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The Impact of Growth Hormone Therapy on Glucose Metabolism of Children with Growth Hormone Deficiency

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Abstract **Original Research Article**

Introduction: Growth hormone (GH) has well known effects on carbohydrate metabolism. The aim of our study is to evaluate the effects of GH therapy on glucose metabolism in children with GH deficiency. ***Materials and methods:*** Fasting glycemia was measured before and after 12, 24 and 36 months of GH therapy (0.035 mg/kg/day). Besides, the data of Glycated heamoglobin perfomed after a treatment duration of 2 years were collected. ***Results:*** The fasting glycemias remained normals with only one patient with impairment fasting glycose. The mean of fasting glycemia after 12, 24 and 36 months was slightly higher than the pre-treatment values. As for the glycated heamoglobin, it was normal for all our patients except three ones. ***Conclusion:*** Our data show that GH therapy in GH deficient children have an increasement impact of the levels of fasting glycemia and glycated heamoglobin, but further studies with large cohort and longuer follow-up ares required to evaluate this impact.

Keywords: Growth hormone-therapy-deficiency-children-carbohydrate metabolism.

INTRODUCTION

Growth hormone deficiency (GHD) is a frequent reason for consultation in Endocrinology. Its etiologies are multiple and their clinical presentations are variable. The diagnosis is often made late, this delay is often due to ignorance of the pathology, and the lack of regular anthropometric monitoring in our patients. The management of GHD is based on a multidisciplinary approach. Treatment requires growth hormone (GH) replacement. GH plays an important and complex role in glucose metabolism. It affects carbohydrate metabolism through direct negative effect on insulin sensitivity and indirectly via insulin like growth factor (IGF-1). Special attention has been paid to changes in glucose and glycated heamoglobin (HbA1c) concentrations during GH replacement therapy. Hence the interest of optimal glucose monitoring.

MATERIELS AND METHODS

Our study was retrospective, conducted in the Endocrinology, Metabolic Diseases and Nutrition Department of the Mohamed VI University Hospital in Marrakech. It included children followed for growth hormone deficiency requiring treatment by somatotropin (0.035mg/kg/day). Data was obtained by reviewing the medical records of patients, over a treatment duration of three years.

The aim of this study was to evaluate the influence of long-term GH treatment on glucose homeostasis. Based on this analysis we wanted to determine the usefulness of HbA1c and fasting glycemia in the monitoring of disturbed glucose metabolism during GH treatment.

The difficulties encountered during this study are the patients lost to follow-up after the start of treatment; the discontinuation of treatment due to the out of stock of GH and patients who missed their appointments due to the state of health emergency due to Covid19; as well as patients who did not realize HbA1c due to lack of resources.

Outcomes

The study enrolled 112 patients treated with GH for 1 to 3 years. The average age of the population was 13 years and 4 months, with extremes ranging from

5 to 21, with the majority age range between 12 and 18 years. Our series included 81 boys (72%), and 31 girls (28%), with a clear male predominance: sex ratio of 2.75.

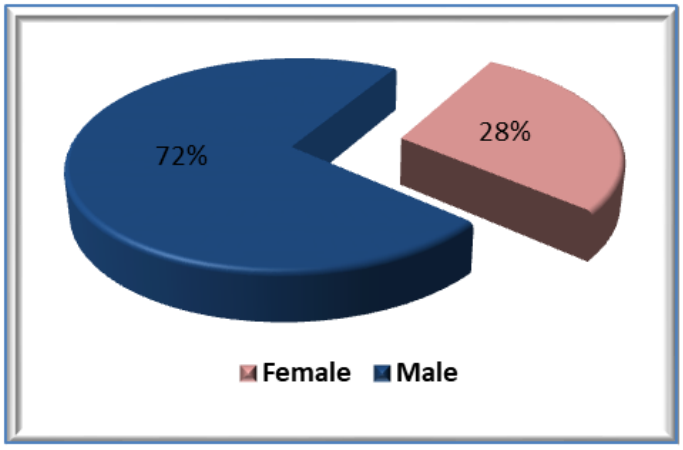

Fig-1: Sex distribution of our patients

All patients received recombinant human GH subcutaneously once daily at bedtime. The average consumption of our patients was 6.95 pens / month, with an average of 17.37 clicks / day. Within the whole study, fasting glycemia (FG) was performed for all patients before GH replacement therapy: the mean glycemia was 0.82 g/l (0.66-0.96)

Ninety-eight patients were monitored by FG after 1 year of GH therapy: the mean glycemia was 0.86 g/l (0.67-0.9).

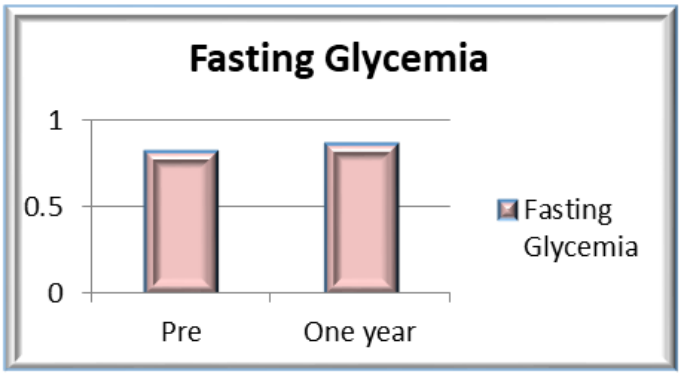

Fig-2: Comparison of FG before and after one year of GH therapy

Seventy-six patients were monitored by FG for 2 years: the mean glycemia was 0.91 g/l (0.77-1.1), only one patient presented impaired fasting glucose (1.1g/l).

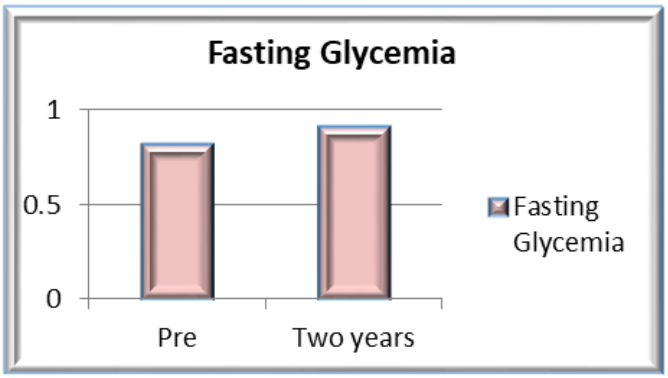

Fig-3: Comparison of FG before and after two years of GH therapy

Fourty-five patients were monitored by FG for 3 years: the mean glycemia was 0.93 g/l (0.8-1.04).

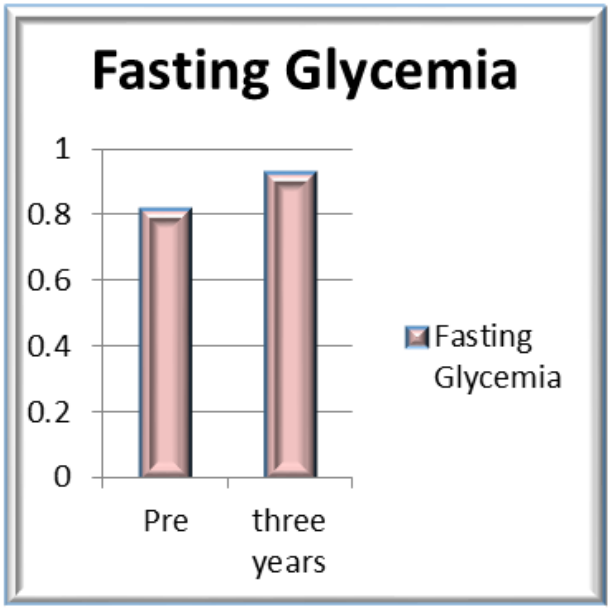

Fig-4: Comparison of FG before and after three years of GH therapy

Glycated heamoglobin was realized in fourty-four patients within a treatment duration of 2 years +/- 9 months, the mean was 5.4% (4.8 -6.1), three of them presented an elevated HbA1c, respectively 5.90 %, 6.10 % and 6.10 %.

DISCUSSION

The relationship between insulin secretion and the GH/IGF-1 axis is well established not only in patients treated with GH, but also in healthy subjects, as well as in diabetic patients [1, 2].

GH treatment improves the body composition, lipid profile and cardiac performance [3, 4], but the anti insulin- like action of GH can lead to insulin resistance with a compensatory elevation in fasting and postprandial insulin secretion, to maintain normal glucose and HbA1c levels [3, 4, 8].

Monitoring of glucose and insulin metabolism during GH treatment has been recommended, especially in GH-deficient children with preexisting concomitant risk factors [9].

Changes in glucose metabolism during GH treatment have been reported in several studies, differing in the length of the follow-up period and the size of the study group. Various markers could be used to evaluate Carbohydrate metabolism, the results of the studies analyzing the influence of GH treatment on insulin sensitivity are divergent, due to the multiple indices used: FG, HBA1C, Fasting insulin and peptide c, OGTT, HOMA, QUICKI... [10-12].

Witkowska-Sedek *et al*., in their retrospective study of 118 children treated with GH for 1 to 4 years, found a significant reduction in insulin sensitivity, as demonstrated by the significant increase in insulin secretion both fasting and during the Oral Glucose Tolerance Test (OGTT) and in the HOMA-IR and a significant decrease in the QUICKI and the Matsuda index. These changes were accompanied by a significant increase in fasting glucose compared to baseline values and unchanged levels of glucose during the OGTT. HbA1c levels did not change significantly after the initiation of GH treatment compared to baseline values, even in patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) found during GH treatment [12].

In a one-year follow-up of 73 patients on GH treatment, Ciresi *et al*., in their study found a significant increase in fasting glucose and HbA1c levels, despite all children remained with a normal glucose tolerance. These results partially match with our data [13].

Seminara *et al*., in their study of 3 years including 20 patients presumed that long-term GH treatment in GH deficient children causes hyperglycaemia (via OGTT) and increased insulin secretion (fasting insulin and peptide C). These effects may in some patients induce glucose intolerance, which is reversible with appropriate dietary measures and does not require discontinuation of treatment [14].

Poidvin *et al*., in their cohort evaluating the risk of diabetes in adulthood after receiving GH replacement therapy in a population of 5100 children with GH deficiency, they concluded that there's No difference in the risk of diabetes between GH-treated patients and the reference population [15].

CONCLUSION

Disturbance of glucose metabolism during GH replacement therapy was documented. Our data show that GH therapy in some GH deficient children may be

associated with an elevation of fasting glycemia and glycated heamoglobin. Therefore the monitoring of carbohydrate parameters is an integral part of the follow-up of children under GH treatment. Further studies with large prospective cohorts are required to evaluate this effect.

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