be a more acceptable and lower risk profile.27

To our knowledge, the combination of a pharmacotherapeutic intervention with a specific dietary regimen has not been previously evaluated as an obesity treatment strategy. The magnitude of the weight reduction rates—13.2% at the 1-year protocol completion and 12.7% at the final (2-4) year follow-up—compares favorably with reported rates at 6 months, 4.5%,28 9.3%,34 and 6-12-months, respectively, 9.7% and 7.3%,29 in patients randomized to carbohydrate-restricted diets in other studies and may be due to the synergism of this regimen. The Diabetes Prevention Program (DPP), which targeted comparably insulin resistant patients, at a discernibly later stage of glucose impairment than the Syndrome W women in our study, evaluated metformin and diet (in addition to other lifestyle modifications) in separate study arms,35 but did not assess the combination of metformin and intensive dietary intervention. Despite differences in the nature of the nutritional component and the primary study outcome of the DPP, its results provide additional evidence for the potential value of a dual metformin-dietary regimen to promote long-term weight loss in insulin-resistant subjects.

Metformin has been widely used and well tolerated, both as monotherapy and in combination with other pharmacotherapies, in the treatment of patients with Type 2 diabetes in the United States and Europe. Its use has been associated with weight loss in placebo-controlled randomized clinical trials36 and prospective studies of patients with diabetes,37 non-diabetic Europeans with central fat distribution,38 insulin-resistant women with polycystic ovarian syndrome,39-42 and men with HIV-related lipodystrophy.43 Metformin delays the rate of progression to diabetes in patients with impaired glucose tolerance,44 and reduces total caloric intake45-46—both clearly desirable drug attributes for the treatment of women with Syndrome W and other obese subjects with documented hyperinsulinemia. This collective research and the long-term safety profile of metformin make it an attractive long-term therapeutic agent, well-suited to the increasingly advocated lifelong treatment of obesity.

Study Limitations

Case series have clear intrinsic methodologic limitations that may include patient selection, the absence of a suitable comparison group, and the inability to discern and control for the placebo effect of treatment. Undefined baseline characteristics of our study population may have contributed to study outcome and might limit study generalizability. Atypically high motivation levels of patients in the study cohort—not representative of the population at large—could have biased estimates of treatment efficacy. However, as demonstrated in population surveys, high percentages of American women currently engage in caloric- or fat-restricted diets or participate in formal exercise programs.47 This suggests that absence of motivation is not the primary cause of the high prevalence of obesity and overweight among US women.

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Our retrospective analysis did not include a placebo or other comparison treatment group. The 2–4-year duration of the follow-up period makes it unlikely that placebo effect of metformin contributed to the study findings, as placebo effect is virtually undetectable after 6 months. Several factors precluded the option of alternate comparison groups in our clinical setting. These included the lack of acceptability or suitability of other FDA-approved weight reduction therapies and clinical concern over discontinuation of metformin in view of the high recidivism rate in our initial report—5 of 6 women who attained goal weight objectives and discontinued metformin gained weight (≥4 kg or 50% of lost weight) within 6 months.\(^\text{13}\)

Research findings from population-based and clinical studies suggest that weight gain is a common phenomenon in midlife women that merits consideration as an important target for preventive intervention. Results from The Women’s Healthy Lifestyle Project Clinical Trial, a 54-month study of 535 midlife women of comparable age and ethnicity, demonstrated a 5.2-lb weight gain in 275 women randomized to the nonintervention arm, compared with a 2.3-lb weight loss in 260 women randomized to caloric and fat-reduction diet plus increased activity.\(^\text{48}\) This may provide a meaningful context in which to evaluate the results of our clinical series.

We fully appreciate the preliminary nature of our retrospective cohort analysis, which is presented as an impetus for additional rigorous clinical and mechanistic research. We also hope, despite clear methodologic limitations, that the study findings will encourage clinicians to contemplate the potential viability of defining and treating insulin abnormalities in euglycemic women with midlife weight gain who have failed to respond to other interventions for obesity, even if they do not meet complete criteria for the Metabolic Syndrome.

**CONCLUSION**

In summary, the preliminary findings suggest the combined regimen of metformin and a carbohydrate-modified diet promotes weight stabilization (as defined by established criteria)\(^\text{1}\) in obese midlife nondiabetic women with documented insulin abnormalities (and other features of Syndrome W) who previously lost weight in a 1-year comprehensive treatment program of lifestyle intervention and nutritional and behavioral counseling. We believe this effective novel obesity treatment, which is easily implemented in a clinical setting, could have important implications for women with Syndrome W, and quite possibly for other subpopulations of obese nondiabetic Americans with progressive weight gain and documented hyperinsulinemia. Additional long-term studies using rigorous scientific methodology are needed to assess the potential relevance of the proposed multimodal therapeutic regimen to the high percentage of overweight and obese Americans.

**ACKNOWLEDGMENTS**

H. Mogul, S. Peterson, and B. Weinstein designed the study, analyzed the data, and wrote the report. J. Li entered and analyzed the data and prepared the graphics. L. Southen contributed to the research design, data analysis, and manuscript.

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**REFERENCES**


**APPENDIX**

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<tr>
<td>Treat (weekly)</td>
<td>Dairy</td>
<td>Fruit</td>
<td>Vegetables</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>CARE-FULL CHOICES</strong></td>
<td><strong>CARBOHYDRATE-RICH CATEGORIES</strong></td>
<td><strong>KEY INGREDIENT</strong></td>
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Food pyramid summarizing recommended number of servings in the carbohydrate-modified diet.