Long-Term Efficacy of Metformin Therapy in Nonobese Individuals With Type 2 Diabetes

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OBJECTIVE — The U.K. Prospective Diabetes Study (UKPDS) has demonstrated that metformin is as effective as sulfonylureas in obese subjects and is associated with less weight gain, fewer hypoglycemic episodes, and better cardiovascular outcomes. It is hence the pharmacological therapy of choice in this subgroup. However, a gap in our present knowledge is the long-term response to metformin in nonobese individuals. In this study, we compared metformin therapy in normal, overweight, and obese individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A database of patients treated at a referral center in Sydney, Australia, were analyzed. Patients with type 2 diabetes and complete HbA_{1c} (A1C) data and treated with metformin or sulfonylurea monotherapy for at least three visits before receiving dual oral therapy were included ($n = 644$). Analysis by BMI and the type of oral agent was performed. Individuals were categorized as normal, overweight, or obese (BMI <25, 25–29.9, and ≥ 30 kg/m^2, respectively).

RESULTS — There were no differences between the initial, follow-up, and last A1C between the three metformin-treated groups. The duration of successful glycemic control with metformin monotherapy in the normal and overweight individuals and their incidences of diabetes-related complications for the entire duration of follow-up were not inferior to those of the obese individuals. The nonobese patients performed better regardless of the type of oral hypoglycemic agent used.

CONCLUSIONS — We conclude that metformin is at least as efficacious in normal and overweight individuals as it is in those who are obese. Our study provides evidence-based data to support metformin use in nonobese individuals with type 2 diabetes.

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The U.K. Prospective Diabetes Study (UKPDS) has demonstrated that metformin is as effective as sulfonylureas in the treatment of obese diabetic patients (defined as >120% ideal body weight) in terms of glycemic control and is associated with less weight gain and fewer hypoglycemic episodes (1,2). The metformin-treated group also had a beneficial effect in the composite "any diabetes-related end point" comparable to that seen with sulfonylurea or insulin therapy. Metformin also appeared to be superior in cardiovascular protection and patient survival (1). As a result, it is now widely accepted that metformin is the first-line pharmacological therapy of choice in obese individuals with type 2 diabetes.

Although a great number of individuals with type 2 diabetes are obese, a significant proportion are not. There remains a gap in the present literature relating to the efficacy of metformin in patients who are nonobese. In the current study, we used our extensive computerized patient database to compare the long-term efficacy of metformin monotherapy in normal, overweight, and obese individuals with type 2 diabetes, both in terms of glycemic control and diabetes complication outcomes. Patients receiving sulfonylurea monotherapy over the same period were also evaluated as comparators.

RESEARCH DESIGN AND METHODS

— A database of patients treated at the Diabetes Centre of Royal Prince Alfred Hospital, a referral hospital in Sydney, Australia, was analyzed. These patients were seen on a shared-care basis. In most cases, treatment was commenced by the primary care physicians. Upon referral, the Diabetes Centre would provide assistance in acute stabilization and diabetes education, give advice about further treatment, and then discharge the patients back to the primary care physicians. Patients will return for diabetes complication assessment, usually on a yearly basis, using a protocol described previously (3). The database information was collected from 1986 onward and included detailed information on demographics, duration of diabetes, glycemic control, body weight, BMI, diabetes medication (types and dosages), and diabetes-related complications at each visit.

Patients were included in the study if they had type 2 diabetes and complete HbA_{1c} (A1C) and diabetes medication data and were receiving either metformin or sulfonylurea monotherapy for at least three visits, each a minimum of 6 months apart, before introducing a second oral hypoglycemic agent. Those who started a second therapy within three visits were excluded as the rate of failure of monotherapy would be difficult to establish in the absence of an adequate period of observation.

Data analysis

Data were analyzed using NCSS 2004 statistical software. Continuous data were checked for normality and, if required, were transformed before analysis. The dosages of tablets taken were normally distributed and are presented as means ±

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Profile of patients at commencement of mono- and dual therapy according to treatment and BMI category*

	Metformin			Sulfonylurea			Test statistics	P value
	BMI ≤25 kg/m^2	BMI 26–30 kg/m^2	BMI ≥30 kg/m^2	BMI ≤25 kg/m^2	BMI 26–30 kg/m^2	BMI ≤30 kg/m^2		
n	27	109	258	102	104	44		
Age at monotherapy (years)	55.52 (46.9–62.6)	56.3 (49.8–63.7)	51.9 (45.0–59.5)	60.2 (47.5–68.8)	59.8 (52.4–69.1)*	61.1 (50.9–66.5)	χ^2_{5df} = 43.1	<0.0001
Duration of diabetes at monotherapy (years)	3.6 (0.3–6.2)	2.3 (0.5–5.4)	1.2 (0.2–3.8)*	4.0 (0.7–9.3)	3.2 (0.7–8.1)	3.2 (0.2–5.9)	χ^2_{5df} = 31.9	<0.0001
Duration of diabetes at dual therapy (years)	7.0 (3.8–11.3)	6.0 (4.2–8.9)	4.9 (3.1–7.4)*	6.4 (3.0–12.7)	7.2 (3.9–11.5)	5.3 (3.4–10.9)	χ^2_{5df} = 27.0	<0.0001
BMI at monotherapy (kg/m^2)	24.7 (23.9–25.6)	28.5 (27.3–29.2)*	34.6 (31.8–38.5)*	23.5 (21.9–24.7)	27.5 (26.6–28.6)*	31.7 (30.8–35.8)*	χ^2_{5df} = 552	<0.0001
Weight at monotherapy (kg)	67.0 (61.5–70.8)	76.2 (71.2–84.5)*	96.1 (87.2–110.0)*	61.9 (56.7–68.4)	77.5 (69.1–82.7)*	88.3 (79.2–94.4)*	χ^2_{5df} = 395	<0.0001
Weight at dual therapy (kg)	67.0 (60.5–72.8)	78.0 (70.3–84.1)*	94.7 (86.5–110.0)*	63.5 (56.1–70.8)	77.0 (70.0–84.0)*	87.1 (79.0–94.6)*	χ^2_{5df} = 339	<0.0001
A1C at monotherapy (%)	7.5 (6.9–8.8)	8.0 (6.8–9.4)	8.3 (7.0–9.7)	8.0 (7.1–9.3)	7.9 (7.0–9.6)	8.2 (6.7–9.3)	χ^2_{5df} = 3.1	0.7
A1C at dual therapy (%)	8.1 (7.0–9.1)	8.0 (7.0–8.9)	8.2 (7.3–9.6)	8.1 (7.3–9.0)	7.7 (6.8–9.1)	7.9 (6.7–8.9)	χ^2_{5df} = 6.7	0.2

Data are median (IQR). Total n = 644. *Kruskal-Wallis multiple comparison test compared to metformin BMI <25 kg/m^2, $P < 0.05$.

SD. All other data are presented as median and interquartile range (IQR). Categorical data are presented as percentages with 95% CIs. The data were stratified by BMI and the type of oral agent used. Patients were considered normal weight, overweight, or obese according to a BMI of <25, 25–29.9, or ≥30 kg/m^2, respectively. The Kruskal-Wallace test was used to compare the medians between the groups and to adjust for multiple comparisons. ANOVA was used to compare weight and A1C changes over time, and the interaction between duration of diabetes and BMI was assessed. The incidence of diabetes-related macro- and microvascular complications was calculated using differences in prevalence at the last visit to the Diabetes Centre and at commencement of monotherapy, and Cox regression analysis was applied to adjust for the effect of time between visits and duration of diabetes. Due to the low number of normal-weight subjects with new complications, the data for normal and overweight individuals were combined.

RESULTS — Of the 8,304 individuals with complete demographic, anthropometric, A1C, and hypoglycemic medication data, a third (n = 2,742) had at least three visits to our Diabetes Centre. Thirty-nine percent (n = 1,072) of these patients were receiving monotherapy for type 2 diabetes at the first visit: 51% were in the metformin group and 49% were in the sulfonylurea group. After excluding those who started dual therapy within the first three visits, 644 individuals receiving monotherapy initially (394 metformin and 250 sulfonylurea treated) were eventually included in the study for analysis of long-term outcomes with treatment.

Baseline and follow-up glycemic control and weight

The number of patients in each treatment category and their ages at commencement of monotherapy are shown in Table 1. The normal- and overweight metformin group had a slightly longer duration of diabetes than the obese metformin group both at commencement of monotherapy and dual therapy. There was no significant difference in their median duration of successful monotherapy (1.9 [IQR 1.4–4.1], 2.9 [1.2–4.7], and 2.8 [1.3–4.3] years, respectively, χ^2_{5df} = 10.3; P = 0.06. At the time of commencement of dual therapy, the subjects in the two nonobese metformin groups were taking an average of 2.5 ± 1.0 tablets and the obese group was taking 2.8 ± 1.1 metformin tablets of 0.5 g strength (P <

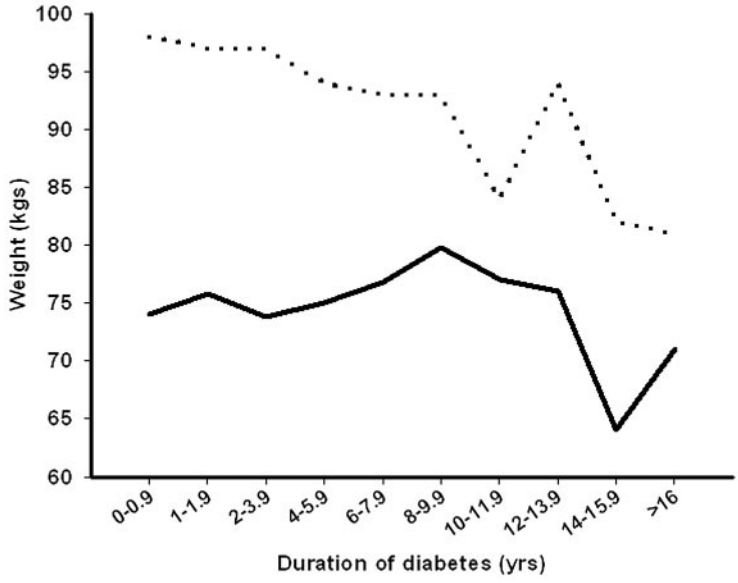

Figure 1—*Body weight (median) during metformin monotherapy over time in the obese and nonobese groups. Duration of diabetes* F = *2.7,* P = *0.004; BMI* F = *119.8,* P < *0.0001; duration of diabetes × BMI* F = *0.9,* P = *0.6. —, BMI <30 kg/m^2; - - -, BMI ≥30 kg/m^2.*

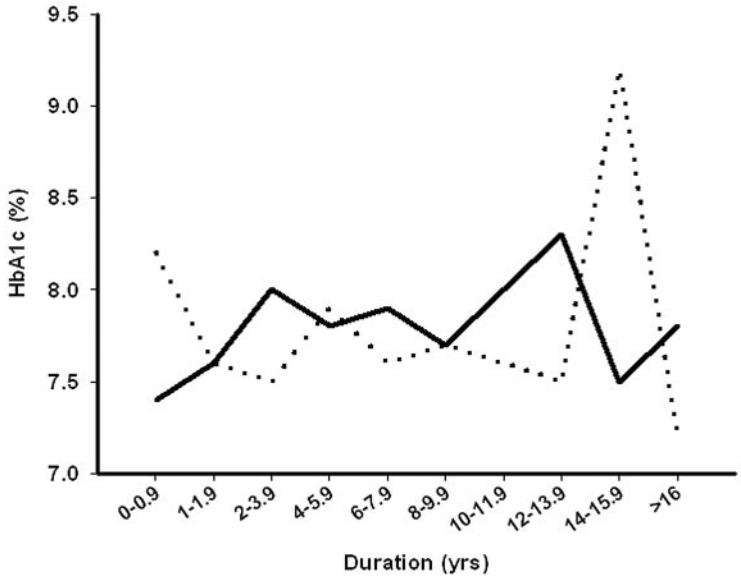

Figure 2—*A1C (median) during metformin monotherapy over time in the obese and nonobese groups. Duration of diabetes* F = *0.5,* P = *0.9; BMI* F = *1.7,* P = *0.2; duration of diabetes × BMI* F = *1.1,* P = *0.3.* —, *BMI <30 kg/m^2;* - - -, *BMI ≥30 kg/m^2.*

0.05). The obese metformin group lost more weight during the follow-up, but the nonobese metformin groups remained thinner at all stages. There was no difference in the A1C level between the groups during follow-up (Figs. 1 and 2 and Table 1). Overall, the nonobese patients required dual therapy after a longer duration of diabetes than their obese counterparts, irrespective of whether they were receiving metformin or sulfonylurea (Table 1).

Incidence of diabetes-related complications

The incidence of macro- and microvascular complications for the entire duration of follow-up is shown in Table 2. There was no significant difference between the obese and nonobese subgroups.

CONCLUSIONS — In addition to the demonstrated equivalence in glycemic response among the two major classes of oral hypoglycemic agents (2), the UKPDS group has shown that intensive blood glucose control with sulfonylureas, insulin, or metformin decreases similarly the progression of microvascular complications (4) and came very close to showing a statistically significant reduction in the risk of acute myocardial infarction (1,5). Of the agents studied, metformin lowers blood glucose without stimulating insulin secretion (6,7), a mechanism distinctive from that of sulfonylurea agents, and many patients treated with metformin initially lose weight (2). These actions of metformin, together with its modest beneficial effects on lipid metabolism, could be expected to reduce atherogenesis (8–10). Indeed, metformin has been reported to reduce cardiovascular disease and improve patient survival (1). These characteristics paved the way to its increasing popularity as a first-line treatment for type 2 diabetes.

However, as metformin use in the UKPDS has been targeted specifically to obese individuals with type 2 diabetes, direct extrapolation of its relative efficacy in subjects who are not obese has been less certain. A recent publication examining prescribing practices in the U.K. demonstrated that the short-term glycemic response to metformin in nonobese and obese patients is similar. However, the drug response was determined by the change of A1C after a minimum of 3 and a maximum of 12 months from the commencement of monotherapy (11). To our knowledge, no medium- to long-term data on glycemic control or diabetes-related complication in metformin-treated nonobese patients have been published. Our aim in this study is to bridge this existing gap in our knowledge.

Analysis of the baseline data of our cohort showed that our primary care physicians generally conformed to the prevailing clinical practice of using metformin as the first-line pharmacological treatment for obese diabetic patients and sulfonylureas for nonobese subjects. It is not possible for us to determine what made the primary care physicians break these rules in a smaller subset of the patients. However, it afforded us the opportunity to evaluate, albeit in a retrospective manner, the impact of body weight on long-term response to metformin treatment. Importantly, this study demonstrated that, even with a slightly lower dosage, there was a longer duration of successful glycemic control with metformin monotherapy in the two groups of nonobese subjects compared with the obese individuals. There was no difference in the A1C threshold at which monotherapy was converted to dual therapy between the three metformin-treated groups. The beneficial effect of metformin on weight loss was less pronounced in the nonobese population, but it is likely to be

Table 2—*Incidence of complications according to treatment and BMI category*

	Metformin		Sulfonylurea		Test statistic	*P* value
	BMI <30 kg/m^2	BMI ≥30 kg/m^2	BMI <30 kg/m^2	BMI ≥30 kg/m^2		
Duration of follow-up since monotherapy (years)	5.3 (3.0–7.7)	4.9 (2.4–7.3)	5.4 (2.6–7.3)	3.6 (2.4–5.5)	$\chi^2_{3df} = 7.6$	0.06
Retinopathy (%)*	8.0 (3.7–14.6)	6.9 (3.9–11.1)	12.0 (7.4–18.1)	13.5 (4.5–28.8)	$Z = 1.0$	0.3
Ischemic heart disease (%)*	12.0 (6.6–19.7)	8.3 (5.0–12.7)	9.8 (5.7–15.4)	5.6 (0.7–18.7)	$Z = -7.0$	0.5
Stroke (%)*	4.9 (1.8–10.4)	2.2 (0.7–4.9)	6.2 (3.1–10.8)	0	$Z = 0.06$	0.9
Peripheral arterial disease (%)*	1.6 (0.2–5.7)	2.6 (1.0–5.7)	1.7 (0.4–4.9)	2.5 (0.06–13.2)	$Z = 2.4$	0.8
Albuminuria (%)*	14.6 (6.1–27.7)	25.0 (17.2–34.3)	14.4 (9.3–28.4)	13.3 (1.7–39.9)	$Z = -0.7$	0.9

Data are value (95% CI). Total *n* = 644.*Cox regression was used for adjusting for time between visits and duration of diabetes.

less emphasized in this group during diabetes education.

The fact that the two groups with lower weight performed better than their obese counterparts, irrespective of whether metformin or sulfonylurea treatment was used initially, suggests that the difference is probably a reflection of the impact of body weight on the disease process rather than a drug effect. The similar incidences of diabetes-related complications in all the subgroups during the entire follow-up period, irrespective of the type of monotherapy used in the first instance, also reaffirms the fact that body weight would not be an important issue in the use of metformin in nonobese individuals. Overall, our results provide evidence that metformin use in the nonobese population is as efficacious as in the obese group. Our data also allowed a comparison between the metformin- and sulfonylurea-treated nonobese groups, and overall the two agents behaved similarly. Although the data are not shown here, an identical pattern of results was observed if all 1,072 patients, irrespective of whether they had at least three follow-up visits, were included in the analysis. Thus, our overall conclusion would not be affected by inclusion of patients who failed to show early responsiveness to metformin or sulfonylurea treatment. Most interestingly, when the 27 metformin-treated patients with BMI <25 kg/m^2 were examined, their median duration of successful monotherapy was longer at 7.0 years, compared with 6.4 years in their sulfonylurea-treated counterparts. Thus, there is evidence that metformin not only performs well in the nonobese individuals but might work even better in thin patients with type 2 diabetes.

This is an observational and retrospective study. As such, it has a number of weaknesses. The subjects were not matched, and the metformin group in general tended to be younger and have a slightly earlier presentation to the Diabetes Centre after diagnosis of diabetes. However, the differences were small, were not clinically significant, and were adjusted statistically. The data on complications were collected according to a standardized clinical protocol but probably were not as rigorously defined as they would be in a prospective clinical trial. It is unlikely that another study like the UKPDS would ever be performed, although the ADOPT (A Diabetes Outcome Progression Trial) study may soon provide valuable information (12). In the meantime, our data provide some insight and reassurance in the use of metformin in diabetic patients who are not obese.

We conclude that metformin is at least as efficacious in the nonobese as it is in the obese. This study provides evidence-based data to support metformin use in nonobese individuals who have type 2 diabetes.

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