Mechanism of Metformin Action in Obese and Lean Noninsulin-Dependent Diabetic Subjects*

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ABSTRACT. The effect of metformin on glucose metabolism was examined in eight obese (percent ideal body weight, 151 ± 9%) and six lean (percent ideal body weight, 104 ± 4%) noninsulin-dependent diabetic (NIDD) subjects before and after 3 months of metformin treatment (2.5 g/day). Fasting plasma glucose (11.5–8.8 mmol/L), hemoglobin-A1c (9.8–7.7%), oral glucose tolerance test response (20.0–17.0 mmol/L: peak glucose), total cholesterol (5.67–4.71 mmol/L), and triglycerides (2.77–1.52 mmol/L) uniformly decreased (P < 0.05–0.001) after metformin treatment; fasting plasma lactate increased slightly from baseline (1.4 to 1.7 mmol/L; P = NS). Body weight decreased by 5 kg in obese NIDD subjects, but remained constant in lean NIDD. Basal hepatic glucose production declined in all diabetics from 83 to 61 mg/m²·min (P < 0.01), and the decrease correlated (r = 0.80; P < 0.01) closely with the fall in fasting glucose concentration. Fasting insulin (115 to 79 pmol/L) declined (P < 0.05) after metformin. During a 6.9 mmol/L hyperglycemic clamp, glucose uptake increased in every NIDD subject (113 ± 15 to 141 ± 12 mg/m²·min; P < 0.001) without a change in the plasma insulin response. During a euglycemic insulin clamp, total glucose uptake rose in obese NIDD subjects (121 ± 10 to 146 ± 9 mmol/m²·min; P < 0.05), but decreased slightly in lean NIDD (121 ± 10 to 146 ± 0.5; P = NS). Hepatic glucose production was suppressed by more than 80–90% in all insulin clamp studies before and after metformin treatment.

In conclusion, metformin lowers the fasting plasma glucose and insulin concentrations, improves oral glucose tolerance, and decreases plasma lipid levels independent of changes in body weight. The improvement in fasting glucose results from a reduction in basal hepatic glucose production. Metformin per se does not enhance tissue sensitivity to insulin in NIDD subjects. The improvement in glucose metabolism under hyperglycemic, but not euglycemic, conditions suggests that metformin augments glucose-mediated glucose uptake. Metformin has no stimulatory effect on insulin secretion. (J Clin Endocrinol Metab 73: 1294–1301, 1991)

METFORMIN is a biguanide which has gained widespread usage in the treatment of noninsulin-dependent diabetes mellitus (NIDDM) in Europe and Canada (1, 2). This drug, unlike phenformin, is rarely associated with lactic acidosis (3–5) and has been used both alone (1, 2, 6–10) and with sulfonylureas (11–13) to treat noninsulin-dependent diabetic (NIDD) patients. Although effective in lowering blood glucose levels in NIDDM, controversy exists concerning its mechanism of action. Multiple mechanisms of action have been suggested, including delayed gastrointestinal absorption of glucose (2, 14), improved peripheral tissue sensitivity to insulin (15–21), and suppression of hepatic glucose production (7, 22) due to an inhibition of gluconeogenesis (23–25). It generally is agreed that biguanides do not alter insulin secretion (1, 7, 18, 21, 26, 27). With respect to metformin's effect on peripheral tissues, both receptor

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Materials and Methods

Subjects

Six normal weight [body weight, 67 ± 5 kg; height, 166 ± 3 cm; percent ideal body weight (IBW), 104 ± 4%, based upon 1959 Metropolitan Life Insurance tables] and 8 obese (weight, 97 ± 5 kg; height, 166 ± 3 cm; IBW, 151 ± 9%) NIDD patients
were studied. There were 2 females and 4 males in the normal weight group and 2 females and 6 males in the obese group. The mean age of the diabetic subjects was 60 ± 3 yr, and mean duration of diabetes was 5 ± 2 yr. Eleven diabetics (5 lean and 6 obese) were receiving sulfonylurea therapy, while 3 were receiving diet treatment alone. In all patients receiving sulfonylureas, the drug was stopped 7 days before the study in order to avoid any acute effect of the sulfonylurea on insulin sensitivity. No change in fasting glucose was observed in any diabetic subject as a result of discontinuation of the sulfonylurea. No subject was taking any other medication known to affect glucose metabolism. None of the subjects was engaged in any unusual physical activity, nor was any excessively sedentary. Weight was stable in all subjects for at least 3 months before the study. Twenty-one normal weight (IBW, 105 ± 1%) age-matched (58 ± 2 yr) healthy subjects (13 males and 8 females) served as controls. Thirteen control subjects received a hyperglycemic clamp, and 8 received a euglycemic insulin clamp. None of the controls was taking any medications, and there was no family history of diabetes mellitus. For 3 days before the study subjects consumed a weight-maintaining diet containing 200–250 g/day carbohydrate. Before participation, the purpose, nature, and potential risks of the study were explained to each subject, and their informed written voluntary consent was obtained. The protocol was approved by the Human Investigation Committee of Yale University School of Medicine.

Experimental procedures

During the week before starting metformin therapy all diabetic subjects received a euglycemic insulin clamp to evaluate insulin sensitivity (35), a hyperglycemic clamp (35) to quantify insulin secretion, and a 100-g oral glucose tolerance test (OGTT). One subject did not participate in the insulin clamp study either before or after metformin treatment. All studies were initiated at 0800 h after an overnight fast and were performed in randomized order.

Euglycemic insulin clamp

A prime-continuous (40 mU/m²·min) insulin infusion was administered to acutely raise and maintain the plasma insulin concentration by 70–80 µU/mL above baseline (35). After the start of the insulin infusion, the plasma glucose concentration in the NIDDM group was allowed to decline to 5.5 mmol/L, at which level it was maintained for 2 h by adjustment of a variable infusion of 20% glucose solution. Control subjects were studied at their basal plasma glucose level. Three hours (2 h in controls) before the start of the insulin clamp, a priming dose (25 µCi × fasting plasma glucose/100) of [3H]glucose (New England Nuclear, Boston, MA) was administered, and this was followed by a continuous infusion at 0.25 µCi/min. One diabetic subject declined the tritiated glucose infusion. Continuous indirect calorimetry was started 60 min before the start of insulin and continued throughout the insulin clamp (36). Blood samples for determination of plasma [3H]glucose specific activity and plasma insulin concentration were drawn at 5- to 10-min intervals during the last 30 min of the baseline period and every 10–15 min during the insulin clamp. Urine was collected during the baseline and insulin clamp periods for determination of nitrogen excretion.

Respiratory gas exchange measurements

Continuous indirect calorimetry was performed as previously described (36). Briefly, a transparent plastic ventilated hood was placed over the subject's head and made airtight around the neck. A slight negative pressure was maintained in the hood to avoid loss of expired air. Ventilation was measured by a dry gas meter. A constant fraction of the air flowing out of the hood was automatically collected for analysis. The oxygen content was continuously measured by electrochemical analysis (model S-3A oxygen analyzer, Applied Electrochemistry, Sunnyvale, CA), and carbon dioxide content was determined by an infrared analyzer (model CD 3A carbon dioxide analyzer, Applied Electrochemistry).

Hyperglycemic clamp study

The plasma glucose concentration was acutely raised and maintained at 6.9 mmol/L above baseline by a prime-variable glucose infusion for 2 h, as previously described (35). The plasma insulin concentration was determined every 10 min over the 30-min period before the start of the hyperglycemic clamp, every 2 min during the initial 10 min of the hyperglycemic clamp, and every 10 min thereafter.

OGTT

All diabetic subjects received a 3-h OGTT. The oral glucose load (100 g) was dissolved in lemon-flavored water and consumed over 15 min. Plasma glucose and insulin concentrations were determined every 15–30 min during basal and postglucose ingestion periods. During the postabsorptive state, blood was drawn for hemoglobin-A1c (HbA1c), total cholesterol, triglyceride, and FFA determinations. In six diabetic subjects (three obese and three lean), blood was drawn for determination of high density lipoprotein (HDL) and total cholesterol and calculation of low density lipoprotein (LDL) cholesterol.

After completion of the above studies diabetic subjects were started on metformin at 500 mg twice daily. The dose was increased every 3–4 days to a maximum of 2.5 g (given as 1.5 g every morning and 1.0 g every evening) or until the fasting glucose level declined to 5.5 mmol/L. To check patient compliance, the plasma metformin concentration was measured on 3 occasions during the last month of the study at 0800 h after an overnight fast. After 3 months on the maximal dose, subjects received a repeat euglycemic insulin clamp, hyperglycemic clamp, and OGTT. On the day of each study no metformin was ingested in order to allow us to examine the chronic effects of the biguanide on glucose metabolism. In 12 of 14 diabetic subjects no side-effects from metformin were encountered. One subject experienced mild nausea, which persisted throughout the 3-month study period. A second subject experienced mild persistent abdominal pain and diarrhea.

Analytical determinations

The plasma glucose concentration was determined using a Beckman Glucose Analyzer II (Beckman Instruments, Fuller-
Plasma tritiated glucose specific activity was determined on deproteinized samples, as previously described (36). Plasma insulin was determined by RIA (39). Methods for the determination of plasma FFA (40), lactate (41), and total cholesterol, HDL cholesterol, and triglyceride levels have been described previously (42). Urinary nitrogen was measured using the Kjeldahl method (43). The plasma metformin concentration described previously (42). Urinary nitrogen was measured using the Kjeldahl method (43). The plasma metformin concentration was determined by high pressure liquid chromatography (44).

**Calculations**

During the euglycemic insulin clamp the glucose infusion rate was determined every 20 min. The rate of total body glucose utilization was calculated by adding the mean rate of residual hepatic glucose production (HGP) to the mean glucose infusion rate (after correction for any change in the glucose space) during the same time period. In all studies a steady state plateau of tritiated glucose specific activity was achieved during the 30 min before the start of insulin infusion. Glucose production in the basal state was determined by dividing the $[^3H]3$-glucose infusion rate by the steady state plateau of $[^3H]3$-glucose specific activity. After glucose/insulin administration, a nonsteady state condition in glucose specific activity existed and the rate of endogenous glucose appearance (Ra) was calculated according to the model described by Radziuk et al. (45). The rate of HGP was calculated by subtracting the glucose infusion rate from the Ra of glucose, as determined by the isotopic tracer technique. Negative numbers for HGP were assumed to be zero. The rate of total body glucose uptake and residual HGP represent values during the last 60 min of the euglycemic insulin clamp period.

The rates of glucose and lipid oxidation were obtained from the nonprotein respiratory quotient (RQ), using the tables of Lusk, which are based upon a 0.707 RQ for 100% fat oxidation and a 1.00 RQ for 100% carbohydrate oxidation (46). Nonoxidative glucose disposal, which primarily represents glycogen formation (47), was determined by subtracting the rate of glucose oxidation from the rate of total body glucose uptake. During the hyperglycemic clamp, HGP was assumed to be completely suppressed by the combined effects of hyperinsulinemia and hyperglycemia (48, 49), and the rate of total body glucose disposal was assumed equal to the glucose infusion rate after a small correction for urinary glucose loss. The early and late plasma insulin responses represent the mean plasma insulin concentration during the 0- to 10-min and 10- to 120-min intervals, respectively.

Because of known differences in the cellular basis of insulin resistance in obesity and NIDDM (37, 38), lean and obese diabetic groups were analyzed separately. Changes from baseline within the obese and normal weight diabetic groups were compared using a paired t test. Differences between the obese and normal weight groups were compared using the unpaired t test.

**Results**

**Body weight and fasting plasma glucose, lipid, lactate, and metformin concentrations**

Body weight decreased from 97 ± 5 to 92 ± 5 kg in obese NIDD subjects and did not change significantly in the normal weight NIDD group (67 ± 5 vs. 66 ± 5 kg) after 3 months of metformin therapy. The fasting plasma glucose concentration (mean of the 3 determinations during the OGTT, insulin clamp, and hyperglycemic clamp) decreased in each of the 14 diabetic subjects from 11.5 ± 0.8 to 8.8 ± 0.7 mmol/L (P < 0.001; Fig. 1), and this was associated with a decline in HbA1c from 9.8 ± 0.6% to 7.7 ± 0.4% (Fig. 2). The decline in fasting glucose was of similar magnitude in the obese (11.4 ± 0.8 to 8.9 ± 0.7 mmol/L) and normal weight (11.4 ± 0.8 to 8.7 ± 0.7 mmol/L) diabetic individuals (P < 0.01). HbA1c fell similarly in obese (9.7 ± 0.7% to 8.2 ± 0.4%) and normal weight (9.9 ± 1.0% to 7.1 ± 0.6%) diabetic subjects.

![Figure 1](#) Plasma glucose and insulin concentrations after oral glucose ingestion (100 g) in NIDD patients before (•) and after (O) 3 months of metformin therapy. All values represent the mean ± SEM.

![Figure 2](#) Fasting plasma glucose, HbA1c, total cholesterol, and triglyceride concentrations before (■) and after (■) 3 months of metformin treatment in NIDD patients. All values represent the mean ± SEM.
fasting plasma total cholesterol and triglyceride concentrations fell from 5.69 ± 0.10 to 4.65 ± 0.18 mmol/L (P < 0.001) and from 2.77 ± 0.15 to 1.52 ± 0.21 mmol/L, respectively (P < 0.001; Fig. 2). Total cholesterol declined similarly in obese (6.08 ± 0.44 to 4.81 ± 0.23 mmol/L) and lean (5.69 ± 0.23 to 4.55 ± 0.16 mmol/L) diabetic groups (P < 0.01). The fasting plasma triglyceride concentration was greater in obese vs. lean (3.27 ± 0.71 vs. 1.30 ± 0.15 mmol/L; P < 0.01) NIDD subjects and demonstrated a greater decrease after metformin treatment in the obese (1.93 ± 0.28 mmol/L) vs. normal weight (0.97 ± 0.16 mmol/L) diabetic group (P < 0.05).

In 6 subjects (3 obese and 3 lean) in whom it was measured, HDL cholesterol rose from 0.93 ± 0.05 to 1.09 ± 0.10 mmol/L (P < 0.05) and LDL cholesterol fell from 3.96 ± 0.36 to 2.97 ± 0.13 mmol/L (P < 0.05). The HDL cholesterol to LDL cholesterol ratio increased from 0.18 ± 0.02 to 0.24 ± 0.02. The fasting plasma FFA concentration declined significantly in the obese group (993 ± 88 to 840 ± 76 μmol/L; P < 0.05), but remained unchanged in the lean diabetics (911 ± 85 vs. 940 ± 85 μmol/L). The basal plasma lactate concentration did not change significantly after metformin treatment (1.4 ± 0.1 vs. 1.7 ± 0.1 mmol/L). Fasting plasma insulin declined from 115 ± 14 to 79 ± 7 pmol/L (P < 0.0 1) when all diabetic subjects were considered together. The fasting plasma insulin was significantly greater in obese vs. lean (151 ± 14 vs. 57 ± 7 pmol/L; P < 0.01) NIDD subjects and demonstrated a greater decline after metformin treatment in the obese (100 ± 7 pmol/L) vs. normal weight (36 ± 7 pmol/L) diabetic group (P < 0.01). The fasting plasma metformin level, measured 24 h after the last oral dose, was 809 ± 142 and 761 ± 160 ng/mL in lean and obese diabetics, respectively, indicating that all subjects had been taking their metformin on a regular basis and had a normal trough level.

OGTT

The fasting plasma glucose (11.6 ± 0.8 to 9.1 ± 0.6 mmol/L), the peak plasma glucose (20.0 ± 1.0 to 17.0 ± 1.0 mmol/L), and the mean plasma glucose (16.6 ± 0.9 to 14.0 ± 0.8 mmol/L) concentrations during OGTT all declined significantly (P < 0.01) during metformin treatment (Fig. 1). The declines in fasting, peak, and mean plasma glucose concentrations during OGTT were of similar magnitude in obese (P < 0.05) and lean (P < 0.05) diabetic groups. The integrated area under the plasma glucose concentration curve was similar in both lean and obese diabetic groups before and after metformin treatment. Both the fasting plasma insulin concentration and the mean plasma insulin response to glucose (265 ± 50 to 187 ± 29 pmol/L; P = NS) were slightly although not significantly decreased by metformin (Fig. 1). This trend did not reach statistical significance in either obese or lean diabetic groups.

HGP

Basal HGP was significantly (P < 0.05) increased in diabetic (83 ± 4 mg/m\(^2\)-min) compared to control (71 ± 2 mg/m\(^2\)-min) subjects and fell after metformin treatment to 61 ± 3 mg/m\(^2\)-min (P < 0.001). The decrement in HGP in NIDD subjects correlated closely (r = 0.80; P < 0.01) with the decline in fasting plasma glucose concentration (Fig. 3). HGP and fasting plasma glucose concentrations declined in every diabetic subject. The decrease in HGP was of similar magnitude in obese (81 ± 3 to 57 ± 4 mg/m\(^2\)-min) and lean (86 ± 11 to 68 ± 4 mg/m\(^2\)-min) diabetic groups (both P < 0.02 vs. baseline).

During the euglycemic insulin clamp, HGP was suppressed by over 90% in control and NIDD subjects in the studies performed both before and after metformin treatment.

Euglycemic insulin clamp (Fig. 4)

The steady state plasma glucose (5.44 ± 0.05 vs. 5.34 ± 0.05 mmol/L) and insulin (I; 660 ± 43 vs. 639 ± 36 pmol/L) concentrations during the insulin clamp studies performed before and after metformin treatment were similar; no differences were observed between obese and lean diabetic subjects. Similar steady state plasma glucose (5.11 ± 0.05 mmol/L) and insulin (538 ± 36 pmol/L) levels were achieved in controls. The coefficients of variation for plasma glucose and insulin were less than 5% and 10%, respectively, in both groups. During the euglycemic insulin clamp in obese NIDD subjects, the rate of total body glucose uptake (M) rose slightly from 121 ± 10 to 146 ± 19 mg/m\(^2\)-min (P < 0.05), while the M/I ratio increased from 1.18 ± 0.11 to 1.65 ± 0.29 mg/m\(^2\)-min.
m²·min per μU/mL × 100 (P < 0.05; Fig. 4). The rise in total body glucose uptake in obese NIDD subjects was primarily accounted for by an increase in nonoxidative glucose disposal (42 ± 18 to 74 ± 20 mg/m²·min; P < 0.05) without a change in the rate of glucose oxidation (79 ± 12 to 76 ± 13 mg/m²·min). In lean NIDD subjects, total body glucose uptake (171 ± 29 to 150 ± 20 mg/m²·min) and the M/I ratio (2.15 ± 0.34 to 1.86 ± 0.12 mg/m²·min per μU/mL × 100) remained unchanged after metformin treatment (Fig. 4). Neither nonoxidative glucose disposal (74 ± 26 vs. 55 ± 11 mg/m²·min) nor glucose oxidation (99 ± 9 vs. 95 ± 15 mg/m²·min) was significantly altered during the insulin clamp study performed after metformin treatment. In both obese and lean diabetic subjects, whole body glucose uptake, nonoxidative glucose disposal, and glucose oxidation during the insulin clamp were significantly less than those in controls, in whom they averaged 295 ± 16, 178 ± 15, and 117 ± 12 mg/m²·min, respectively.

Hyperglycemic clamp (Fig. 5)

The steady state plasma glucose concentrations during the pre- and postmetformin hyperglycemic clamp studies were 19.09 ± 0.78 (increment, 7.11) and 16.26 ± 0.83 (increment, 7.33) mmol/L, respectively, with coefficients of variation of less than 5%. Since no differences in plasma insulin response (early, late, and total) or total body glucose uptake were observed between lean and obese NIDD, data from both groups have been combined for simplicity of presentation. The early (86 ± 14 vs. 72 ± 7 pmol/L), late (172 ± 29 vs. 151 ± 21 pmol/L), and total (165 ± 28 vs. 144 ± 14 pmol/L) plasma insulin (I) responses were similar before and after metformin (Fig. 4). The present results demonstrate that single therapy with metformin is effective in treating both obese and lean type 2 diabetic patients. The decrease in fasting glucose concentration was nearly identical in obese (2.66 mmol/L) and lean (2.72 mmol/L) diabetic groups. This decrement is similar to that reported by other investigators who have employed this biguanide (5, 10, 12, 13, 22, 27) and at least comparable to previous studies that employed sulfonylurea agents (55–57) have shown, the primary determinant of the fasting plasma glucose concentration is the basal rate of HGP. In diabetic subjects, basal HGP was significantly (P < 0.05) increased compared to that in controls. After treatment with metformin for 3 months, a significant decrease in basal HGP was observed, and the decrement in HGP correlated closely (r = 0.80; P < 0.001) with the decrement in fasting plasma glucose concentration. Since the fasting plasma insulin concentration declined, our results suggest that the biguanide may exert a direct inhibitory action on hepatic glucose output. This observation is consistent with in vitro studies which have demonstrated that biguanides, and metformin in particular, inhibit gluconeogenesis in isolated hepatocytes and the perfused liver (23–25). Basal HGP fell similarly in obese (81 ± 3 to 57 ± 4 mg/m²·min; Δ, 24) and normal weight (86 ±
Hyperglycemic Clamp in NIDDM and Controls

Fig. 5. Total body glucose uptake, mean plasma insulin response (0–120 min), and glucose clearance during the hyperglycemic clamp in all 14 diabetic patients before (□) and after (●) metformin therapy. □, Control subjects. All values represent the mean ± SEM. *, \( P < 0.01 \) in diabetic subjects after vs. before metformin treatment.

11 to 68 ± 4 mg/m²·min; △, 18) NIDDM groups, indicating that the inhibitory effect of metformin on HGP cannot be explained by weight loss alone.

Metformin treatment was also associated with a significant improvement in oral glucose tolerance. Since the plasma insulin response to both oral and iv (hyperglycemic clamp) glucose either remained unchanged or fell slightly, the improvement in glucose disposal cannot be attributed to a stimulatory effect of metformin on the β-cell. This observation is consistent with previous reports that also failed to detect any change in either fasting or glucose-stimulated plasma insulin levels after metformin treatment (1, 7, 18, 21, 26, 27). It is noteworthy that the increment in plasma glucose concentration above baseline during the OGTT in both the obese and lean diabetic groups was similar before and after metformin. Thus, the major beneficial effect of metformin on the OGTT was related to a reduction in fasting plasma glucose, which, in turn, was closely related to a decline in basal HGP.

To further explore the actions of metformin on glucose metabolism, we compared the results obtained from eu- and hyperglycemic insulin and hyperglycemic clamp studies performed before and after 3 months of metformin therapy. During the insulin clamp, the effect of metformin on insulin-mediated glucose disposal was significantly different in obese and lean NIDD subjects. In the lean diabetic group, body weight remained unchanged after metformin treatment, and insulin-mediated glucose disposal either remained unchanged or declined slightly; no significant changes in either glucose oxidation or non-oxidative glucose disposal were observed. In contrast, metformin therapy was associated with an increase in insulin sensitivity in the obese NIDD group, and this was due entirely to an improvement in nonoxidative glucose disposal. Suppression of HGP by insulin was unaffected by metformin in obese NIDD subjects. Thus, enhanced peripheral tissue sensitivity to insulin was responsible for the beneficial effect of metformin in this group. It is noteworthy that each obese diabetic subject experienced a significant reduction in body weight (mean, 5 ± 1 kg). We interpret these results to indicate that the primary effect of metformin to enhance insulin sensitivity in the obese diabetic group is mediated via a reduction in body weight rather than by a direct action of the drug on insulin-mediated glucose disposal. It is well established that weight loss per se will enhance tissue sensitivity to insulin (55). Conflicting results have been reported concerning the effect of metformin on insulin sensitivity. Some studies have suggested that metformin enhances insulin action (22, 58), while others have failed to confirm this observation (27). In part, these discrepancies may result from the failure to take into account changes in body weight that may occur during metformin treatment (22, 27, 58), to the concomitant administration of insulin or glyburide (58), or to the small number of diabetic patients studied (22). In the present study glucose tolerance uniformly improved in lean and obese diabetic subjects during both the hyperglycemic clamp and the OGTT. Since insulin-mediated glucose disposal (insulin clamp) increased only in the obese NIDD group, changes in tissue sensitivity to insulin cannot completely explain the beneficial effect of metformin on glucose metabolism. Although it could be argued that a persistent effect of sulfonylurea therapy in the present study masked a beneficial action of metformin on insulin sensitivity, we believe that this is unlikely, since an improvement in insulin sensitivity was observed in those diabetics who lost weight.
In contrast to the euglycemic insulin clamp, all diabetic subjects experienced a significant 24% improvement in glucose utilization during the hyperglycemic clamp, even though the plasma insulin response remained unchanged or decreased slightly. These results suggest that the mass action effect of glucose to promote its own uptake (37, 59) is enhanced by metformin in NIDDM.

Metformin treatment was associated with a significant improvement in the plasma lipid profile. Plasma triglyceride and total cholesterol concentrations fell significantly in all diabetic patients, both lean and obese. In six diabetic patients (three lean and three obese) in whom they were measured, HDL cholesterol increased and LDL cholesterol decreased significantly. This was accompanied by a rise in the HDL/LDL cholesterol ratio. These findings are consistent with previous observations (27). Although our results do not address the mechanism by which metformin lowers plasma lipid levels, the combined glucose-, triglyceride-, and cholesterol-lowering effects of the drug make it an ideal therapeutic agent for the treatment of NIDDM, especially in overweight individuals.

An important observation of the present study is that metformin improved glucose tolerance without significantly elevating basal plasma lactate levels. This observation is in distinct contrast to phenformin, which elevates the fasting plasma lactate concentration and is associated with a high incidence of lactic acidosis (3, 5, 10, 18). This difference is directly related to the known biochemical actions of the two biguanides. In vitro phenformin inhibits oxidative phosphorylation and causes a shift to anaerobic glycolysis, whereas metformin has no inhibitory effect on the Krebs cycle and glucose oxidation (4, 19, 18, 19, 34). The present in vivo results are consistent with these in vitro observations. Thus, in both the obese and normal weight diabetics, basal and insulin-stimulated glucose oxidation was unaltered after metformin treatment. These results provide strong evidence that metformin does not inhibit aerobic glycolysis in vivo and are consistent with the low incidence of lactic acidosis observed after metformin treatment of NIDDM patients (1–5, 10, 18).

In summary, metformin is an effective drug for the treatment of NIDDM. It lowers the fasting plasma glucose concentration and enhances glucose tolerance, while at the same time improving the plasma lipid profile. The beneficial effects of metformin on glucose metabolism appear to be related to three factors: 1) suppression of basal HGP, 2) improvement in glucose-mediated glucose uptake, and 3) enhancement of tissue sensitivity to insulin, which, in turn, is related to a reduction in body weight. The mechanism by which metformin promotes weight loss in obese diabetics remains unknown.

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