

# GLYCEMIC CONTROL BEFORE AND AFTER STARTING INSULIN THERAPY IN OBESE AND OTHER TYPE 2 DIABETICS

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*Key words: diabetes, obesity, insulin therapy, complications*

## SUMMARY

*Type 2 diabetes mellitus is a chronic progressive disease slowly reaching a pandemic extent. Its prevalence is growing in the younger population, probably due to the epidemic of obesity. Numerous clinical and randomized studies have shown that morbidity and mortality due to chronic complications are decreased significantly by good glycemic control. The aim of our study was to assess the glycemic control in patients prior to starting insulin therapy and to establish the extent to which glycated hemoglobin ( $HbA_{1c}$ ) level decreased upon the introduction of therapy in patients grouped according to their body mass index. According to the American Diabetes Association (ADA) and International Diabetic Federation (IDF) guidelines,  $HbA_{1c}$  was too high prior to insulin therapy. All patients, i.e. those with normal body weight and overweight, benefited from insulin therapy. The introduction of insulin therapy resulted in a statistically significant decrease in  $HbA_{1c}$  level and*

*less new microvascular complications. A more rapid recruiting of patients for insulin therapy would significantly decrease the respective morbidity and mortality rates, and serve to approach glycemic control in accordance with ADA and IDF guidelines.*

## INTRODUCTION

Type 2 diabetes mellitus is a chronic progressive disease arising from insulin resistance and gradual decrease in beta cell activity (1). The latest reports mention an 8% prevalence of type 2 diabetes in the Slovenian population aged between 20 and 79 years. In the USA, 9.6% of the population over age 20 have diabetes, its prevalence increasing with age, so that it is already present in 20.6% of the population aged over 60 (2). The growing prevalence of type 2 diabetes mellitus in the younger population is probably the result of the epidemic of obesity observed in recent years. Late macro- and microvascular diabetes-related complications increase the morbidity and mortality in these patients significantly. In patients with diabetes, death from coronary heart disease is twofold to threefold that in the general population (3). This shortens the life expectancy of diabetics by 5-10 years (4). The large randomized studies, United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study, which included type 2 diabetics, showed that

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good glycemic control greatly decreases morbidity due to microvascular complications, regardless of the type of treatment (5). At the onset of the disease, it can be attained by general measures, particularly by reducing body weight (6). Later on, pharmacological treatment is inevitable, initially with peroral antidiabetics, then with insulin. We decide on a modification of treatment when the desired therapeutic results are not reached, i.e. an HbA<sub>1c</sub> level below 7% in accordance with the American Diabetes Association (ADA) guidelines. An HbA<sub>1c</sub> level over 8% urgently requires a modification of therapy (4). The International Diabetic Federation (IDF) has set even stricter criteria. According to these, a modification of therapy is necessary at HbA<sub>1c</sub> values over 7.5%, while the aim of treatment is a value under 6.5% (13). Insulin therapy is the final step in the treatment of type 2 diabetes, one that we frequently decide on too late (7,8). Numerous studies show that early insulin therapy is important (9-11) since it decreases the frequency of macrovascular complications by decreasing the damage to the endothelium (12).

In our study, we wished to assess glycemic control in patients prior to insulin treatment and half a year, a year, and two years after starting insulin therapy. We wanted to establish which patients, with respect to their body mass index (BMI), would gain more by the introduction of insulin and how the newly introduced therapy would affect body weight. We followed the occurrence of microvascular complications (retinopathy, microalbuminuria) prior to and for two years of the introduction of insulin therapy.

## PATIENTS AND METHODS

The study included 99 patients starting insulin therapy between January 2003 and February 2004. Two years later, 81 patients remained in the study, one died, three moved to another diabetologic outpatient clinic, and 15 patients were excluded from the study due to incomplete data. The patients were divided into two groups according to BMI: <30 kg/m<sup>2</sup> and >30 kg/m<sup>2</sup> before insulin therapy introduction. Prior to the introduction of premixed insulin twice *per* day, the values of body weight, HbA<sub>1c</sub> level, frequency of microvascular complications and dyslipidemia were

recorded. Then the level of HbA<sub>1c</sub> was measured at 1/2 year, one year and two years of insulin therapy initiation. At two years, the presence of microvascular complications and dyslipidemia was recorded and body weight was measured.

Prior to the introduction of insulin therapy, 60 patients were treated with combined peroral therapy with sulfonylurea and metformin, 36 patients with sulfonylurea alone, and three patients did not take any peroral therapy. Those who were treated with metformin before, continued so after therapy modification.

HbA<sub>1c</sub> was determined using the high-performance liquid chromatography (HPLC) method. Funduscopy was performed by an ophthalmologist to assess the presence and progression of retinopathy. Microalbuminuria was determined from 24-hour urine specimen, and the diagnosis was made if the microalbuminuria findings were positive on two occasions. Statistical data analysis was carried out with the SPSS program; the linear regression procedure was used.

## RESULTS

The mean HbA<sub>1c</sub> level prior to the introduction of insulin therapy was 10.1%. In patients with BMI <30 kg/m<sup>2</sup> and >30 kg/m<sup>2</sup> it was 10.2% and 10.1%, respectively. Six months of the introduction of insulin therapy, we observed a statistically significant improvement of glycemic control in both groups; the mean HbA<sub>1c</sub> level was 8.0%: 7.8% in the group with BMI <30 and 8.2% in the group with BMI >30. There were no statistically significant between-group differences in HbA<sub>1c</sub> on any follow-up examination (Table 1).

After two years of insulin therapy, weight gain was evident in all patients. The greater body weight increase in the group with BMI <30 kg/m<sup>2</sup> was not statistically significant; these patients gained a mean of 4.4 kg, and those with BMI >30 kg/m<sup>2</sup> 2.6 kg (Table 2).

Table 1. HbA<sub>1c</sub> levels before and after the introduction of insulin therapy

| Patient group             | HbA <sub>1c</sub> level |                |              |               |
|---------------------------|-------------------------|----------------|--------------|---------------|
|                           | Before                  | After 1/2 year | After 1 year | After 2 years |
| All                       | 10.18148                | 8.003704       | 7.82963      | 8.041975      |
| BMI <30 kg/m <sup>2</sup> | 10.22653                | 7.859184       | 7.663265     | 7.891837      |
| BMI >30 kg/m <sup>2</sup> | 10.1125                 | 8.225          | 8.084375     | 8.271875      |

Table 2. Body weight before and after 2 years of insulin therapy (N=81)

| Patient group             | Body weight (kg) |             |
|---------------------------|------------------|-------------|
|                           | Before           | After 2 yrs |
| All                       | 78.9             | 82.575      |
| BMI <30 kg/m <sup>2</sup> | 70.54167         | 74.9375     |
| BMI >30 kg/m <sup>2</sup> | 91.4375          | 94.03125    |

Table 3. Microvascular complications and dyslipidemia before insulin therapy (N=81, BMI <30 n=49, BMI >30 n=32)

| Patient group             | Diabetic    |                  |              |
|---------------------------|-------------|------------------|--------------|
|                           | retinopathy | Microalbuminuria | Dyslipidemia |
| All                       | 15          | 35               | 63           |
| BMI <30 kg/m <sup>2</sup> | 5           | 22               | 37           |
| BMI >30 kg/m <sup>2</sup> | 10          | 13               | 26           |

The number of microvascular complications and the frequency of dyslipidemia before the introduction of insulin therapy are presented in Table 3. At two years of therapy, new microvascular complications or deterioration of the existing ones were recorded in 13 patients.

## DISCUSSION

As numerous studies confirmed (9-11) that good control of diabetes results in a significant decrease in morbidity and mortality due to chronic complications, the ADA and IDF have set strict limits of glycemic control, determining when it is necessary to take action and modify the treatment of diabetes (4,13). Our study showed the patients requiring insulin

therapy to be recruited too late, at the time when HbA<sub>1c</sub> had already reached 10.1% on an average. There was a statistically significant improvement in glycemic control, both overall and in particular groups according to BMI, at six months, one year and two years of insulin therapy initiation. In these periods, there were no significant differences in the control of diabetes, showing that the newly introduced therapy was efficacious and well tolerated by the patients. In both groups, body weight increased after two years; weight gain was slightly greater in the group with BMI <30. To evaluate the progression of chronic complications of diabetes, we observed the frequency of microalbuminuria and retinopathy prior to the introduction of insulin and two years after therapy modification. At two years of insulin therapy, microvascular complications recurred in only 13 patients, implying better control and more favorable long-term prognosis.

## CONCLUSION

It is concluded that all patients irrespective of BMI benefit from insulin therapy, which is well tolerated. Although the goal of glycemic control according to ADA and IDF criteria was not reached, the level of glycosylated hemoglobin decreased significantly, implying fewer chronic complications. For our clinical work, however, the awareness of the fact that patients are recruited too late for insulin therapy is of utmost importance. Earlier recruitment of patients would also improve long-term control and would be of help in approaching the aims of glycemic control according to the valid criteria.

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