The predictive role of HbA_{1c} and previous medications in initiation of insulin treatment

Hakan Demirci[1] & Yıldırım Çınar[2]

ABSTRACT

INTRODUCTION: Subjects (n = 46) with type 2 diabetes who responded inadequately to two and three oral medications (HbA_{1c} > 8.0%) were consecutively recruited for treatment with premixed insulin 30/70 two times a day in order to investigate whether previous oral therapies may predict insulin requirements.

MATERIAL AND METHODS: In this prospective study, men and women were eligible to participate if they were aged between 30 and 65 years, had had a diagnosis of type 2 diabetes mellitus for at least 12 months, were insulin-naive and had been treated unsuccessfully with either two or three oral antidiabetic drugs for at minimum of three months. Clinical and laboratory findings were analyzed at one year follow-up.

RESULTS: The average required insulin doses were significantly higher in patients in whom previous triple oral medication had failed than in patients in whom two oral drugs had failed.

CONCLUSIONS: Evaluation of the previous number of oral antidiabetic drugs and HbA_{1c} values may help us predict the insulin requirement when oral drugs have failed.

Treatment of patients with type 2 diabetes (T2DM) aims at controlling intestinal glucose absorption, normalize hepatic glucose production, reverse insulin resistance, and at preventing the occurrence of long-term complications [1].

A combination of diet, exercise and metformin is recommended as the first line of therapy for patients with T2DM [2, 3]. However, few patients achieve adequate control of blood glucose levels in time using this approach alone due to the progressive nature of T2DM [4-8].

Sulphonylureas, biguanides and alpha-glucosidase inhibitors are well-known oral antidiabetic drugs (OADs), and nowadays new generation OADs such as dipeptidyl peptidase 4 (DPP-4) inhibitors, amylin mimetics and incretin mimetics have increased the capability of oral therapy [9, 10]. All of the agents mentioned above have a potential therapeutic effect equivalent to an approximately 1-2% decrease in HbA_{1c} levels if used in appropriate doses [1].

Insulin is indicated in patients with T2DM who fail to respond to an adequate dietary regimen and to oral hypoglycaemic agents. While transferring to insulin, many subjects fear injections and such fear may affect their compliance with insulin therapy [11-14]. Consequently, oral therapy has generally been the preferred treatment approach for patients with T2DM.

Patients with type 1 diabetes mellitus (T1DM) who have no endogenous insulin secretion generally require between 0.5 and 1.0 IU/kg insulin per day. Diabetes Control & Complications Trial patients with T1DM on average receive 40 IU insulin per day. Because of insulin resistance in T2DM, especially obese patients with T2DM usually require more insulin. Insulin requirements sometimes reach 2.0 IU/kg per day.

The purpose of this study was to investigate whether the number of oral antidiabetic drugs prescribed before shifting to insulin affects later insulin requirements when the oral therapy failed.

MATERIAL AND METHODS

Subjects were selected randomly among the T2DM patients whose oral antidiabetic treatment had failed. The study population comprised a total of 46 patients divided into two groups each counting 23 patients who were using two OADs (group A) or three OADs (group B). They were all willing to initiate insulin therapy and had previously received at least three months of continuous treatment with failure of either two or three OADs (HbA_{1c} > 8.0%). Categories of OADs previously used were ignored. All participants gave fully informed consent to participation in the study and the investigators declare that the study complies with the Helsinki Declaration.

Insulin therapy was initiated with premixed insulin 30/70 twice a day (starting dose, 0.3 IU/kg per day). At baseline, approximately two thirds of the dose was given before breakfast and the remainder before dinner. To avoid hypoglycaemia, dose adjustments in the form of a 10% increase of the current dose were suggested every other day until reaching pre-prandial glycaemic targets in the morning and evening. For all patients, adequate dietary counselling was provided to facilitate management of the meal-related part of the insulin therapy. Treatment efficacy was evaluated after one year of follow-up. The

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1) Nilüfer Toplum Sağlığı Merkezi, Department of Family Medicine, Turkey
2) Trakya Üniversitesi Tıp Fakültesi, Department of Internal Medicine, Turkey

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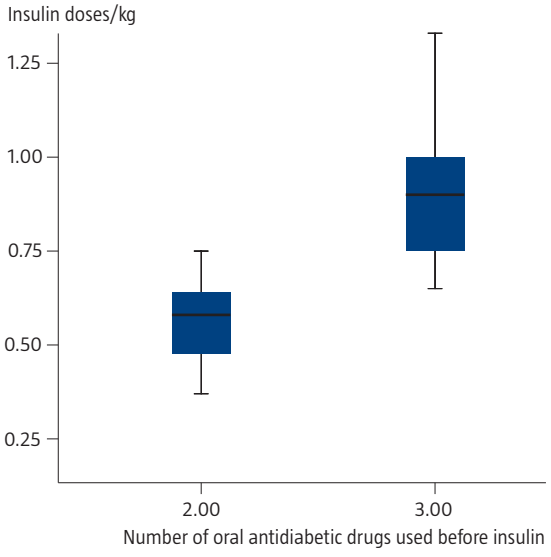
TABLE 1

Demographics, baseline values, and comparisons.

	Group A	Group B	p-values
Subjects randomized (n)	23	23	–
Age (years)	56	57	0.834
Female/male (n)	13/10	16/7	
Duration of diabetes (years)	8.6	9.6	0.369
Baseline weight (kg)	67	77	0.06
Weight gain (kg)	7.1	6.0	0.22
Body mass index (kg/m²)	30	31	0.304
HbA_{1c} before insulin (%)	10.5	10.7	0.535
HbA_{1c} at one year of insulin (%)	6.5	7.0	0.106
Insulin dose (IU/kg/day)	0.56	0.90	0.001

FIGURE 1

Relationship between number of oral antidiabetic drugs used and insulin doses needed.



exclusion criteria were diagnosis of T1DM, having used insulin at any time in life, relatively efficient treatment of diabetes mellitus (DM) ($HbA_{1c} \leq 8.0\%$), acute complications of DM, diagnosis of an additional disease, using or starting a new drug, fever states, falling outside the 40-65 year-old age span, lactating women, pregnancy, and changing business and life style during the study period.

On the basis of these data obtained in the first part of the study, we compared the two groups in terms of age, gender, duration of diabetes, baseline weight (kg) and weight gain (kg) achieved at the end of the study, body mass indexes (BMI), HbA_{1c} values and insulin requirements. HbA_{1c} values were measured with high-performance liquid chromatography. All results were reported as mean values +/- standard error of the mean. Statistical analysis was done with the use of the unpaired, two-tailed t test; p values of less than 0.05 were considered statistically significant.

RESULTS

Demographics of both groups are shown in **Table 1**. No significant difference was found in age, gender or duration of diabetes between the two groups. BMIs were similar in the two groups. The increases in weight after insulin therapy were also similar in the two groups.

HbA_{1c} values before insulin therapy were not significantly different between the two groups. One year after the initiation of insulin therapy, HbA_{1c} values had changed markedly in both groups. All of the patients reached HbA_{1c} values below 8%. Insulin doses per kg of body weight per day were significantly higher in group B ($p < 0.001$) than in group A. We observed no hypoglycaemic attacks or fluctuations in blood glucose concentrations during the study. Two patients in group B transferred into intensive insulin therapy.

The number of oral antidiabetic agents used before insulin therapy correlated with the insulin doses needed at the end of the study (**Figure 1**).

No subjects were excluded according to the criteria, and no patients refused to participate in the study.

DISCUSSION

We have shown that patients who were previously using double drug therapy (two oral antidiabetic drugs) needed less insulin than patients who were using triple drug therapy. Patients' pre-insulin HbA_{1c} levels also predicted insulin dosing.

In this study, we hypothesized that pre-insulin therapy may hold clues to the insulin dosing needed when oral agents have failed. We demonstrated that a mean insulin dose of 0.56 IU/kg/day was required in patients who had previously been treated with two OADs as compared to a mean insulin dose of 0.90 IU/kg/day in patients previously treated with three OADs.

The response to the OADs (HbA_{1c}) also correlated with insulin doses at the end of the first year of follow-up. Thus, the HbA_{1c} values of the two groups were similar before insulin treatment began, which implies that double and triple OAD treatment had been equally unsuccessful in the two groups prior to the commencement of insulin therapy.

HbA_{1c} levels were also similar after insulin injections. If the HbA_{1c} values are similar, differences in insulin deficiency between these two groups can therefore be estimated by the number of OADs which had failed.

It would have been better if we had examined the individual oral antidiabetic agents used by the patients, but the aim of the study was to investigate if the number of

OADs affected the final insulin doses. And it is well-known that an ordinary OAD causes a 1-2% HbA_{1C} decrease.

The rise in patients' weights after insulin therapy is a side effect of insulin therapy and an indication for the use of drugs such as glucagon-like peptide 1 analogues. However, due to their non-licensed state, these drugs were not available for use in the country where the study was conducted.

All parameters explored in this study, including baseline weights of the two groups, were statistically similar, except for their demand for insulin.

CONCLUSIONS

In this study we have shown that similar HbA_{1C} values and unsuccessful triple oral drug therapy means that we need more insulin to control diabetes (Figure 1). In conclusion, further investigation is required to ascertain whether this observation is linked to the stage of DM at the time of institution of insulin therapy.

CORRESPONDENCE: *Hakan Demirci*, Nilüfer 9 Nolu Fethiye Bulvar Aile Sağlığı Merkezi, Department of Family Medicine, Turkey.
E-mail: drhakandemirci@hotmail.com

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LITERATURE

1. Andreoli TE, Carpenter CCJ, Griggs RC et al. Cecil essentials of Medicine 7th Edition. Philadelphia: Saunders Elsevier:688-90.
2. Schernthaner G, Barnett AH, Betteridge DJ et al. Is the ADA/EASD algorithm for the management of type 2 diabetes (January 2009) based on evidence or opinion? Diabetologia 2010;53:1258-69.
3. Hee MK, Herrick K, Ziemer DC et al. Many Americans have pre-diabetes and should be considered for metformin therapy. Diab Care 2010;33:49-54.
4. Brown JB, Conner C, Nichols GA. Secondary failure of metformin in clinical practice. Diab Care 2010;33:501-6.
5. Plat A, Penning-van Beest F, Kessabi S et al. Change of initial oral antidiabetic therapy in type 2 diabetic patients. Pharm World Sci 2009;31:622-6.
6. Dodd AH, Colby MS, Boye KS et al. Treatment approach and HbA_{1c} control among US adults with type 2 diabetes: NHANES 1999-2004. Curr Med Res Opin 2009;25:1605-13.
7. Alvarez GF, Mavros P, Nocea G et al. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008;10:8-15.
8. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs 2005;65:385-411.
9. Salvatore T, Carbonara O, Cozzolino D et al. Progress in the oral treatment of type 2 diabetes: update on DPP-IV inhibitors. Curr Diabetes Rev 2009;5:92-101.
10. Pratley RE, Salsali A. Inhibition of DPP-4: a new therapeutic approach for the treatment of the type 2 diabetes. Curr Med Res Opin 2007;23:919-31.
11. Kabadi UM. Starting insulin in type 2 diabetes: Overcoming barriers to insulin therapy. Int J Diab Dev Ctries 2008;28:65-8.
12. Meneghini L. Why and how to use insulin therapy earlier in the management of type 2 diabetes. South Med J 2007;100:164-74.
13. Nakar S, Yitzhaki G, Rosenberg R et al. Transition to insulin in Type 2 diabetes: family physicians' misconception of patients' fears contributes to existing barriers. J Diabetes Complications 2007;21:220-6.
14. Grant RW, Wexler DJ, Watson AJ et al. How doctors choose medications to treat type 2diabetes: a national survey of specialists and academic generalists. Diab Care 2007;30:1448-53.