# Metformin Improves Glucose, Lipid Metabolism, and Reduces Blood Pressure in Hypertensive, Obese Women

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**OBJECTIVE**— To determine the effects of metformin on blood pressure, left ventricular mass, and some metabolic and endocrine parameters in nondiabetic, obese, hypertensive women.

**RESEARCH DESIGN AND METHODS**— Twelve obese, nondiabetic, hypertensive women received 850 mg metformin 2 times/day for 12 wk and placebo for another 12 wk, according to a double-blind, cross-over, randomized design. All patients were hospitalized 4 times, i.e., before randomization and after each treatment (metformin or placebo), to conduct metabolic and cardiovascular investigations (oral glucose tolerance test, euglycemic clamp associated with indirect calorimetry, and echocardiography).

**RESULTS**— Fasting glucose, $HbA_{1c}$, fasting and glucose-stimulated insulin, blood pressure and left ventricular mass, cholesterol, triglycerides, and fibrinogen decreased significantly after metformin treatment, whereas high-density lipoprotein cholesterol increased. The improvement in glucose metabolism resulted from increased sensitivity to insulin.

**CONCLUSIONS**— These findings suggest that metformin treatment in obese, nondiabetic, hypertensive women produces a more favorable cardiovascular risk profile.

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Type II diabetes, non-insulin-dependent diabetes mellitus; BP, blood pressure; dBP, diastolic blood pressure; sBP, systolic blood pressure; Gox, glucose oxidation; NDDG, National Diabetes Data Group; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; TG, triglycerides; RIA, radioimmunoassay; CV, coefficient of variation; ANOVA, analysis of variance; BMI, body mass index; $LVM_i$, left ventricular mass index; GIR, glucose infusion rate; IRI, immunoreactive insulin; WHR, waist-to-hip ratio.

Many epidemiological, clinical, and experimental data have documented relationships between reduced tissue sensitivity to insulin, upper-body obesity, states of glucose intolerance, high BP, and various abnormalities of lipoprotein metabolism (1). Whatever the unifying pathogenetical mechanism proposed (insulin resistance, hyperinsulinism, or both), these abnormalities tend to cluster in the same individual, all being more or less risk factors for atherothrombosis. Although insulin sensitivity can be improved by weight loss, which generally has a beneficial effect on vascular risk factors (2), weight reduction rarely is successful in obese patients, particularly in those with insulin resistance. In type II diabetic subjects, metformin lowers the fasting plasma glucose, lowers insulin concentrations, and decreases plasma lipid levels independent of changes in body weight (3). We have conducted a study in obese, hypertensive, nondiabetic subjects and evaluated the effect of metformin on the level of many known risk factors for cardiovascular disease.

## RESEARCH DESIGN AND METHODS

— Informed consent was obtained from 12 obese women who volunteered to participate in the study. The study was approved by the University of Naples Ethical Committee. Their clinical and metabolical characteristics are given in Table 1. The inclusion criteria were the following: *1*) dBP in the range of 90–105 mmHg after withdrawal of any

**Table 1—*Clinical characteristics of the study patients***

| | |
|---|---|
| *n* | 12 |
| Age (yr) | 47 ± 2.5 |
| BMI (kg/m$^2$) | 34 ± 0.9 |
| WHR | 0.99 ± 0.06 |
| Glucose (mM) | 5 ± 0.22 |
| $HbA_{1c}$ (%) | 5.5 ± 0.23 |
| Insulin (mU/L) | 22.5 ± 4.0 |
| sBP (mmHg) | 150 ± 9 |
| dBP (mmHg) | 100 ± 4 |

Data are means ± SE.

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previous antihypertensive drug for at least 4 wk, 2) normal glucose tolerance according to NDDG criteria (4), and 3) no regular exercise or other medications. Subjects with secondary forms of hypertension, grades 3–4 hypertensive retinopathy, serum creatinine >135 μm/L, or a history of cerebrovascular disease were excluded. After an initial physical and metabolic characterization, the subjects who met the inclusion criteria were given, in a randomized order, metformin (850 mg 2 times/day) or placebo for 12 wk according to a double-blind procedure; then they were evaluated again and once more 12 wk after they inverted treatments—those who first took placebo changed to metformin and vice versa. Six patients were started initially on metformin.

They were hospitalized 3 times for a few days to conduct metabolic investigations; BP and anthropometric measures were recorded every tenth day. When hospitalized, each subject was submitted to a euglycemic glucose clamp with the aid of Biostator (Ames-Miles, Milau, Italy). The rate of insulin infusion was 0.5 $mU \cdot kg^{-1} \cdot min^{-1}$; glucose was infused as a 30% solution, and 0.26 mEq KCl was added to prevent hypokalemia. Gox was measured by indirect calorimetry (Deltatrac, Datex, Milan, Italy). Gas exchange was measured during a 45-min basal period after the subject's breathing pattern stablized for at least 30 min. In the standard oral glucose tolerance test, each subject drank 75 g of anhydrous glucose flavored with lemon juice. Plasma glucose was determined by the glucose-oxidase method (Beckman 2 Glucose Analyzer, Fullerton, CA). Serum HDL cholesterol was determined after precipitation of LDLs and VLDLs with dextran sulphate-MgCl 2 (5). Commercial enzymatic methods were used in the determination of cholesterol (6) (Monotest, Boehringer Mannheim, Mannheim, Germany) and TG (7) (Peridocrome, Boehringer Mannheim). Fibrinogen was analyzed by the clotting method (8) with reagents from Boehringer Mannheim. $HbA_{1c}$ was measured by column chromatography (Bio-Rad, Milan, Italy), urinary albumin excretion by an immunoturbidimetric assay in the first morning sample (Ames, Milan, Italy), and insulin by an RIA method (Sorin-Biomedica, Milan, Italy) from frozen sample stored at −70°C; the intra-assay and interassay CVs were 6 and 11.5%, respectively.

Plasma norepinephrine was measured by a radioenzymatic assay (9). The left ventricular mass normalized by the surface area was measured by echocardiography. BP was measured with appropriate cuff size after a 10-min rest in the supine position. Two readings were taken at 2-min intervals, and the latter was used in statistical analyses. sBP and dBP were read to the nearest 2 mmHg. The point of disappearance of the Korotkoff sounds (phase V) was recorded at the dBP value.

### Statistical analysis

The Student's *t* test was used for paired data after preliminary ANOVA and was corrected by the Bonferroni test. The statistical analysis was made on an IBM computer using the SOLO software package (BMDP statistical software). All data are presented as means ± SE.

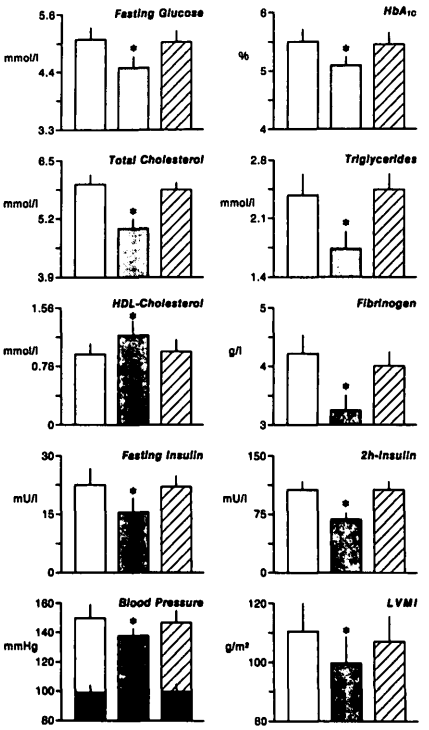


**Figure 1**—*Metabolic and cardiovascular effects of metformin in obese, hypertensive women. (□), Baseline values; (▦), values after metformin; (▨) values after placebo; (■), dBP values; and (*), significant differences versus basal values.*

**RESULTS**— After 3 mo of treatment with metformin, a reset of glucose metabolism at a lower level was observed, as judged by the lower fasting glucose (from 5 ± 0.22 to 4.5 ± 0.21 mM, −9 ± 1.5%) and $HbA_{1c}$ values (from 5.5 ± 0.23 to 5.1 ± 0.2%, −9.5 ± 1.6%) ($P < 0.02$). Fasting insulin decreased by 21 ± 3.6% (from 22.5 ± 4 to 16 ± 4 mU/L, $P < 0.01$) and the 2-h insulin value by 35% (from 105 ± 14 to 68 ± 7 mU/L, $P < 0.01$). (Fig. 1). All of this was associated with an increased biological effect of insulin: glucose disposal rate increased from a mean value of 3.2 ± 0.4 to 4.1 ± 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.025$) despite similar plasma insulin concentrations during the second hour of the clamp (56 vs. 52 mU/L, NS). Basal and insulin-stimulated Gox increased after metformin 16 (2.5)% and 10 (1.6)%, respectively, $P < 0.05$) (Fig. 2). Changes in blood lipids were detected after treatment: total cholesterol decreased by 18 ± 2.4%, TG decreased by 27 ± 3.2%, and HDL cholesterol increased by 28 ± 3.2% (all $P < 0.01$). Fibrinogen decreased by 24 ± 3.8% ($P < 0.02$). After metformin sBP, dBP, and LVMi were significantly lower ($P < 0.01$) (Fig. 1). Plasma norepinephrine concentrations decreased from a mean value of 398 ± 58 to 321 ± 44 ng/L ($P < 0.05$). Urinary albumin excretions show a trend to decrease after metformin (basal 66 ± 15 mg/24 h; post-treatment: 49 ± 13 mg/24 h, NS). Body weight did not change significantly during the whole study: BMI was 34 ± 0.9 after 3 mo of treatment with metformin.

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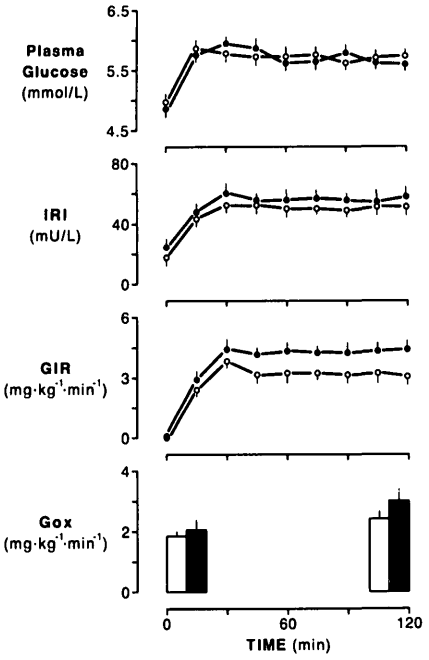


**Figure 2**—*Plasma glucose concentration, IRI concentrations, GIR, and Gox during the euglycemic insulin clamp in obese, hypertensive women after metformin (●) or placebo (○).*

No correlation was observed between changes in insulin action after metformin and the decrease in BP or blood lipids; however, a correlation was found between changes in insulin action and the decrease in fasting insulin concentration ($r = 0.37$, $P < 0.05$). Additionally, a correlation between the reduction in fasting insulin and the decrease of mean BP was detected ($r = 0.32$, $P < 0.05$).

The tolerance of metformin was good. Two women reported diarrhea during the initial treatment period, with spontaneous remission within some days. No hypoglycemic episodes occurred during the study.

**CONCLUSIONS**— The relationship between body weight and BP is well established. So, the prevalence of obesity in middle-aged, hypertensive individuals is high (10). Because both obesity and hypertension are said to be insulin-resistant states (1), the reason hypertension is more common in obese individuals may be because they tend to be hyperinsulinemic.

The patients we studied had normal glucose tolerance according to standard criteria, but were hyperinsulinemic both in the fasting state and after the glucose challenge. This finding, confirmed by the low infusion rates of GIR, indicated insulin-resistance. Metformin treatment decreased both glucose and insulin fasting concentrations. In the fasting state, essentially all glucose entering the circulation comes from the liver and muscle takes up little glucose because peripheral insulin levels are low (11), therefore, it is likely that the drug exerts a direct inhibitory effect on hepatic glucose output. This coincides with inhibition of gluconeogenesis by metformin in isolated hepatocytes and the perfused liver (12). This hypothesis currently remains speculative because we did not measure glucose turnover; moreover, it is also likely that hepatic glucose production was not completely suppressed at the insulin levels present during the clamps.

The plasma insulin response to the oral glucose load decreased significantly after treatment; so, the improvement of insulin sensitivity cannot be attributed to a stimulatory effect of metformin on the β-cells. During the clamp, insulin-mediated glucose utilization increased by 40%, and this was partially caused by improvement of oxidative glucose metabolism, as inferred from the data of indirect calorimetry. Evidence states that therapeutic concentrations of metformin increase Gox in skeletal muscle and adipose tissue (13–15).

The mechanism we found underlying the BP-lowering effect of metfomin is obscure, but agrees with previous reports (16). A decrease in peripheral hyperinsulinism may be implicated. Landin et al. (17) obtained similar results on BP in nonobese, nondiabetic, nonsmoking, middle-aged men with untreated hypertension. Moreover, a reduction in the dose of exogenous insulin administered to type II diabetic patients is associated with a significant fall in BP (18). A decrease in sympathetic nervous system activity, as suggested by a 25% reduction in plasma norepinephrine after metformin, could also have contributed.

Left ventricular hypertrophy is a major risk factor for cardiovascular morbidity and mortality independent of the arterial pressure. The mechanism by which metformin reduces $LVM_i$ is a current matter of speculation possibly resulting from nonhemodynamic mechanisms (inhibition of the adrenergic system, hormonal substances, and growth factors), which are supposed to be implicated in the reduction of $LVM_i$ within a period of weeks (19). Additionally, it is important to emphasize that the body weight of all subjects remained stable throughout the study.

Metformin treatment was associated with significant alterations in plasma lipids. Plasma TG and total cholesterol concentrations fell significantly in all patients, whereas HDL cholesterol increased. Fibrinogen is now viewed as an important cardiovascular risk factor (20), and metformin significantly reduced its plasma concentration. Independent of the pathophysiological implications of this study, it seems best to state that metformin treatment in nondiabetic, obese, hypertensive women produces a more favorable cardiovascular risk profile.

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