# Adding Metformin Versus Insulin Dose Increase in Insulin-treated but Poorly Controlled Type 2 Diabetes Mellitus: an Open-label Randomized Trial

**F. Relimpio*, A. Pumar, F. Losada, M.A. Mangas, D. Acosta, R. Astorga**

*Servicio de Endocrinología, Hospital Universitario Virgen del Rocío, Seville, Spain*

**To compare the effect of adding metformin to insulin therapy with a moderate increase in insulin dose alone in insulin-treated, poorly controlled Type 2 diabetic patients, 47 consecutive such patients (baseline daily dose >0.5 IU $kg^{-1}$ and $HbA_{1c}$ >8 %) were openly randomized either to a combination of their previous insulin schedule plus metformin (2.55 g daily in three divided doses, $n = 24$) or to a moderate insulin dose increase (20 % of baseline, $n = 23$). The patient status/biochemical profile was assessed at entry and at 4 months. Among those assigned to insulin + metformin, 18 took the drug. Upon an intention-to-treat basis, patients assigned to insulin dose increase had a statistically significant weight gain (1.16 + 1.9 vs 0.3 ± 4.5 kg, $p < 0.05$). Patients assigned to the insulin + metformin regimen experienced a significantly greater fall in $HbA_{1c}$ (−1.87 ± 2.16 vs 0.03 ± 1.68 %, $p < 0.01$), total cholesterol (−0.56 ± 0.89 vs 0.14 ± 0.72 mmol $l^{-1}$, $p < 0.05$) and LDL-cholesterol (−0.51 ± 0.73 vs 0.19 ± 0.6 mmol $l^{-1}$, $p < 0.01$). These data suggest that adding metformin to insulin in poorly controlled Type 2 DM patients offers an advantage in terms of glycaemic control and lipid plasma profile.**


***Diabet. Med.* 15: 997–1002 (1998)**

KEY WORDS **Type 2 diabetes mellitus; insulin therapy; insulin resistance; metformin; LDL-cholesterol**

**Received 1 April 1998; revised 3 July 1998; accepted 17 July 1998**

## Introduction

Sulphonylureas are an efficacious therapeutic tool for many Type 2 diabetic patients inadequately controlled on diet and exercise. However, uncontrolled fasting hyperglycemia frequently ensues after a variable length of time and additional or alternative modes of therapy are then required.[1,2] Exogenous insulin therapy, alone or combined with sulphonylureas,[3,4] has been commonly used with variable success and some side-effects (mainly weight gain).[3] Due to their insulin-resistance, insulin-requiring patients often need high daily doses of insulin to achieve acceptable glycaemic control, and some of them never reach their targets in spite of increasing insulin doses.

Biguanides act by inhibiting hepatic glucose production[5] and increasing peripheral insulin-induced glucose uptake,[6–9] although their exact mechanism of action is not known. Their most serious potential side-effect, the risk of lactic acidosis,[10] is mainly associated with phenformin,[11] usually when there is a clear contraindication for its use. The relative safety of metformin,[12] the central role attributed to insulin-resistance in Type 2 diabetes[13] and the beneficial effect of biguanides upon coagulation,[14] plasma lipids,[9,11,14] endogenous insulinaemia,[15] body weight,[16] and possibly blood pressure[17] (in addition to their antihyperglycemic effect[15,16,18]), have led to their use as first-line drugs or combined with sulphonylureas. Double-blind, placebo-controlled trials have shown beneficial effects of adding biguanides to poorly controlled Type 2 diabetic patients, either on other oral agents[18,19] or, in one study, on insulin.[20]

This open-label randomized clinical trial was designed to compare the effect of adding metformin to the therapeutic regimen of insulin-treated but poorly controlled Type 2 diabetic patients with our current practice of a moderate increase in insulin dose.

## Methods

### *Subjects*

Poorly controlled (baseline $HbA_{1c} > 8$ %) , insulin-treated Type 2 diabetic patients, treated with at least 0.5 daily insulin IU $kg^{-1}$ body weight in two or more daily

Sponsors: Novo Nordisk Pharma
* Correspondence to: Dr Federico Relimpio, Unidad de Endocrinología, Centro de Especialidades Virgen de los Reyes, c/Marqués de Paradas s/n, 41001 Seville, Spain. E-mail: mjuez@cica.es

CCC 0742–3071/98/120997–06$17.50

injections were eligible for study. Presence of any life threatening condition and commonly accepted contra-indications for the use of biguanides[12] were exclusion criteria. A serum creatinine lower than 132.6 μmol $l^{-1}$ was required.

Patients were recruited from those currently attending our outpatient diabetes unit, and all had been instructed in lifestyle and dietary recommendations for diabetes care. Every patient was supplied with a home glucose reflectance meter and instructed in its use. From January 1996 to April 1997, 60 consecutive patients fulfilled the inclusion criteria, gave informed consent, and were subsequently randomized (31 to insulin + metformin and 29 to insulin dose increase).

## *Protocol*

After documenting a $HbA_{1c}$ level higher than 8 % with their current insulin regimen and having excluded as far as possible failure of compliance as a cause of poor glycaemic control, patients were randomized into two study groups following an experimental design of open-label randomization. Baseline information such as patient weight and blood pressure and a biochemical profile including measurement of fasting blood glucose, uric acid, creatinine, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apolipoprotein $A_1$, apolipoprotein B and the urinary albumin excretion rate was collected.

Patients assigned to the insulin + metformin group (I+M) were initially prescribed metformin hydrochloride 1.275 g daily, to be taken with meals. Patients were warned about the possible appearance of gastrointestinal symptoms and the likelihood of tolerance developing with continued drug intake. In case of persistent gastrointestinal upset, they were recommended to reduce to the highest tolerable dose and to try to increase later to the prescribed dose. Patients in this group were instructed to maintain their current insulin dose and regimen, although a small reduction in their insulin dose was introduced in the presence of hypoglycaemia. The first scheduled visit was 1 month after randomization to monitor patient compliance and the presence of side-effects. If the drug was well tolerated, an increase in the daily dose up to 2.550 g daily (Glucophage 850©, Boehringer-Mannheim SA, Barcelona, Spain, t.d.s) was introduced. If the drug was not well tolerated, patients were instructed to maintain the highest tolerable dose. If the drug had been stopped, patients were encouraged to reintroduce it and maintain it at the highest tolerable dose.

At baseline, the presence of hypertension was defined by the need to take antihypertensive drugs or if resting systolic blood pressure was greater than 160 mmHg and/or diastolic blood pressure greater than 90 mmHg. Systolic (SBP) and diastolic (DBP) pressures (fifth phase) were measured to the nearest 5 mmHg both at baseline and at the third (final) visit, after the intake of the morning antihypertensive treatment (if needed) and a 10-min rest period in the sitting position. Height and weight were measured with the subjects wearing light clothes, without shoes. The body mass index (BMI) was calculated as weight in kg divided by height in $m^2$.

Patients assigned to the insulin dose increase group (IDI) were instructed to increase their daily insulin dose by 10 % initially. No changes were made either in the type of insulin used or the number of daily injections. Blood glucose monitoring data were used to decide which insulin dose to alter. Patients were encouraged to maintain their new insulin dose and regimen, only reducing the dose a little should hypoglycaemia occur. The first scheduled visit was 1 month after randomization to monitor patient compliance with the new regimen and the results of home blood glucose self-monitoring. If every value was then under 11 mmol $l^{-1}$, no further insulin dose modification was undertaken. If values were above this figure, a further 10 % insulin dose increase was applied.

For both groups, no other treatment modification was allowed. A second visit was scheduled 3 months later (4 months since entry) for assessing patient status, insulin regimen and dose, drug compliance (in the first group), body weight and blood pressure, as well as obtaining a new biochemical profile.

At baseline, insulin was administered in two daily injections (before breakfast and before dinner) in 23 patients in the I+M group and in 22 patients in the IDI group, and three daily injections (one injection before each main meal) were used by one patient in each group. At the end of the study, a single injection regimen (before breakfast) was used by one patient in the I+M group, two daily injections by 22 patients in each group, and three daily injections regimen was used by one patient in each group. Both at baseline and end of the study, the type of insulin used was a premixed formulation of soluble and NPH insulin in 21 patients in each group, and NPH insulin in three and two patients in the I+M and IDI group, respectively. The frequency of use of antihypertensive drugs able to alter insulin-sensitivity (ACE inhibitors and thiazide diuretics) was not statistically significantly different between both groups either at the beginning or at the end of study (Table 1).

## *Biochemical Measurements*

Blood samples for biochemical determinations were taken from an antecubital vein after a 10 h fast, previously to drug intake and/or insulin administration. Fasting blood glucose (FBG) was measured by a hexokinase method (Gluco-quant® Glucose, Boehringer-Mannheim SA, Barcelona, Spain); serum creatinine by an enzymatic colorimetric test (Creatinine-PAP®, Boehringer-Mannheim SA, Barcelona, Spain), and urinary albumin excretion rate (UAER) in one overnight urine collection using laser immunonephelometry (Behring nephelometer analyser, Behring, Marburg, Germany). An UAER $< 20$ μg $min^{-1}$ was considered normoalbuminuria, $> 20$ and



 

Table 1. Absolute and relative frequency of use of antihypertensive drugs able to alter insulin-sensitivity in both groups at baseline and end of the study

| | Insulin+ metformin | Insulin dose increase | *p* |
|---|---|---|---|
| Thiazide diuretic use (*n*,%)[a] | | | |
| Baseline | 2 (8.3) | 4 (17.3) | ns |
| End | 2 (8.3) | 5 (21.7) | ns |
| ACE inhibitors use (*n*,%)[b] | | | |
| Baseline | 10 (41.6) | 7 (30.4) | ns |
| End | 13 (54.1) | 8 (34.7) | ns |

Statistical comparisons were achieved by means of either [a]Fisher's exact test or [b]Pearson's $\chi^2$ test.
ns, statistically non-significant differences.

$< 200\ \mu g\ min^{-1}$ was considered microalbuminuria and UAER $> 200\ \mu g\ min^{-1}$ was considered macroalbuminuria. $HbA_{1c}$ was measured by HPLC (HPLC autoanalyzer, DIC (Menarini, Barcelona, Spain) non-diabetic range $< 5.5$ %); total serum cholesterol by a fully-enzymatic method (CHOD-PAP®, Boehringer-Mannheim SA, Barcelona, Spain). HDL-cholesterol was measured after precipitation of VLDL and LDL with phosphotungstic acid and magnesium chloride. Friedewald's formula was used to compute LDL-cholesterol. Serum triglycerides were measured by an enzymatic method (GPO-PAP®, Boehringer-Mannheim SA, Barcelona, Spain) normal values and serum uric acid by an enzymatic colorimetric test (Uric Acid PAP® Boehringer-Mannheim SA, Barcelona, Spain).

### *Statistical Analysis*

Quantitative variables are expressed as mean ± SD. Data were analysed according the intention-to-treat principle. Differences between both groups of study were assessed by means of the Mann–Whitney U test for quantitative variables and either Pearson's $\chi^2$ test or Fisher's exact test for categorical variables. Relationships between quantitative variables were assessed by means of the non-parametric Spearman's correlation coefficient ($r_s$). All contrasts are two-tailed; $p < 0.05$ was considered significant. All statistical calculations were made by means of the statistical software package SPSS for Windows (SPSS Inc.) by using a PC.

## Results

From the 60 patients initially randomized, 47 (78.3 %) completed the study protocol and were available for analysis (24 assigned to I+M and 23 to IDI). For the rest, 3 (2 assigned to I+M and 1 to IDI) failed to comply with the visit schedule and 10 (5 assigned to I+M and 5 to IDI) were lost to follow-up. The groups did not differ significantly in any variable at baseline (Tables 2 and 3). Lipid-lowering therapy use at baseline was more frequent in the IDI group, this did not reach statistical significance. Among the patients assigned to I+M, 18 (75 %) took the drug (14 at a final dose of 2.550 g, 1 at 2.125 g, 1 at 1.700 g, 1 at 1.275 g and 1 at 850 g) and 6 did not (3 did not modify their insulin dose and 3 increased it). Gastrointestinal symptoms accounted for every total or partial non-compliance with drug intake.

Patients assigned to I+M had a small reduction in insulin dose during the study (Table 2). Among the patients assigned to IDI, 21 increased their insulin dose and 2 of them did not modify it. These patients increased their daily insulin dose by an average of 9 IU, thus reaching a significantly greater daily insulin dose than the I+M group at the end of the study (Table 2). Apart from gastrointestinal symptoms in the I+M group and minor hypoglycaemic episodes in both groups, no other relevant clinical event was observed.

Final values for demographic and biochemical variables and their difference with baseline values are shown in Tables 2 and 3. Patients assigned to IDI experienced a small but statistically significant increase in body weight and BMI, as compared with the I+M group (Table 2). The I+M group experienced a significant fall in $HbA_{1c}$, as compared with the IDI group, in whom no change was observed (Table 3). Likewise, the I+M group had modest falls in total and LDL-cholesterol and apolipoprotein B levels, compared with the IDI group, for whom small rises in these three variables were observed. Differences were statistically significant for total and LDL-cholesterol (Table 3).

Among the patients assigned to I+M who took the drug, the $HbA_{1c}$ change ($-2.03 \pm 2.37$ % for this subset) had statistically significant negative correlations with baseline $HbA_{1c}$ ($r_s = -0.58$, $p < 0.05$) and with baseline SBP ($r_s = -0.49$, $p < 0.05$). Likewise, hypertensive patients had a statistically non-significant greater $HbA_{1c}$ fall ($-2.94 \pm 3.08$ vs $-1.12 \pm 0.73$ %) compared with normotensives in this subset. Similar relationships were not observed in the patients assigned to IDI that increased their insulin dose. No other baseline demographic or biochemical variable had a statistically significant correlation with the $HbA_{1c}$ change in any group of study. Particularly, BMI at entry did not have a statistically significant correlation with $HbA_{1c}$ change in those patients assigned to I+M that took the drug.

## Discussion

This open-label randomized trial demonstrated significant falls in $HbA_{1c}$, total and LDL-cholesterol in patients assigned to add metformin to their insulin treatment (I+M), as compared to patients assigned to a 20% increase in insulin dose. Patients in the latter group experienced a modest weight gain. These differences were statistically significant, even though the compliance was not complete and data were analysed on an intention-to-treat basis.

Individuals included in this study were mainly elderly and obese Type 2 diabetic patients, submitted to relatively



 

Table 2. Baseline and final demographic variables for both groups of study. For quantitative variables, the comparison between both groups of study was made by means of the Mann–Whitney U test. For each quantitative variable, the difference was calculated as the final – baseline value

| Variable | Insulin+metformin | Insulin dose increase | *p* |
|---|---|---|---|
| Age (yr) | 65.4 ± 7.9 | 66.7 ± 6.2 | ns |
| Known duration of diabetes (yr) | 15.4 ± 7.7 | 15.3 ± 6 | ns |
| Gender (*n*(%) of males/females) | 5 (20.8)/19 (79.2) | 8 (34.8)/15 (65.2) | ns |
| Weight (kg) | | | |
| Baseline | 76.8 ± 12.6 | 78.04 ± 12.9 | ns |
| End | 77.09 ± 11.7 | 79.2 ± 13.5 | ns |
| Difference | 0.3 ± 4.5 | 1.16 ± 1.9 | <0.05 |
| Body mass index (kg $m^{-2}$) | | | |
| Baseline | 33 ± 4.7 | 31.9 ± 4.5 | ns |
| End | 33.06 ± 4.3 | 32.3 ± 4.6 | ns |
| Difference | 0.07 ± 1.97 | 0.45 ± 0.75 | <0.05 |
| Daily insulin dose (UI) | | | |
| Baseline | 47.9 ± 10 | 51.8 ± 9.6 | ns |
| End | 45 ± 12.4 | 61 ± 11.2 | <0.001 |
| Difference | –2.9 ± 7.4 | 9.1± 5.1 | <0.001 |
| Insulin dose/body weight (UI $kg^{-1}$) | | | |
| Baseline | 0.63 ± 0.12 | 0.67 ± 0.11 | ns |
| End | 0.59 ± 0.15 | 0.78 ± 0.14 | <0.001 |
| Difference | –0.04 ± 0.09 | 0.11 ± 0.08 | <0.001 |
| Systolic blood pressure (mmHg) | | | |
| Baseline | 153.5 ± 24 | 148.4 ± 24.8 | ns |
| End | 150.4 ± 21.4 | 154.6 ± 30.7 | ns |
| Difference | –3.09 ± 20.5 | 6.2 ± 30.5 | ns |
| Diastolic blood pressure (mmHg) | | | |
| Baseline | 81.6 ± 10.8 | 80 ± 14.4 | ns |
| End | 82 ± 10.8 | 82.9 ± 15.5 | ns |
| Difference | 0.39 ± 9.73 | 2.91 ± 15.63 | ns |
| Hypertension (n, %) | 13 (54.2) | 13 (56.2) | ns |
| Fibric acid derivative use (n, %) | 2 (8.3) | 4 (17.3) | ns |
| HMG CoA inhibitor use (n, %) | 1 (4.1) | 5 (21.7) | ns |

Quantitative variables are expressed as mean ± SD.
ns, statistically non-significant differences.

high doses of insulin and not achieving good glycaemic control. Conventional therapeutic options in this clinical setting are limited to improved adherence to dietary prescriptions, encouragement of moderate physical activity and increasing insulin doses, as well as intensification of the insulin injection regimen. Increasing the insulin dose is often associated with significant weight gain. Biguanides are attractive tools to include in the daily management of patients for whom a considerable degree of insulin resistance can be anticipated.[5–12,14–19]

In one double-blind placebo-controlled clinical trial,[20] metformin improved glycemic control in obese, insulin-treated diabetic patients. The presence of type 2 diabetes,[13] the advanced age and long known duration of diabetes, the adiposity,[21–23] the frequency of hypertension,[24–27] and the lack of adequate glycaemic control in spite of the relatively high insulin doses, suggests a degree of insulin resistance in these patients and a rationale for metformin use.

The randomization procedure ensured comparable groups of patients at baseline. For patients given metformin, compliance was not complete due to gastrointestinal upset. This and episodes of minor hypoglycaemia, were the only adverse effects of the I+M regimens. There was a small reduction in insulin dose in those patients assigned to I+M and a significant increase in those patients assigned to incremental insulin alone (IDI). As expected, body weight increased in patients assigned to IDI.[28]

A significant benefit in terms of $HbA_{1c}$ was observed for the I+M group. Should this short-term effect persist, the addition of metformin to insulin in insulin-treated Type 2 patients has not only an insulin sparing effect but a real potential advantage in terms of prevention of micro- and probably macrovascular complications. The significant improvement in the lipid plasma profile (towards a lesser atherogenicity) observed in the I+M group confirms previous observations[20] and should have a beneficial repercussion upon the macrovascular complications of diabetes. However, this effect must be viewed in the context of the greater frequency of hypolipidaemic drug use in the IDI group. Drug-induced alleviation of



 

Table 3. Baseline and final biochemical variables for both groups of study. For quantitative variables, the comparison between both groups of study was made by means of the Mann–Whitney U test. For each quantitative variable, the difference was calculated as the final – baseline value

| Variable | Insulin+metformin | Insulin dose increase | *p* |
|---|---|---|---|
| Fasting blood glucose (mmol $l^{-1}$) | | | |
| Baseline | 13.52 ± 3.69 | 14.12 ± 2.7 | ns |
| End | 10.6 ± 3.88 | 12.66 ± 3.47 | = 0.09 |
| Difference | –2.9 ± 4.45 | –1.44 ± 3.45 | ns |
| $HbA_{1c}$(%) | | | |
| Baseline | 9.63 ± 1.42 | 9.57 ± 1.2 | ns |
| End | 7.76 ± 1.58 | 9.6 ± 1.79 | <0.01 |
| Difference | –1.87 ± 2.16 | 0.03 ± 1.68 | <0.01 |
| Total cholesterol (mmol $l^{-1}$) | | | |
| Baseline | 5.84 ± 0.99 | 5.92 ± 1.2 | ns |
| End | 5.28 ± 1.1 | 6.06 ± 1.24 | <0.05 |
| Difference | –0.56 ± 0.89 | 0.14 ± 0.72 | <0.05 |
| LDL cholesterol (mmol $l^{-1}$) | | | |
| Baseline | 3.84 ± 0.51 | 3.71 ± 1.15 | ns |
| End | 3.31 ± 0.79 | 3.9 ± 1.05 | <0.05 |
| Difference | –0.51 ± 0.73 | 0.19 ± 0.6 | <0.01 |
| Apolipoprotein B (mg $dl^{-1}$) | | | |
| Baseline | 122.4 ± 20.3 | 123.5 ± 29.8 | ns |
| End | 109.4 ± 22.1 | 126.3 ± 31.6 | = 0.07 |
| Difference | –13 ± 23.4 | 2.77 ± 21.5 | = 0.05 |
| HDL cholesterol (mmol $l^{-1}$) | | | |
| Baseline | 1.36 ± 0.18 | 1.26 ± 0.26 | ns |
| End | 1.36 ± 0.3 | 1.34 ± 0.35 | ns |
| Difference | –0.003 ± 0.17 | 0.08 ± 0.25 | ns |
| Apolipoprotein $A_1$ (mg $dl^{-1}$) | | | |
| Baseline | 149.2 ± 18.5 | 140.7 ± 23.7 | = 0.06 |
| End | 144.7 ± 20.6 | 145.5 ± 31.1 | ns |
| Difference | –4.5 ± 16.1 | 4.7 ± 20.9 | ns |
| Triglycerides (mmol $l^{-1}$) | | | |
| Baseline | 2.01 ± 1.12 | 2.41 ± 1.53 | ns |
| End | 1.65 ± 0.75 | 2.32 ± 1.05 | <0.05 |
| Difference | –0.36 ± 0.7 | –0.08 ± 1.18 | ns |
| Uric acid ($\mu$mol $l^{-1}$) | | | |
| Baseline | 277.7 ± 79.1 | 281.9 ± 65.4 | ns |
| End | 304.5 ± 77.9 | 308.7 ± 107 | ns |
| Difference | 26.7 ± 32.7 | 27.3 ± 83.2 | ns |
| UAER (*n*(%) of normo, micro and macroalbuminurics) | 11 (45.8)/8 (33.3) /5 (20.8) | 13 (56.5)/7 (30.4) /3 (13) | ns |

UAER, urinary albumin excretion rate.
Quantitative variables are expressed as mean ± SD.
ns, statistically non-significant differences.

insulin resistance in insulin-treated Type 2 diabetes may be achieved by means of other drugs. Recently, troglitazone was proved beneficial for these kinds of patients by means of a double-blind, placebo-controlled clinical trial.[29] This drug was substantially better tolerated than metformin, although it caused a slight weight increase and did not have the beneficial impact upon the lipid plasma profile reported for metformin in several studies.

Thus, this open-label randomized trial reinforces this relatively novel therapeutic strategy for a difficult-to-deal-with subset of Type 2 diabetic patients. This approach is safe and beneficial both in terms of glycaemic control and plasma lipids. In spite of it, widespread confirmation should be awaited from other study groups before changing current recommendations. Alternatively, it remains to be tested if a greater increase in the insulin dose could add any benefit to this kind of patients. In any case, the increasing number of patients attaining this situation warrants further work in this area, either to confirm these results or to offer new alternatives.

**Acknowledgements**

We are indebted to Novo Nordisk Pharma for their support. We are also grateful to I. Ríos, B. Ballell, J. Chaves, B. González and R. Berzosa for their enthusiastic help in all our activities.



 

## References


1. Gerich JE. Oral hypoglycemic agents. *N Engl J Med* 1989; **321**: 1231–1245.
2. Groop LC. Sulphonylureas in NIDDM. *Diabetes Care* 1992; **15**: 737–754.
3. Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, *et al*. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1992; **327**: 1426–1433.
4. Lebovitz HE, Pasmantier RM. Combination insulin-sulphonylurea therapy. *Diabetes Care* 1990; **13**: 667–675.
5. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean non-insulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 1991; **73**: 1294–1301.
6. Widen EIM, Eriksson JG, Groop LC. Metformin normalizes nonoxidative glucose metabolism in insulin-resistant normoglycemic first-degree relatives of patients with NIDDM. *Diabetes* 1992; **41**: 354–358.
7. Hother-Nielsen O, Schmitz O, Andersen PH, Beck-Nielsen H, Pedersen O. Metformin improves peripheral but not hepatic insulin action in obese patients with type II diabetes. *Acta Endocrinol* 1989; **120**: 257–265.
8. Klip A, Leiter LA. Cellular mechanism of action of metformin. *Diabetes Care* 1990; **13**: 696–704.
9. Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992; **15**: 755–772.
10. Nattrass M, Alberti KGMM. Biguanides. *Diabetologia* 1978; **14**: 71–74.
11. Hermann LS, Melander A. Biguanides: basic aspects and clinical uses. In: Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, eds. *International Textbook of Diabetes Mellitus*, vol. 1. Chichester: Wiley, 1992: 773–795.
12. Bailey CJ, Turner RC. Drug therapy: metformin. *N Engl J Med* 1996; **334**: 574–579.
13. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, *et al*. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima indians. *N Engl J Med* 1993; **329**: 1988–1992.
14. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects: a study of two ethnic groups. *Diabetes Care* 1993; **16**: 621–629.
15. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *Br Med J* 1995; **310**: 83–88.
16. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **333**: 550–554.
17. Landin K, Tengborn L, Smith U. Treating insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. *J Intern Med* 1991; **229**: 181–187.
18. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **333**: 541–549.
19. Hermann LS, Schersten B, Bitzen PO, Kjellstrom T, Lindgarde F, Melander A. Therapeutic comparison of metformin and sulphonylurea, alone and in various combinations: a double-blind controlled study. *Diabetes Care* 1994; **17**: 1100–1109.
20. Giugliano D, Quatraro A, Consoli G, Minei A, Ceriello A, DeRosa N, d'Onofrio F. Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. *Eur J Clin Pharmacol* 1993; **44**: 107–112.
21. Polonsky KS, Given BD, Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 1988; **81**: 442–448.
22. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995; **96**: 88–98.
23. Bergstrom RW, Newell-Morris LL, Leonetti DL, Shuman WP, Wahl PW, Fujimoto WY. Association of elevated C-peptide level and increased intra-abdominal fat distribution with development of NIDDM in Japanese-American men. *Diabetes* 1990; **39**: 104–111.
24. Ferrannini E, Buzzigioli G, Bonadonna R. Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**: 350–357.
25. Zavaroni I, Bonora E, Pagliara M. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 1989; **320**: 702–706.
26. Laakso M, Sarlund H, Mykkänen L. Essential hypertension and insulin resistance in non-insulin-dependent diabetes. *Eur J Clin Invest* 1989; **19**: 518–526.
27. Wasada T, Kuroki H, Arii H, Maruyama A, Aoki K, Katsumori K, *et al*. Relationship between insulin resistance and risk factors for cardiovascular disease in Japanese non-insulin-dependent diabetic patients. *Diabetes Res Clin Pract* 1994; **25**: 191–198.
28. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.
29. Schwartz S, Raskin P, Fonseca V, Graveline JF and the Troglitazone and Exogenous Insulin Study Group. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 1998; **338**: 861–866.




 