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The Short-Term Results of Intensive Insulin Therapy in Preadolescent Children with Type-1 Diabetes

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Abstract : Purpose: The aim of this study was to observe the effects of and compliance with an intensive insulin regimen in preadolescent children with type-1 diabetes.

Patients and methods: Eleven insulin-dependent diabetic patients, five girls and six boys aged 8 - 11 years (mean 9 years 3 months) with a mean±SD diabetes duration of 2±1.07 years, participated in this study. The results of the intensive insulin regimen were evaluated after one-year follow-up in 11 patients, and in 8 patients at 18 months. In the first year of this study we aimed to bring about higher blood glucose than is generally advised, in order to avoid hypoglycemia. After one year, we encouraged the patients to promote strict metabolic control.

Results: Blood glucose and HbA1c levels had significantly decreased after the intensive insulin regimen at the 12th month of treatment ($p<0.05$ and $p<0.01$, respectively), and at the 18th month of treatment ($p<0.01$ and $p<0.01$, respectively). The mean body weight and mean body mass index (BMI) changes were insignificant at 12 months ($p>0.05$), but had significantly increased at 18 months ($p<0.05$ and $p<0.01$, respectively). None of the patients experienced symptomatic hypoglycemic episodes during the 12-month follow-up, but severe symptomatic hypoglycemic episodes were determined at an incidence of 36% between 12th and 18th months. Diastolic blood pressure decreased significantly ($p<0.05$). Total triglycerides, VLDL triglycerides and total cholesterol as well as LDL cholesterol (LDL-C), VLDL cholesterol (VLDL-C) and apoprotein B (apo B) decreased ($p<0.05$) but high-density lipoprotein cholesterol (HDL-C) and apoprotein A1 (apo A1) increased ($p<0.05$). The glomerular filtration rate (GFR) and microalbumin excretion rate did not change ($p>0.05$).

Conclusion: Although the patients had no symptomatic hypoglycemic episodes in the first 12 months, they had symptomatic hypoglycemia between 12th and 18th months, when there was stricter metabolic control. We conclude that this regimen is appropriate for preadolescent children.

Key Words: Type 1 diabetes mellitus, intensive insulin therapy, multiple injections, preadolescent children

Introduction

Mortality due to diabetes mellitus has diminished since the invention of insulin, but morbidity has gradually increased. Thus, the aim of diabetes treatment has been to prevent or delay complications. The results of the Diabetes Control and Complications Trial (DCCT) have shown that the degree of metabolic control obtained in adolescents and adults with type-1 diabetes significantly influences the onset and progression of microvascular complications (1). We examined the effect of an intensive insulin regimen in preadolescent diabetic patients, an approach that has not been used with this age group (2,3).

Methods

Eleven insulin-dependent diabetic patients aged 8-11 years (mean, 9 years 3 months) followed up at Karadeniz Technical University Farabi Hospital were included in this study. The mean duration of the diabetes was 2 ± 1.07 years. The inclusion criteria were failure to respond to previous treatment (a regimen of twice-daily injections) and residence close to the hospital. Failure to respond to treatment was defined as poor metabolic control with a HbA1c level higher than 9%, daily blood glucose fluctuations higher than 100-150 mg/dL, symptomatic hypoglycemic/hyperglycemic periods, and inadequate adapta-

tion to treatment in the presence of a conflict between lifestyle (attendance at school) and the requirements of conventional treatment. All the patients exhibited normal growth and development, with no proliferative retinopathy, clinical nephropathy or clinical neuropathy.

The conventional regimen was changed to an intensified insulin therapy, consisting of preprandial short-acting insulin three times a day and NPH insulin at night.

The blood glucose levels were evaluated four times a day and two times at night (2 and 4 a.m.) one or two nights a week. The initial NPH dosage was calculated at 25-30% of the total daily dose, and preprandial crystalline zinc insulin boluses were individualized for each patient according to meal intake and blood glucose levels. The glucose levels were maintained within the range 5.55-11.10 mmol/L. The patients were advised to have a balanced diet containing 50% to 55% carbohydrates, 20% protein, and approximately 30% fat. Calorie intake was determined according to need, simple sugars were restricted and a meal-planning program was individualized according to each patient's family income, lifestyle and school schedule.

A routine physical examination was performed monthly in the first three months and at 3-month intervals thereafter. Blood pressure was measured after 15 minutes sitting.

Blood samples were drawn in the morning in the fasting state for serum glucose, HbA1c, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, VLD cholesterol, total triglyceride, VLDL triglyceride, apo A1, apo B and anti-insulin antibody. Twenty-four-hour urine samples were collected at 3-month intervals for albumin excretion rate and glomerular filtration rate. Only the mean body weight, BMI and HbA1c of eight patients were evaluated at 18 months.

Blood samples for plasma lipids and lipoproteins were also taken from two healthy children for each diabetic subject so as to serve as sex-age matched controls.

The sample analyses were evaluated as follows: HbA1c by latex immunoagglutination (Bayer diagnostic); microalbumin excretion by an immunohistochemical method (Beckman Assay); glucose, creatinine, triglyceride, VLDL triglyceride, total cholesterol, HDL, LDL and LDL cholesterol by commercially available enzyme methods (Boehringer Mannheim Biochemicals); apo A1 and apo B by the Beckman Protein Assay; and anti-insulin antibody by the RIA method.

BMI was calculated as BMI=weight / height^2 and the glomerular filtration rate (GFR) was calculated as GFR = K x height / plasma creatinine (K=0.45 for 1-5-year-olds, 0.55 for 5-10-year-olds, 0.55 for adolescent girls and 0.7 for adolescent boys) (4).

Statistical analysis: The results were recorded as the mean ± SD. For paired samples (before versus after treatment) the Wilcoxon test was used, and for unpaired samples (diabetic versus control) the Mann Whitney-U test was used.

Results

The mean age of our patients was 9 years and 3 months. The mean diabetes duration was two years. None of the patients had growth retardation or obesity (mean weight, 27.02 ± 4.66 kg; mean height, 130.37 ± 15.06 cm; and mean BMI, 20.18 ± 3.28 kg/m^2).

The initial, first month and 12th month mean blood glucose, HbA1c, insulin dosage and anti-insulin antibody levels are given in Table 1. Although the insulin dosage (U/kg) ($p>0.05$) and antibody-against-insulin levels ($p>0.05$) were unchanged, blood glucose levels ($p<0.05$)

Table 1. Mean blood glucose, HbA1c, insulin dosage and insulin antibody levels.

	Initial (mean ± SD)	First month (mean ± SD)	12th month (mean ± SD)
Blood glucose (mmol/L)	16.13 ± 2.54*[a]	10.83 ± 1.66	8.38 ± 2.70*[b]
HbA1c (%)	12.28 ± 0.47	11.84 ± 0.59	9.00 ± 1.45
Insulin dosage (U/kg)	0.73 ± 0.04**[c]	0.71 ± 0.21	0.65 ± 0.04**[d]
Anti-insulin Ab (%)	22.22 ± 3.49	19.20 ± 3.00	20.00 ± 4.55

*$p<0.05$ (a, b),
**$p<0.01$ (c, d)

and HbA1c levels ($p<0.01$) had significantly decreased after the intensive insulin treatment.

The mean albumin excretion rate, GFR, and systolic and diastolic blood pressure values are given in Table 2. The GFR and microalbumin excretion rates were unchanged ($p>0.05$). Systolic and diastolic blood pressure were found to have decreased after intensive treatment, but only the decreased diastolic blood pressure was statistically significant ($p<0.05$).

The plasma triglyceride, VLDL triglyceride, total cholesterol, HDL-C, LDL-C, VLDL-C, apo A1 and apo B levels of the diabetic patients and control group are given in Table 3. At the beginning of treatment the plasma triglyceride, cholesterol, LDL-C, VLDL-C, apo A1 levels were higher ($p<0.05$) and HDL-C, and apo B levels were lower ($p<0.05$) in the diabetic group than in the control group. After one year of intensive treatment the levels of total LDL-C and VLDL-C as well as triglycerides, VLDL triglycerides and apolipoprotein B had significantly decreased ($p<0.05$). Conversely, the levels of HDL cholesterol, and apolipoprotein A1 had significantly increased ($p<0.05$).

After this one-year period, the patients were advised to promote stricter metabolic control as described previously (5). Eight of the 11 patients were assessed while 3 were withdrawn from the study due to poor compliance. At the end of the 18th month when compared with the pretreatment levels, the mean HbA1c of these eight patients had decreased, to 7.5±1.01 ($p<0.01$), the mean body weight and BMI had increased, to 33.20±1.80 kg/m^2 ($p<0.05$) and 23.21±1.52 kg/m^2 ($p<0.01$) respectively, while symptomatic hypoglycemic periods occurred at an incidence of 36%.

Table 2. Twenty four hour urine microalbumin excretion rate, glomerular filtration rate, and systolic and diastolic blood pressure.

	Initial (mean±SD)	First month (mean±SD)	12th month (mean±SD)
Twenty-four-hour urine			
Microalbumin (mg/dl)	10.52 ± 8.08	13.24 ± 6.70	10.37 ± 6.35
GFR (ml/sn/1.73)	113.09 ± 23.67	108.9 ± 23.58	118.00 ± 14.18
Blood pressure			
systolic (mmHg)	113.63 ± 2.32	110.45 ± 2.18	110.53 ± 1.57
diastolic (mmHg)	71.36 ± 3.23*^{a}	65.9 ± 3.00*^{b}	66.42 ± 3.95*^{c}

*$p<0.05$ (a, b), (b, c)

Table 3. Mean total plasma triglyceride, VLDL triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, apoprotein A1 and apoprotein B levels of diabetic patients and control group.

	Initial (mean±SD)	First month (mean±SD)	12th month (mean±SD)	Control (mean±SD)
Triglyceride (mg/dl)	114.09±52.84^a	100.27±50.92	90.18±52.15^b*	90.31±33.60^c**
VLDL triglyceride (mg/dl)	84.09±52.84^a	72.24±40.91	62.14±34.15^b*	60.21±22.60^c**
T. cholesterol (mg/dl)	173.09±31.64^a	163.27±31.39	154.27±55.41^b*	147.54±27.23^c**
HDL-c (mmol/L)	1.06±0.30^a	1.12±0.26	1.17±0.34^b*	1.21±0.20^c**
LDL-c (mmol/L)	2.50±0.63^a	2.30±0.84	2.29±0.88^b*	2.27±0.55^c**
VLDL-c(mg/dl)	29.51±9.82^a	23.15±11.83	22.11±10.87^b*	23.10±9.11^c**
ApoA1 (mg/dl)	135.20±28.53^a	130.61±43.40	120.12±21.26^b*	114.05±17.31^c**
ApoB (mg/dl)	85.53±34.10^a	90.09±28.12	96.75±32.28^b*	90.15±42.58^c**

*$p<0.05$ (a, b), **$p<0.05$ (a, c), $p>0.05$ (b, c)

Discussion

Impaired growth is a well-recognized complication of uncontrolled diabetes (Mauriac syndrome), and less severe metabolic derangements commonly observed with conventional treatment may adversely affect growth potential. Intensive insulin treatment has been shown to correct metabolic abnormalities and accelerate linear growth (6). In the present study, all the patients receiving both conventional and intensive treatment had normal linear growth. Greater weight gain has been reported for patients treated with one of the intensive insulin regimens than for patients treated conventionally (7,8). Our results did not confirm these observations in the first 12 months of the study, but weight gain was observed between 12 and 18 months.

The blood glucose and HbA1c levels fell significantly with no difference in the insulin need as in the results of Nathan et al. (9). Although increased antibody production against insulin with no significant clinical effects has been reported (10,11), we did not find any difference between the anti-insulin antibody levels before and after intensive treatment.

Hypertension is one of the most important risk factors for initiation and progression of nephropathy and premature coronary artery disease in diabetic patients. Although the pre-study blood pressure was not abnormal and fell within the normal range, the intensive insulin regimen caused blood pressures to decrease further, especially diastolic pressure. Aoki et al. found that tight glycemic control not only decreased the blood pressure but also improved the abnormal circadian blood pressure pattern seen in diabetic patients (12). This observation supports the view that an intensive insulin regimen tends to reverse or at least prevent further deterioration of blood pressure abnormalities.

Microalbuminuria is also a reliable indicator for the progression of diabetic nephropathy (13-16). Intensive therapy reduces the cumulative incidence and overall risk of the development of microalbuminuria and clinical albuminuria (17-19). The expected beneficial effect of the intensive therapy is to prevent the onset or at least delay the progression of nephropathy (20). In our study, albuminuria was within normal limits, both in the patients receiving conventional therapy and in those who underwent a one-year period of intensive therapy. None of the patients developed microalbuminuria during the follow-up. Normalization of blood pressure and the prevention of microalbuminuria might be important factors for the prevention of chronic diabetic complications such as nephropathy and coronary artery diseases.

Since insulin has important regulatory effects on plasma lipids and glucose metabolism, plasma lipid and lipoprotein abnormalities in patients with type-1 diabetes mellitus change with the absence or presence of insulin treatment (21-23). The degree of metabolic control in type-1 diabetes may also influence the lipid and lipoprotein levels. Most studies have shown moderate plasma lipid and lipoprotein abnormalities in type-1 diabetes patients treated adequately with conventional insulin therapy (24,25). With poor control, when insulin administration is subnormal, plasma triglyceride, total cholesterol, LDL-C, VLDL-C, and apo A1 are elevated and HDL-C and apo B are decreased. When better metabolic control has been achieved, serum lipid levels return to the normal levels similar to age- and sex-matched healthy controls (26). In the present study, we found high cholesterol, VLDL-C, LDL-C, triglyceride,VLDL triglyceride, apo A1 and low HDL-C and apo B levels in patients treated with a conventional insulin regimen, after treatment was changed to an intensive insulin regimen. Although we did not achieve optimal metabolic control, total triglyceride, VLDL triglyceride, cholesterol, VLDL-C, LDL-C, and apo A1 levels decreased, while HDL-C and apo B levels increased to the control levels. Since coronary artery disease is one of the most common causes of premature death in diabetics, secondary hyperlipidemia must be one of the goals of chronic diabetes treatment in order to prevent arteriosclerosis.

In this study, even though the desired metabolic control was not obtained, some remarkable improvements were made. First of all, although our patient age group was very young, the patients easily adapted to the multiple injection therapy because they had more freedom with regard to meal times than with the conventional regimen. Moreover, due to decreased diastolic blood pressure, normalized plasma lipid levels and the prevention of microalbuminuria, it is expected that they will have a low risk of developing complications in the future. In addition, we did not observe any complications resulting from the intensive insulin therapy, such as severe hypoglycemia or obesity (8,27,28). In the first 12 months, in order to avoid hypoglycemia the patients were instructed to have higher target blood glucose levels than those usually reported in

the literature because of their relatively young ages, but after the 12th month we observed symptomatic hypoglycemia with strict metabolic control.

Multiple insulin regimens have been widely used around the world in the past few decades. They are recommended for adolescents and young adults (2,29). This study shows that a multiple injection regimen can be safely applied in the preadolescent age group.

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