Pediatr Nephrol (1996) 10: 261–263

Pediatric Nephrology

Original article

Carbohydrate metabolism in children receiving growth hormone for 5 years

Chronic renal insufficiency compared with growth hormone deficiency, Turner syndrome, and idiopathic short stature

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Received October 30, 1995; received in revised form January 18, 1996; accepted January 25, 1996

Abstract. Carbohydrate metabolism was evaluated by fasting and postprandial glucose, insulin, and hemoglobin (Hb)A_{1c} levels in children with chronic renal insufficiency and various other growth disorders treated with growth hormone. Mean fasting and postprandial glucose remained unchanged throughout the 5-year study period in all four study groups. Median fasting insulin levels rose from low-normal levels into the normal range after 5 years of growth hormone. Average fasting insulin level after 5 years was 10 mU/l. Median postprandial insulin values also rose, yet remained within the normal range at the 5-year mark. Mean Hb A_{1c} levels remained within low to middle end of the normal range in the patients with growth hormone deficiency, Turner syndrome, and idiopathic short stature. Mean Hb A_{1c} levels at the 5 years were slightly elevated to 6.3% for the patients with chronic renal insufficiency.

Key words: Carbohydrate metabolism – Chronic renal insufficiency – Growth hormone

Introduction

While growth hormone treatment is approved and well established for children with growth hormone deficiency and chronic renal disease prior to transplantation, growth hormone therapy is still considered experimental in the United States for Turner syndrome and for children with idiopathic short stature. In order to evaluate legitimate concerns about the side effects of growth hormone therapy such as negative impact on carbohydrate metabolism or increased insulin resistance, we evaluated the effect of growth hormone treatment on carbohydrate metabolism in four separate multi-center studies, in children with chronic renal insufficiency, growth hormone deficiency, Turner syndrome, and idiopathic short stature, respectively [1–7].

We measured changes in carbohydrate metabolism, as assessed by glucose and insulin levels in the fasting state and after a standard glucose load and glycohemoglobin (Hb A_{1c}) levels. We also studied the effects of up to 5 years of growth hormone therapy in these children on levels of L-thyroxine, cholesterol, triglycerides, sodium, and potassium.

Patients and methods

The study groups comprised 16 patients with chronic renal insufficiency prior to renal transplant, 66 patients with growth hormone deficiency, 45 patients with Turner syndrome, and 25 patients with idiopathic short stature. Equal numbers were used throughout the study i.e. only patients with complete data are used. Each study was carried out for at least 5 years. The growth hormone dose for each study was as follows: chronic renal insufficiency 0.35 mg/kg per week, growth hormone deficiency 0.30 mg/kg per week, Turner syndrome 0.375 mg/kg per week, and idiopathic short stature 0.30 mg/kg per week. Pre-existing insulin-dependent diabetes mellitus was one of the exclusion criteria. Laboratory data were reported at yearly or more frequent intervals during treatment. Blood chemistry, liver function tests, serum thyroxine, blood glucose, insulin, and Hb A_{1c} levels were measured at Smith-Kline Bioscience Laboratories (Van Nuys, California, USA) Hb A_{1c} levels were determined using a chromatographic method (normal values $<6.2\%$). Blood glucose was measured at 0 min in the fasting state and at 120 min after a standard glucose load consisting of 1.75 g of glucose solution/kg, with a maximum of 75 g per dose.

Baseline levels and postprandial responses in normal controls, as established by Smith Kline Biosciences Laboratories, are depicted in the shaded area of the figures. Median levels were used for insulin throughout because of the skewed nature of the data. Institutional review board approval was obtained for all studies at the individual performance sites.

Statistical methods. The analysis was based on results at baseline and annually thereafter. Within-treatment group comparisons were made with two-tailed paired *t*-tests, except for insulin where, median values were used because of skewing of data. In the statistical analysis of insulin levels, the mean of $\log_{10}$ value was used. Unless otherwise indicated, *P* values are for the comparison of results at baseline and the 60-month time point.

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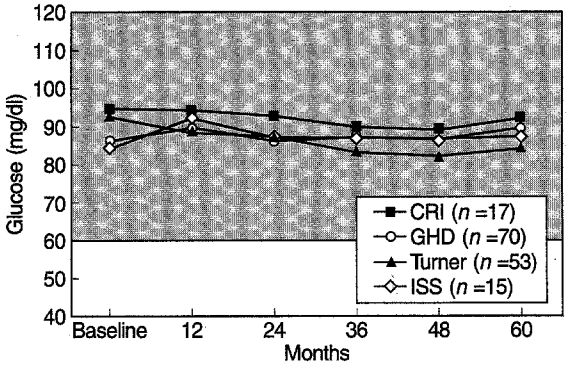

Fig. 1. Fasting glucose (mean) throughout the 5-year study period in children with chronic renal insufficiency (*CRI*) and other growth disorders receiving growth hormone treatment. *GHD*, Growth hormone deficiency; *ISS*, idiopathic short stature

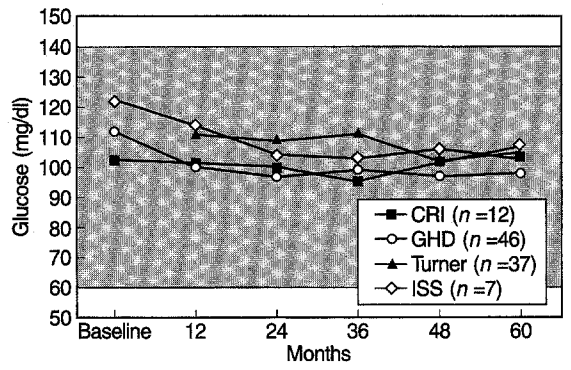

Fig. 2. Postprandial glucose (mean) levels throughout the 5-year study period. Baseline postprandial glucose levels are not available for the Turner syndrome patients

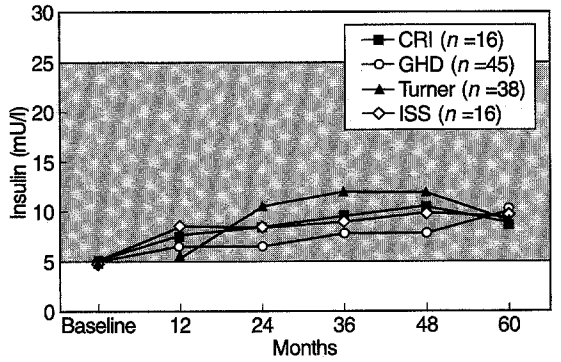

Fig. 3. Fasting insulin (median) levels throughout the 5-year study period. Baseline postprandial insulin levels are not available for the Turner syndrome patients

Results

There were no statistically significant changes in mean sodium, potassium, thyroxine, cholesterol, and triglyceride concentrations throughout the studies. Mean fasting and postprandial glucose levels remained unchanged throughout the 5-year study period in all four study groups ($P = NS$ for all four study groups at all time points).

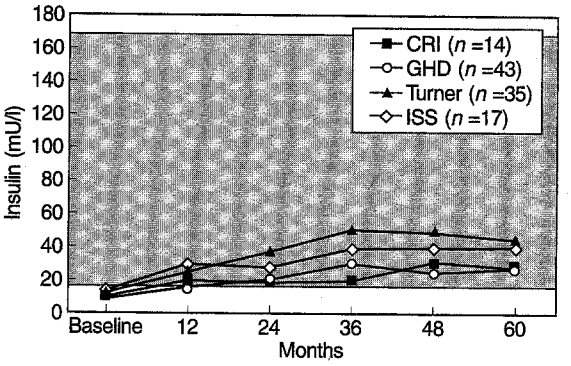

Fig. 4. Postprandial insulin (median) levels throughout the 5-year study period. Baseline postprandial insulin levels are not available for the Turner syndrome patients

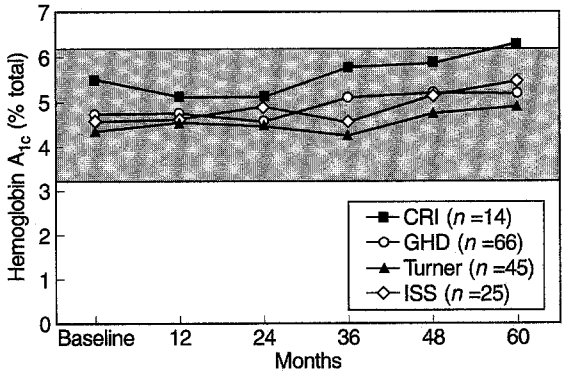

Fig. 5. Hemoglobin A_{1c} (mean) levels throughout the 5-year study period

Median fasting insulin levels rose from low-normal levels into the normal range after 5 years of growth hormone. The average fasting insulin level after 5 years was 10 mU/l. Comparison of median fasting insulin between chronic renal insufficiency patients ($n = 16$, month 60 vs. baseline) shows a significant rise, $P < 0.002$, yet levels remained within the normal range. Median postprandial insulin values also rose for the chronic renal insufficiency group, $P < 0.0003$ month 60 vs. baseline, yet remained also within the normal range, shown by the hatched area in Figs. 3 and 4, at the 5-year mark (Fig. 1–4). Both fasting and postprandial insulin levels remained thus within the low to middle end of the normal range.

Mean Hb A_{1c} levels remained within the normal range in the patients with growth hormone deficiency, Turner syndrome, and idiopathic short stature (Fig. 5). Mean Hb A_{1c} levels for the chronic renal insufficiency group rose from 5.4% to 6.3%, $p < 0.006$, when comparing month 60 and baseline.

Discussion

The design of our multi-center studies does not allow for more sophisticated evaluation of carbohydrate tolerance

and insulin sensitivity in the patients reported here. The data are reassuring in that only a modest rise in median insulin levels within the normal range was seen. Increasing carbohydrate intolerance in chronic renal insufficiency is well established and may occur prior to administration of growth hormone [1, 8, 9].

In previous studies [1] of growth hormone treatment of children with chronic renal insufficiency significant increases in fasting as well as 2-h postprandial insulin levels were seen during the 1st year. Mean insulin levels fell during the 2nd year and were not significantly increased at 24 months compared with baseline values. Other workers [10–12] have demonstrated a clear increase in insulin secretion without impairment of glucose disposal after growth hormone administration for chronic renal disease and other growth disorders. In several of these studies insulin levels during oral glucose tolerance tests exceeded the normal range [10, 11]. Lesage et al. [13] observed reversal of hyperinsulinism within 12 months of discontinuation of growth hormone in their group of ten pubertal children with idiopathic short stature treated with growth hormone doses 2 to 3 times the dose utilized in the study reported here. Even with the substantially higher dose of growth hormone, maximum levels of serum insulin during oral glucose tolerance tests were only modestly higher than the insulin levels found in our studies. Similarly we recently demonstrated reversal of postprandial hyperinsulinism after growth hormone therapy was discontinued in patients with Turner syndrome [14].

In summary, continued monitoring over a 5-year span has not revealed any currently discernible metabolic side effects of clinical significance during the study of growth hormone therapy in children with chronic renal insufficiency, growth hormone deficiency, Turner syndrome, or idiopathic short stature. Median fasting as well as 2-h postprandial insulin levels increase but do not rise above the normal range. Hb A_{1c} levels for the group with chronic renal insufficiency show a significant rise, which by 60 months is slightly above the upper limit of normal. Nonetheless, possible as yet nondiscernible effects on beta-cell mass, insulin action, as well as microvascular integrity require continued careful follow-up and evaluation. It will also be of interest to re-evaluate carbohydrate metabolism after growth hormone therapy is discontinued. These studies are now in progress as part of the ongoing analysis of these clinical investigations.

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