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Disorders Glucose Tolerance in Sheehan's Syndrome

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Summary: *Through a comparative prospective study of 51 control subjects matched for sex, body mass index and age, We investigated 46 patients with post-partum pituitary disease (Sheehan Syndrome), conventionally substituted and having a disease history of at least 10 years.*
The patients have an android obesity with a mean waist circumference significantly higher than that of the controls: average waist circumference at 100 cm versus 92.90 cm for the controls. 73.91% of patients had multiple metabolic syndrome (IDF 2005) compared to 33.33% of controls. 21% of patients have diabetes mellitus compared with only 3.92% of controls.
Keywords*: Sheehan Syndrome, Growth hormone deficiency, recombinante growth hormone, vascular risk, insulin resistance*

I. Introduction

Over the past two decades, several studies have demonstrated a significant increase in cardiovascular risk factors in subjects with hypopituitarism treated conventionally (unsubstituted Growth hormone deficiency) (1, 2, 3, 4, 5, 6). Anterior pituitary insufficiency is accompanied by a shortened life expectancy. This was suggested by 4 retrospective epidemiological studies and one prospective study (7, 8.6, 9, 10). It is associated with an increased incidence of cardiovascular and cerebrovascular diseases (11, 12). The causes are not clearly established (13). Among all the causes raised (craniopharyngioma, radiotherapy, unsubstituted gonadotropic deficiency, inadequate substitution of corticotropic deficiency), unsubstituted growth hormone deficiency (GHD) seems to be the main factor Several elements appear to contribute to increased vascular risk (14): Subjects adult hypopituitarism conventionally treated and whose growth hormone deficiency has not been substituted, have a marked decrease in insulin sensitivity (15, 16, 17).

Fasting blood glucose is usually normal, but glucose intolerance is more common than in controls (18, 19). During the hyper insulinic euglycemic clamp there is an insulin resistance most often. There is a reduction in the non-oxidative use of glucose (decreased synthesis of glycogen synthetase by insulin) and decreased muscle oxidation of glucose. There is also a decrease in the inhibitory action of insulin on lipolysis in adipose tissue (at the end of the clamp, the concentration of free fatty acids remains high). The implication of growth hormone deficiency or the distribution of fat is difficult to define.

II. Materials and methods

A) Patients:

The study included 49 patients with an unequivocal history Of Sheehan syndrome with agalactorrhea and amenorrhea after delivery.

At the end of the study we eliminated three patients (lost from sight). We retained 46 patients. The disease history was at least 10 years old.

These patients are all monitored in the endocrinology department. At baseline, 42/46 (91.3%) had a confirmed thyrotropin deficiency and the mean dose of levothyroxine was 117.39 ± 45.6 µg / d (50-200). All patients had corticotropic deficiency and were substituted with hydrocortisone at an average dose of 21.08 ± 7.04 mg / day (10-35). Finally, 44/46 (95.7%) had a gonadotropic deficit. Of these, 30/44 (68.2%) were or were substituted by estrogen-progestin therapy

(B) Controlled subjects:

We recruited during the same period 51 Controlled subjects working at the hospital (doctors, nurses, housekeepers)

They had no known cardiovascular disease or high blood pressure, dyslipidemia, or known diabetes mellitus and had no estrogen-progestogens for at least three months.

These control subjects have a BMI and age comparable to patients with Sheehan syndrome and of course are of the same sex.

All patients and controls received careful questioning and clinical examination. The weight gain, the size , the waist circumference are systematic as well as the calculation of the BMI. The blood pressure is taken several times and the average of 3 takes is retained.

All patients and controls underwent a blood test after 12 hours of fasting the day of collection.

Fasting Blood Glucose:

Fasting blood glucose testing was performed in all patients and controls by colorimetric method. (Glucose oxidase, para-amino phenazone and peroxidase).

The glycated hemoglobin (20):

The glycated hemoglobin was measured in all patients and controls in one reference laboratory by the same reference method: Method Immunoturbidimetric (Recommended and certified) .Calibration according to IFCC recommendations (21). Results according to the DCCT recommendations (22).

III. Results

There was no significant difference in mean age between patients and control subjects (DNS with p = 0.167)(TableI).

Table I: Results for age (years)

Age(years)	**Patients**	**Control subjects**	**P**
N (Number)	46	51	**DNS**
Mean	55,41 ± 8 (36-69)	52,90 ± 10,1 (40-75)	**0,167**
Médian	56	50,5	

The mean waist circumference is higher in the patient group compared to that of the controls with a significant difference (DS with p <0.001) although in both groups this waist circumference is high.
(TableII)

Table II: Results for waist circumference (cm)

waist circumference(cm)	**Patients**	**Control subjects**	**P**
N	46	51	**DS**
Mean	100,13 ± 10,18 (70-123)	92,90 ± 10,81 (71-113)	**< 0,001**

There was no significant difference in mean BMI between patients and control subjects. (DNS with p = 0.45); Both groups are overweight (TableIII)

Table III: Results for BMI :

BMI (kg / m2)	**Patients**	**Control subjects**	**P**
Number	46	51	**DNS**
Mean	27,80 ± 4,40 (20-38)	28,41 ± 3,38 (22-38)	**0,45**

There was a significant difference in mean blood glucose between patients and controls (SD with p <0.01). Although mean blood glucose is normal in both groups, it tends to be higher in patients (Table IV)

Table IV : Results For blood glucose

blood glucose(g / l)	**Patients**	**Control subjects**	**P**
Number	46	51	**DS**
Men	1,00 ± 0,35 (0,7-2,7)	0,87 ± 0,16 (0,68-1,45)	**< 0,01**
Médian	0,89	0,85	
V	0,12	0,02	

Table V: Results for HbA1c

HbA1c (%)	**Patients**	**Control subjects**	**P**
Groupe 1	18 (39,13 %)	36 (70,6 %)	**DS**
Groupe 2	28 (60,87 %)	15 (29,4 %)	**0,001**
Total	46 (100 %)	51 (100 %)	

Group 1: HbA1c less than 5.5%.
Group 2: HbA1c greater than or equal to 5.5%.

39.13% of patients had HbA1c <5.5% versus 70.6% for controls subjects.
There was a significant difference for HbA1c between patients and control subjects
(DS with p = 0.001) (chi2 test).
60.87% of patients had HbA1c ≥ 5.5% versus 29.4% for controls (TableV).

IV. Discussion

The hypopituitarism treated conventionally associated with disorders of glucose tolerance. In our study 10 patients (21.74%) had diabetes mellitus while only 1.96% (1/51) of the controls had diabetes mellitus, the difference between patients and controls was significant despite a comparable age and BMI. It is true that the waist of the patients was significantly higher than controls. The mean blood glucose of the patients is 1 g / l significantly higher than that of the controls subjects (0.87 g / l, p <0.01). The relative contribution of fasting blood glucose and postprandial blood glucose in HbA1c depends on the level of the glycated hemoglobin. Most of the abnormal elevation above 7% of HBA1c in a diabetic is related to fasting glucose, while it is related to post-prandial blood glucose levels below 7%. Indeed, observational and interventional studies have established that postprandial hyperglycemia is an independent cardiovascular risk factor.

Postprandial hyperglycemia and acute blood glucose changes are accompanied by activation of oxidative stress. Observations led to the concept of "dangerous waves" and then to that of the "dangerous glycemic roll" constituted both by ascending (post prandial) and descending (inter-prandial) acute glycemic variations (23).

Alssema. M et al (24) found an intimate association between postprandial glucose and carotid intima media thickness in normoglycemic women, suggesting that postprandial glycemia is a marker or risk factor for atherosclerosis in Postmenopausal women without diabetes. Postprandial blood glucose is a more sensitive risk.

Alssema. M et al (24) found an intimate association between postprandial glucose and carotid intima media thickness in normoglycemic women, suggesting that postprandial glycemia is a marker or risk factor for atherosclerosis in postmenopausal women without diabetes. Post-prandial glucose is a risk indicator that is more sensitive than blood glucose OGTT or post prandial triglyceride levels.

Wuster et al (25) and Rosen et al (12) found no increase in the incidence of "clinical" diabetes mellitus in patients with hypopituitarism compared to the general population.An ancient series of Brasel in 1965 (reported by Beshyah and Johnston (5)) noted an impaired glucose tolerance in 45% of young adults treated in childhood for craniopharyngioma.

Beshyah et al (4) reported an increased incidence of diabetes mellitus and impaired glucose tolerance in patients with hypopituitarism treated conventionally. Cuneo (26) and Weaver (27) found an increase in fasting insulin levels in this type of patient. Other studies did not find statistically significant differences compared to control subjects. In other studies insulinemia was significantly correlated with BMI and TT / TH ratio (28) with body fat mass (26.4) and central fat mass (27).

In the Beshyah study (4),

OGTT was performed in patients with anterior pituitary insufficiency; The results showed an increase in postprandial glucose at 2 hours and insulinaemia Compared with the control subjects.

And using the HOMA index, sensitivity is reduced by 43% (12-100%) and the insular β function is appropriately increased from 174% to compensate for a fall in insulin sensitivity (27).

Beshyah et al (29) found in patients with hypopituitarism and with impaired glucose tolerance high pro insulin levels. Hwu et al (30) reported a significant increase in the blood glucose nadir during insulin hypoglycemia in patients with hypopituitarism treated conventionally. As well as the glucose assimilation index (KITT) which is significantly higher

Weaver et al (27) studied 22 diabetic hypopituitarism patients, their fasting insulin levels were positively correlated with BMI, TT / TH and central fat (insulin resistance was calculated by HOMA method).

Finally, in a recent study (31), it was found that in healthy adults ≥ 65 years of IGFB1 low levels are associated with an increased incidence of impaired glucose tolerance. GH is a hormone lipolytic effect that reduces body, abdominal and visceral fat in deficient adults.

- Several studies have reported a substantial reduction in visceral fat following treatment with recombinant growth hormone in this population.

However, other studies have found a worsening of insulin resistance and an increase in blood glucose levels during the first weeks of GH treatment and these deterioration may persist even after reduction of visceral fat (32).

Individual titration of GH levels according to IGF1 levels does not alter insulin sensitivity and this is confirmed by Mc Connel's study (33).

After 6 months of recombinant GH therapy, fasting glucose and HbA1c were slightly increased but there were no effects on peripheral or hepatic sensitivity to insulin.

V. Conclusion

Our results are in agreement with several studies showing decreased glucose tolerance more commonly found in conventionally treated hypopituitarism patients; L insulin resistance and post-carbohydrate hyperinsulinism that are observed increase vascular risk.

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