

Weight loss delays the onset of pharmacological treatment in type 2 diabetes

Francisco Escobar, María del Carmen Díaz, José Jorge Pérez-Pascual, Rubén Escribá, Elena Cerezo, Fernando Molina

Type 2 diabetes is the result of a combination of β -cell failure and insulin resistance; however, the metabolic abnormalities associated with insulin resistance can be reduced by weight reduction (Paisey et al, 2002). In particular, lowering of fasting blood glucose levels has been demonstrated to be associated with a reduction in centralised body fat (Markovic et al, 1998; Walker et al, 1999). In this article, the authors present a retrospective cohort study, with the aim of elucidating the time from diagnosis of type 2 diabetes to the initiation of pharmacological treatment; and evaluating the variables that determine this by conducting a survival analysis.

Around half of all people with type 2 diabetes are obese and obesity itself causes some degree of insulin resistance (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002; Centers for Disease Control and Prevention, 2004). People who are not obese by traditional criteria ($\text{BMI} > 30 \text{ kg/m}^2$) may have a high amount of body fat distributed predominantly in the abdominal region (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002). Weight loss is therefore an important therapeutic objective for people with type 2 diabetes as it is associated with decreased insulin resistance, improved glycaemia, improved dyslipidemia and reduced blood pressure. However, long-term data assessing the extent to which these improvements can be maintained

are not available (Brown et al, 1996; American Diabetes Association [ADA], 2002).

For people with type 2 diabetes, the priority at diagnosis should be lifestyle changes (Franz et al, 2003; Goldhaber-Fiebert et al, 2003). If acceptable glycaemic control is not achieved and maintained by such an approach it will eventually become necessary to introduce at least one pharmacological agent.

Aims

The objective of this study was to measure the time between diagnosis of type 2 diabetes to initiation of pharmacological treatment and to evaluate the variables that determine it. The authors specifically examine whether or not weight loss increases the time it takes to initiate pharmacological therapy.

Article points

1. In this study, 68% of people with type 2 diabetes were eventually prescribed pharmacological therapy.
2. The median time from diagnosis to onset of pharmacological therapy was 35 months.
3. Onset of pharmacotherapy was more likely in those who had high values for glycaemia and BMI.
4. In those who were overweight or obese, weight loss delayed the onset of pharmacological therapy.

Key words

- Obesity
- Weight loss
- Lifestyle intervention
- Pharmacological intervention

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Page points

1. This was a retrospective cohort study performed at an urban healthcare centre in Spain.
2. The clinical records of 1066 individuals diagnosed with type 2 diabetes before October 1999 were analysed for suitability for inclusion in the study using the following inclusion criteria from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

Box 1. Other independent variables and the statistical tests used.

Independent variables

- illness
- concomitant treatment
- diabetes-related complications
- diabetes treatment.

Statistical tests used

- comparing qualitative variables
 - Pearson Chi-squared
- quantitative variables
 - t-test for normal distribution
 - Mann-Whitney U test
 - Wilcoxon test
- survival analysis
 - Kaplan-Meier
 - Cox regression

Box 2. Significance of other variables versus time to pharmacotherapy initiation.

Variable	P-value
Age	0.78
Profession	0.56
Education	0.16
Dyslipidaemia	0.48
Other illness	0.48
Sex	0.12

Methods

This was a retrospective cohort study performed at an urban healthcare centre in Spain. The clinical records of 1066 individuals diagnosed with type 2 diabetes before October 1999 were analysed for suitability for inclusion in the study using the following inclusion criteria from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002):

- symptoms of diabetes plus random plasma glucose concentration ≥ 11.1 mmol/l (200 mg/dl)
- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)
- two hours postload blood glucose >11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test.

The main exclusion criterion was a previous diagnosis of type 1 or type 2 diabetes.

The following data were collected.

- Date of diagnosis of type 2 diabetes, as determined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002).
- Whether or not pharmacological intervention was initiated.
- For those people who were receiving pharmacological intervention: the date on which it was initiated and the time between diagnosis and initiation date if initiation was before October 2000 (this was as far back as records would allow).
- For those not receiving any agents, the date of

Box 3. Profession (n=366) and education level (n=109) of study participants.

Profession	Number	Percentage
Managers/owners	3	0.8
Intermediate staff	7	1.9
Manual workers	72	19.7
Housewives	110	30.1
Pensioners	73	19.9
Others	15	4.1
Unknown	86	23.5

Education level	Pharmacological treatment	
	No	Yes
Illiterate	8	16
Primary unfinished	15	26
Primary	16	22
Secondary	2	0
Higher level	4	0

their last visit to their physician or the date of their last annual review.

Independent data collected included:

- sex
- height
- age at time of diagnosis
- occupation at time of diagnosis
- level of education at time of diagnosis.

The following data were examined at baseline; between 6 months and 12 months; and then between 13 months and 24 months. Data were also collected during appointments when an individual was not initiated onto pharmacological agents. These variables included:

- weight
- BMI
- fasting blood glucose (FBG)
- HbA_{1c}
- lipid profile (total cholesterol, HDL-c, LDL-c and triglycerides)
- systolic and diastolic blood pressures.

Other independent variables and statistical tests are outlined in *Box 1*. Data were analysed using the Statistical Package for Social Sciences (SPSS Inc, Chicago).

Results

A total of 1066 patient records were assessed initially; 366 fulfilled all inclusion criteria. Of these, 193 (52.7%) individuals were female. The age range was 23–87 years (mean: 59.6 years; SD: 10.7 years). Age was not found to be significantly related to whether or not the individual was initiated on pharmacological agents (*Box 2*).

For people on pharmacological therapy, mean time from diagnosis to drug initiation was 54 months (95% confidence interval [CI]: 48–61; median: 35 months [95% CI, 27–43]). Of the 336, seventy-two people (24.4%) began pharmacological treatment within 1 month of diagnosis.

Women were found to start drug therapy at a median of 48 months and men at a median of 24 months post diagnosis. Men received pharmacotherapy in a smaller proportion compared with women (66% versus 70%,

respectively; $P=0.0038$). Those without hypertension received pharmacological treatment at a median of 21 months post diagnosis and those with hypertension at a median of 48 months. A higher proportion of those who were non-hypertensive received pharmacological treatment (75% versus 64%, respectively; $P<0.0001$). FBG at diagnosis was considered a categorical variable, using the quartiles as cut-off points in order to form four groups with a similar number of records.

Mean BMI at diagnosis was 31.3 kg/m^2 (SD: 5.0) and the median was 30.7 kg/m^2 . There were significantly more individuals who were not overweight (BMI $<25\text{ kg/m}^2$) among men than women (24.8% and 4.4%, respectively; $P<0.0001$).

In the entire study population ($n=366$), people who were not overweight (BMI $<25\text{ kg/m}^2$) were found to begin drug treatment earlier than those who were overweight, and these before obese people; however, this was a non-significant result ($P=0.42$). There were no differences in the timing of pharmacological treatment initiation in relation to the other variables (Box 2).

The professions and education levels of those whose cases were reviewed are shown in Box 3. It appears that those who were less well educated were more likely to begin pharmacological treatment earlier in the course of their diabetes; however this was not shown to be significant owing to the small number of cases (Box 2). This could translate into a topic for investigation in a future study.

The mean FBG at diagnosis for all 366 people was 9.9 mmol/l (177.9 mg/dl ; SD: 3.7 mmol/l). FBG levels were significantly higher in those who later commenced pharmacological therapy than those who had not: 10.7 mmol/l (193.3 mg/dl ; SD: 4.1 mmol/l) versus 8.1 mmol/l (145.2 mg/dl ; SD: 1.5 mmol/l), respectively ($P<0.0001$).

In those currently being treated with pharmacological agents, the mean FBG was 10.9 mmol/l (SD: 3.6 mmol/l), while

in the non-pharmacologically treated group, the mean FBG at their final visit was 7.0 mmol/l (SD: 1.1 mmol/l), the difference being statistically significant ($P<0.0001$).

Six months post diagnosis, 271 people (74%) were not being pharmacologically treated. For 215 of these, FBG levels were available from their 6- and 12-month clinic visits. They were significantly lower than at diagnosis (mean: 7.3 mmol/l ; SD: 1.6 mmol/l versus 8.5 mmol/l ; SD: 2.0 mmol/l , respectively; $P<0.0001$). Twelve months post diagnosis, 244 people (66.7%) were not being treated pharmacologically. FBG levels were available for 197 cases between 13 and 24 months post diagnosis and continued to be significantly lower than at diagnosis (7.3 mmol/l ; SD: 1.4 mmol/l ; $P<0.0001$). FBG was lower in people who had a greater decrease in weight than in those who did not decrease weight.

By 30 September 2000, 117 people (32.0%) were on lifestyle intervention alone. In the 249 people who received pharmacological treatment, sulphonylureas were the most frequently prescribed as initial treatment (81.9%; $n=204$).

In the Cox regression analysis, the models that best predicted the beginning of pharmacological treatment are shown in Table 1. They include the presence of the following variables: arterial hypertension (dichotomic), glycaemia and BMI at diagnosis (both continuous; hazard ratio [HR]: 0.59, 1.01 and 1.05; 95% CI: 0.39–0.90, 1.01–1.02 and 1.01–1.08; respectively). Initially, sex was included as a variable in the model, but it was not shown to be significant (Box 2). When we removed it from the model, the coefficients of the other variables improved. Sex was therefore shown to be a confounding factor. In our sample, arterial hypertension occurs more frequently in women than men (64% versus 36%, respectively; $P<0.0001$). These results suggest that arterial hypertension, rather than sex, delays the onset of pharmacological therapy.

In those with normal weight at diagnosis,

weight loss was not considered a therapeutic objective, however, in certain individuals weight maintenance was an objective. Only those who were overweight or obese and had not begun pharmacological treatment by the sixth month or the first year after diagnosis were included in the analysis. The model that best predicted the beginning of pharmacological treatment for people who had not begun pharmacological treatment by the sixth month after diagnosis included the following variables: glycaemia and BMI at diagnosis, presence of arterial hypertension, the variation in BMI (continuous variable, defined as: BMI at the diagnosis – BMI at 6–12 months; HR: 0.69; 95% CI: 0.55–0.88). In the analysis of the individuals who had not received pharmacological treatment after the first year, the variable ‘diagnosis of arterial hypertension’ was removed from the model, as it was non-significant ($P=0.22$).

We studied the variation in BMI between months 6 and 12 and in the second year after the diagnosis in relation to the initial reading. This was a dichotomic variable, thus using the median as a cut-off point. Individuals whose BMI decreased by 0.38 kg/m² or more between months 6 and 12 took longer to receive pharmacological treatment (median: 72 versus 42 months) and they received it in a smaller proportion (44.8% versus 70.2%; $P=0.058$). A similar trend was

observed in the analysis of those who had not received pharmacological treatment 1 year after the diagnosis, although the results move away from statistical significance ($P=0.07$).

Discussion

The main aim of this paper was to describe the time between diagnosis of type 2 diabetes to the initiation of pharmacological therapy and, as far as the authors are aware, this is the first study to do so. Looker et al (2001) point out that few published datasets compare the natural history of weight change after diagnosis of type 2 diabetes in individuals receiving standard medical care to that of individuals participating in a clinical trial.

The mean time until the beginning of the pharmacological treatment was 54 months, with a median of 35 months, but there was wide variability. Seventy-two people (around 20%) began pharmacological treatment less than 1 month after diagnosis while at the other end of the scale, approximately 20% of cases received drugs after an interval of ≥ 70 months (the greatest interval being 165 months).

Most people with type 2 diabetes will need drug treatment for the condition at some point (UK Prospective Diabetes Study [UKPDS] Group, 1995) and the majority will need multiple therapies to attain glycaemic targets

Page points

1. Individuals whose BMI decreased by 0.38 kg/m² or more between months 6 and 12 took longer to receive pharmacological treatment (median: 72 versus 42 months) and they received it in a smaller proportion (44.8% versus 70.2%; $P=0.058$).
2. The mean time until the beginning of the pharmacological treatment was 54 months, with a median of 35 months, but there was wide variability.
3. Most people with type 2 diabetes will need drug treatment for the condition at some point and the majority will need multiple therapies to attain glycaemic targets in the long term.

Table 1. Cox regression analysis: models that best predicted pharmacological treatment initiation in those without pharmacological treatment between 0 and 6 months and after 1 year. Those who began treatment within the first month were excluded from the analysis.

Variables predicting time to pharmacotherapy initiation within 1–6 months of diagnosis (n=174).							
Variable	β	SE	Wald	df	P	Exp (β)	95% CI for Exp (β)
Baseline glycaemia	0.103	0.002	34.75	1	0.00001	1.013	1.009–1.018
Baseline hypertension	-0.529	0.215	6.024	1	0.014	0.589	0.386–0.899
Baseline BMI	0.045	0.018	6.186	1	0.013	1.046	1.010–1.084
Variables predicting time to pharmacotherapy initiation at 6–12 months post diagnosis (n=115)							
Variable	β	SE	Wald	df	P	Exp (β)	95% CI for Exp (β)
Baseline glycaemia	0.016	0.004	19.866	1	0.00001	1.016	1.009–1.024
Hypertension	-0.919	0.312	8.684	1	0.003	0.399	0.217–0.735
Baseline BMI	0.090	0.030	8.747	1	0.003	1.094	1.031–1.161
BMI change	-0.370	0.117	10.024	1	0.001	0.690	0.549–0.868
Variables predicting time to pharmacotherapy initiation 12 months post diagnosis							
Variables	β	SE	Wald	df	P	Exp (β)	95% CI for Exp (β)
Baseline glycaemia	0.018	0.004	20.687	1	0.00001	1.019	1.010–1.027
Baseline BMI	0.068	0.033	4.377	1	0.036	1.071	1.004–1.141
BMI change	-0.203	0.0996	4.508	1	0.034	0.816	0.676–0.984

BMI change: Baseline BMI - BMI at moment of analysis; CI: Confidence intervals; df: degrees of freedom; Exp: Exponential; SE: Standard error.

Page points

1. In those people who have made lifestyle changes, initiation of pharmacological therapy can be delayed.
2. Appropriate targets for treatment should be determined by considering individual clinical variables, such as baseline HbA_{1c} levels, presence of pre-existing microvascular disease, individual risk profiles and personal preferences.
3. The higher the BMI, the more likely that person is to be initiated on pharmacological agents.
4. In those people with diabetes who are overweight or obese, the loss of weight in the 2 years following diagnosis delays the beginning of pharmacological treatment.

in the long term (IDF Clinical Guidelines Task Force, 2006; Nathan et al, 2006; Turner et al, 1999). Nevertheless, many people with type 2 diabetes do not need pharmacological treatment, at least for some time, if they control the condition with lifestyle interventions during the period following diagnosis. At the end of this study, 117 people (32%) were still managing their condition through diet and exercise alone.

So, what conditions are associated with the initiation of the pharmacological treatment in people with type 2 diabetes? Those with arterial hypertension received pharmacological treatment later and in a smaller proportion than those without it. In those people who have made lifestyle changes, initiation of pharmacological therapy can be delayed. On the other hand, doctors could delay beginning of further pharmacological treatment in those already treated with antihypertensive drugs by employing non-pharmacological treatments and thus avoiding drug–drug interactions, iatrogenic effects or undesirable effects. In the analysis of individuals who remained without pharmacological treatment after the first year, arterial hypertension no longer appeared in the model; that is to say, in the second year following diagnosis, the presence of arterial hypertension ceased to be a protective factor for the beginning of pharmacological treatment.

Appropriate targets for treatment should be determined by considering individual clinical variables, such as baseline HbA_{1c} levels, presence of pre-existing microvascular disease, individual risk profiles and personal preferences (Woolf et al, 2000). Glycaemic values at the time of diagnosis would not necessarily justify the beginning of a pharmacological treatment. However, we have observed in this study that more of those who presented with higher glycaemia at the time of diagnosis received treatment with drugs earlier than those who presented with lower glycaemia.

The higher the BMI, the more likely that person is to be initiated on pharmacological agents. Nevertheless, people with normal weight began pharmacological treatment earlier, perhaps because in these people weight loss is not a therapeutic option.

When we analysed the records of those who were overweight or obese (BMI > 25 kg/m² who had not begun pharmacological treatment at the sixth and twelfth months after diagnosis, the model in the Cox regression included the variation of the BMI in relation to the initial measurement. That is, those people with diabetes whose BMI diminished in these periods had less probability of receiving drugs. In light of these results, we can confirm that in those people with diabetes who are overweight or obese, the loss of weight in the 2 years following diagnosis delays the beginning of pharmacological treatment.

This has relevant implications to clinical practice by reinforcing the role of non-pharmacological measures, specifically weight control in obese people, as initial treatment for type 2 diabetes. It is well known that the loss of weight diminishes insulin resistance resulting in better control of glycaemia (Markovic et al, 1998). This was confirmed in this study as FBG was lower in individuals who had a greater decrease in weight.

The UKPDS provided useful information on initial dietary treatment of type 2 diabetes (UKPDS Group, 1990). In the UKPDS, mean weight loss was 5 kg over the initial 3 months. In total, 16% of 3044 newly diagnosed individuals with diabetes achieved a fasting plasma glucose of less than 6.0 mmol/l after 3 months of dieting, and 50% reached 6–8 mmol/l. People who had higher initial FBG levels and/or lost more weight experienced the greatest decrease in levels of FBG. The initial FBG alteration was considered as much a response to the decrease in energy intake as it was to the decrease in body weight. Furthermore, fasting plasma glucose levels of less than 6.0 mmol/l were only maintained in individuals who continued a hypocaloric diet. In people who increased their energy intake, fasting plasma glucose levels increased even if weight loss was maintained.

The benefit of initial loss of weight following a diagnosis of type 2 diabetes is supported by other studies with individuals receiving standard medical care (Looker et al, 2001). In Pima Indians with diabetes, a tendency to lose weight has been seen in which BMI declines at a rate of 0.4–0.6 kg/m² per year (1–1.8% per year) after

the onset of diabetes in individuals who are not taking diabetes medication (Looker et al, 2001).

Limitations

An important limitation of our study is related to the completeness of data recording because the missing data in the records has determined the loss of cases in the corresponding analyses. This is not surprising since previous studies in general practice have found that important clinical data may be poorly recorded (20–70% of the variables not recorded) even when physicians have a special interest in the management of diabetes (Goudswaard et al, 2003).

Another possible limitation of our study is the diagnostic criteria we have applied, which would not necessarily have been those followed by the GPs caring for these individuals. However, those identified as having impaired glucose tolerance should have received counselling about changes in their lifestyles (Tuomilehto et al, 2001).

Conclusion

Since many people with type 2 diabetes are overweight and insulin resistant, medical nutrition therapy should emphasise lifestyle changes that result in reduced energy intake and increased energy expenditure through physical activity (ADA, 2002). Many people with diabetes also have dyslipidemia and hypertension, making reductions in dietary intake of saturated fat, cholesterol and sodium desirable (ADA, 2002). Therefore, the emphasis of nutrition therapy should be implemented as soon as the diagnosis of diabetes is made. In addition, although exercise by itself has only a modest effect on weight loss, it has to be encouraged because it improves insulin sensitivity, acutely lowers blood glucose levels and is important in the long-term maintenance of weight loss (ADA, 2002). We agree with Brown et al (1996) in underlining that although healthcare providers may feel that they have failed to help overweight adults with diabetes to lose weight, they should be encouraged to know that their efforts may have improved the health outcomes of people under their care, despite the fact that these individuals may not have attained ideal body weight ($\text{BMI} < 25 \text{kg/m}^2$).

As diabetes is a chronic condition,

pharmacological treatment should be part of a long-term plan. For this reason, any measure that can delay its onset should be taken into consideration for the benefits that the individual would receive (pharmacological treatment is not exempt from the possibility of secondary effects and potential decrease in quality of life) and for the benefit of the clinic in terms of the pharmaceutical expense that can be avoided. ■

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Page points

1. Since many people with type 2 diabetes are overweight and insulin resistant, medical nutrition therapy should emphasise lifestyle changes that result in reduced energy intake and increased energy expenditure through physical activity.
2. Since diabetes is a chronic illness, pharmacological treatment in these people should be part of a long-term plan.