

FEASIBILITY OF APPLYING RECOMMENDATIONS FROM THE DIABETES CONTROL AND COMPLICATIONS TRIAL TO SAUDI ADOLESCENTS WITH INSULIN-DEPENDENT DIABETES

Najya Attia, MD; Ramla Saif, MD; Abdulla Al-Ashwal, MD, FRCPC, FAAP;
Nadia Sakati, MD; Claire Dolinski, RN, BSN, CDE; William V. Tamborlane, MD

Results of the Diabetes Control and Complications Trial (DCCT) indicate that the benefits of intensive therapy outweigh the increased risk of hypoglycemia in adolescents, as well as adults with IDDM.¹ Consequently, the DCCT Research Group recommended that most adolescents should be treated with closely monitored, intensive treatment regimens aimed at achieving plasma glucose levels as close to the nondiabetic range as possible.¹ While translation of the DCCT finding into clinical practice poses special problems for pediatric health care providers regardless of locality,^{2,3} it was considered that cultural barriers might make implementation of the DCCT recommendations almost impossible in Middle Eastern countries such as Saudi Arabia. To address this issue, we examined the feasibility and efficacy of applying intensive treatment techniques, modelled after the DCCT, to a representative sample of adolescents attending the Children's Diabetes Clinic at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh, Saudi Arabia.

Patients and Methods

To be eligible, patients had to be Saudi nationals between 12 and 17 years of age, have a disease duration of over two years, be free of other major illnesses, and have a glycosylated hemoglobin (HbA_{1c}) >8.6%, i.e., more than 3 SD above the mean of nondiabetic subjects (mean 6.30±0.75%). The aim was to recruit 10 patients out of the approximately 48 adolescents enrolled in the clinic who met these criteria. All but one of the first eleven patients who were invited to participate agreed to be entered in the study. The group consisted of five boys and five girls aged 14±1 years and with IDDM duration of 4±1 years. No

patient was obese or had advanced complications, and they were all receiving a two-injection regimen of neutral protamine Hagedorn (NPH) and regular insulin before breakfast and dinner. After obtaining informed consent, each patient was asked to perform self-blood glucose monitoring (SBGM) three to four times daily, while leaving insulin doses unchanged for two weeks prior to the start of intensive treatment. They were told to carefully consider whether they wished to continue in the study during this time, and all elected to do so.

Intensive Treatment and Follow-up

After two weeks, patients were seen in the clinic where a baseline HbA_{1c} level was obtained. All were then switched to a three-injection regimen, consisting of a mixture of Ultralente[®] and regular insulin before breakfast and dinner, and regular insulin alone at lunch. They were initially continued on the same total daily dose that they had been receiving, with approximately 70% given as Ultralente. The rest was divided among the pre-meal doses of regular insulin, based on SBGM results during the two-week pre-study period. They were asked to perform SBGM three to four times daily, and instructed on adjustments of doses of regular insulin based on SBGM results.

Rather than being admitted to the hospital for initiation of intensive treatment, they were seen every 1-2 weeks for the first month and then monthly for the next five months. During monthly outpatient visits, HbA_{1c} levels were obtained and clinical data were collected using report forms adapted from the DCCT Manual of Operations Form 21.

Analyses

Total glycosylated hemoglobin (HbA_{1c}) levels were measured by a boronate affinity binding assay (Abbott Laboratories, Abbott Park, IL). The significance of differences in HbA_{1c} levels was tested by repeated measures (analysis of variance, or ANOVA), and paired *t*-tests were employed in post-hoc analysis to localize the effects. Paired *t*-tests were also used to compare differences

From the Departments of Pediatrics King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, and Yale School of Medicine, USA.

Address reprint requests and correspondence to Dr. Al-Ashwal, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, MBC-58, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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in insulin doses before and after intensive treatment. $P < 0.05$ was considered statistically significant. HbA_{1c} z-scores as well as mean values are given. Data in the text are presented as mean \pm SD.

Results

As shown in Figure 1, there was a highly significant reduction in HbA_{1c} values during the study ($P < 0.001$, ANOVA). The mean HbA_{1c} level at baseline was $13.6 \pm 1.8\%$ (z-score 9.7 ± 2.4), and levels fell sharply to $11.1 \pm 0.7\%$ (z-score 6.6 ± 0.9) after only two months ($P < 0.01$), and to $9.7 \pm 0.6\%$ (z-score 4.5 ± 0.8) after six months of intensive therapy ($P < 0.01$). Moreover, as shown in Figure 2, a substantial lowering of HbA_{1c} levels was observed in all but one patient. During conventional treatment, the total daily dose averaged 0.98 ± 0.08 units/kg body weight/day and the dose increased to 1.14 ± 0.06 units/kg/day ($P < 0.05$) with intensive therapy. Regular insulin comprised $23 \pm 2\%$ of the total daily dose during conventional treatment, as compared to $34 \pm 4\%$ during intensive therapy ($P < 0.050$). Patients reported performing SGBM 3.1 ± 0.4 times daily during the study.

None of the subjects had a severe hypoglycemic event during the six months before or during the study, and weight gain was appropriate. All reported subjective improvement in well-being, and all elected to remain on the three-shot regimen at the end of the study.

Discussion

Results of the present study demonstrate that intensive treatment techniques can be successfully implemented in Saudi adolescents with IDDM, at least over the short term. Despite concerns that cultural traditions might preclude such an aggressive approach to treatment, our patients were able to achieve a statistically significant and clinically meaningful lowering of HbA_{1c} levels, which compares very favorably with that achieved by intensively treated adolescents in the DCCT.¹ Adolescents in the DCCT had baseline HbA_{1c} levels approximately 10 SD above the mean of nondiabetic subjects during conventional treatment, and HbA_{1c} levels were lowered to approximately 5 SD above the nondiabetic mean after the first six months of intensive management, z-scores that are nearly identical to values in our patients.

A number of well-recognized factors, including the close follow-up and support of the diabetes treatment team, frequent SGBM and increased insulin dosage, undoubtedly contributed to the improvement in metabolic control in our patients. It should also be noted that the classical, North American twice-a-day regimen of mixtures of NPH and regular insulin before breakfast and dinner⁴ is particularly

ill-suited for the usual meal pattern of Middle Eastern schoolchildren. They typically eat a light breakfast between 6:30 and 7:30 a.m., a large lunch between 1:30 and 2:30 p.m., and late dinner between 7:30 and 8:30 p.m. The light breakfast and late lunch limit the amount of NPH and regular insulin that can be given before breakfast without inducing late morning hypoglycemia. This in turn, contributes to marked postprandial hyperglycemia following the large midday meal. Many of these difficulties

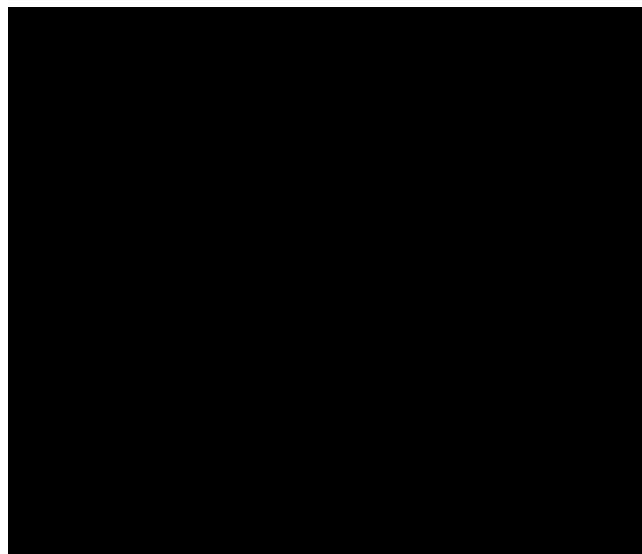


FIGURE 1. Effect of intensive treatment on HbA_{1c} levels in the study group (nondiabetic range 4.8%-7.8%) mean \pm SD are shown. P -values refer to significance of difference vs. levels during conventional treatment (mon. 0). * $P < 0.01$.

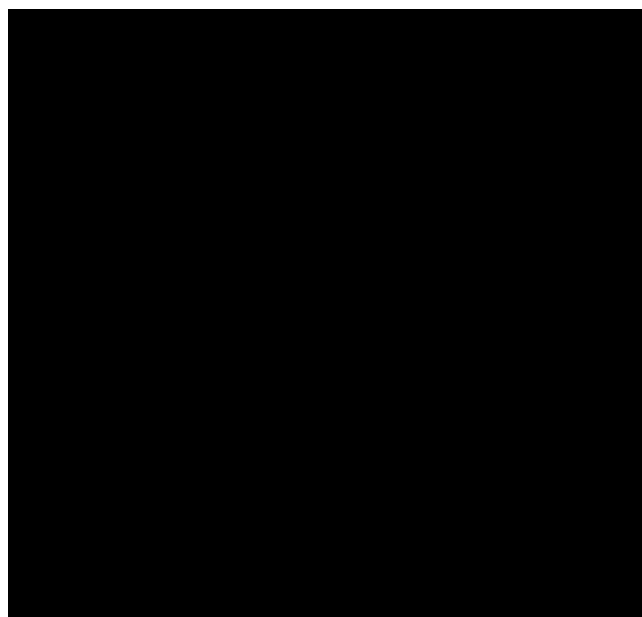


FIGURE 2. HbA_{1c} levels in individual patients before and after six months of intensive therapy.

were overcome using Ultralente and regular insulin in the three-shot regimen employed in this study. Since the study was designed to recruit a representative sample of adolescents with IDDM at our center, the success of our patients in achieving improved control argues for the more widespread use of such multiple daily injection regimens at other tertiary care centers in the region. However, it remains to be determined whether similar success can be achieved in more rural and less affluent areas.

Improved control of diabetes was achieved in our patients without major adverse events. Nevertheless, the DCCT experience indicates that the frequency of severe hypoglycemic events will increase as improved control is maintained over longer periods of time,⁵ and if larger numbers of adolescents in the region receive this therapy. Nevertheless, since the benefits of intensive treatment in adolescents outweighs the risk of hypoglycemia,¹ the long-term prognosis for such patients should be markedly improved.

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