DM e GH: impatto e correlazione

Dott. Piernicola Garofalo

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Il sottoscritto *Piernicola Garofalo*
in qualità di Docente del presente corso,
consapevole che chiunque rilascia dichiarazioni mendaci è punito ai sensi del codice penale e delle leggi speciali in materia, ai sensi e per gli effetti dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009

DICHIARA
che negli ultimi due anni ha avuto rapporti diretti e indiretti di consulenza con finanziamenti con le seguenti ditte, portatrici di interessi commerciali in campo sanitario:

Merck-Serono, Lilly, Ferring, Novo Nordisk, IBSA, Novartis-Sandoz, Menarini

DM e GH: impatto e correlazione

Both Human Pituitary Growth Hormone and Recombinant DNA–Derived Human Growth Hormone Cause Insulin Resistance at a Postreceptor Site

RON G. ROSENFELD, DARRELL M. WILSON, LAURA A. DOLLAR, ANN BENNETT, RAYMOND L. HINTZ

The Journal of Clinical Endocrinology & Metabolism, Volume 54, Issue 5, 1 May 1982, Pages 1033–1038,
https://doi.org/10.1210/jcem-54-5-1033

Acta Paediatr Scand Suppl. 1991;379:104-7; discussion 108.

Growth hormone treatment and diabetes: survey of the kabi pharmacia international growth study.

Czernichow P[1], Albertsson-Wikland K, Tuvemo T, Gunnarsson R.

Author information

Abstract

Out of a total of 8136 children registered in the Kabi Pharmacia International Growth Study, 12 have been reported to have diabetes either before or during treatment with growth hormone (GH). Two of these have non-insulin-dependent diabetes mellitus (NIDDM), of whom one had risk factors for the development of his condition, namely gross obesity and familial occurrence of NIDDM. One is a rare case of McCune-Albright's syndrome with insulin-dependent diabetes mellitus (IDDM), and 9 other patients have IDDM. Of these 9, 6 have idiopathic GH deficiency. In 8 of the 9 patients with IDDM, the condition was diagnosed before GH therapy was commenced, at ages ranging from less than 2 years to 16 years. The association is probably fortuitous, however, as the onset of IDDM in 7 patients was immediately before or during puberty, as often occurs in IDDM in general.

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J Pediatr. 1993 Oct;123(4):590-2.

Symptomatic non-insulin-dependent diabetes mellitus during therapy with recombinant human growth hormone.

Botero D[1], Danon M, Brown RS.

⊕ Author information

Abstract

In a 12-year-old girl, hyperglycemia and an elevated glycohemoglobin concentration developed after therapy with growth hormone for familial short stature. Both clinical and biochemical abnormalities disappeared after therapy was discontinued. The insulin response to an oral glucose tolerance test was abnormal 3 months after discontinuation of growth hormone; 18 months later, it remained delayed but was normal quantitatively.

Endocrinol Jpn. 1984 Apr;31(2):201-6.

Long term effects of human growth hormone on 1,959 patients with pituitary dwarfism throughout Japan.

Shizume K.

Pts. with GHD treated for at least 6 months between 1975 and 1982.

- **3/1959** (0.15%) developed glucose intolerance.

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THE LANCET
Volume 355, Issue 9204, 19 February 2000, Pages 610-613

Articles

Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-horm

Dr Wayne S Cutfie
Kerstin Albertsso
David A Price

GH treatment did not affect the incidence of type 1 diabetes mellitus in any age group. We postulate that the higher than expected incidence of type 2 diabetes mellitus with GH treatment may be an acceleration of the disorder in predisposed individuals (the persistence of diabetes mellitus after GH therapy was stopped excludes a transient drug-induced effect such as that seen with high dose glucocorticoid treatment)

Retrospective analysis of data from an international pharmacoepidemiological survey of children treated with GH.

- 85 (0.36%) of 23,333 children were reported with abnormal glucose metabolism.
- 43 had confirmed glucose disorders (11 with type 1 diabetes, **18 with type 2 diabetes**, and **14 with impaired glucose tolerance**).
- The incidence and age at diagnosis of type 1 diabetes in children treated with GH did not differ from expected values. The incidence of type 2 diabetes was 34.4 cases per 100 000 years of GH treatment which was six-fold higher than reported in children not treated with GH. Type 2 diabetes did not resolve after GH therapy was stopped.

KIGS Sudy 1987-1997

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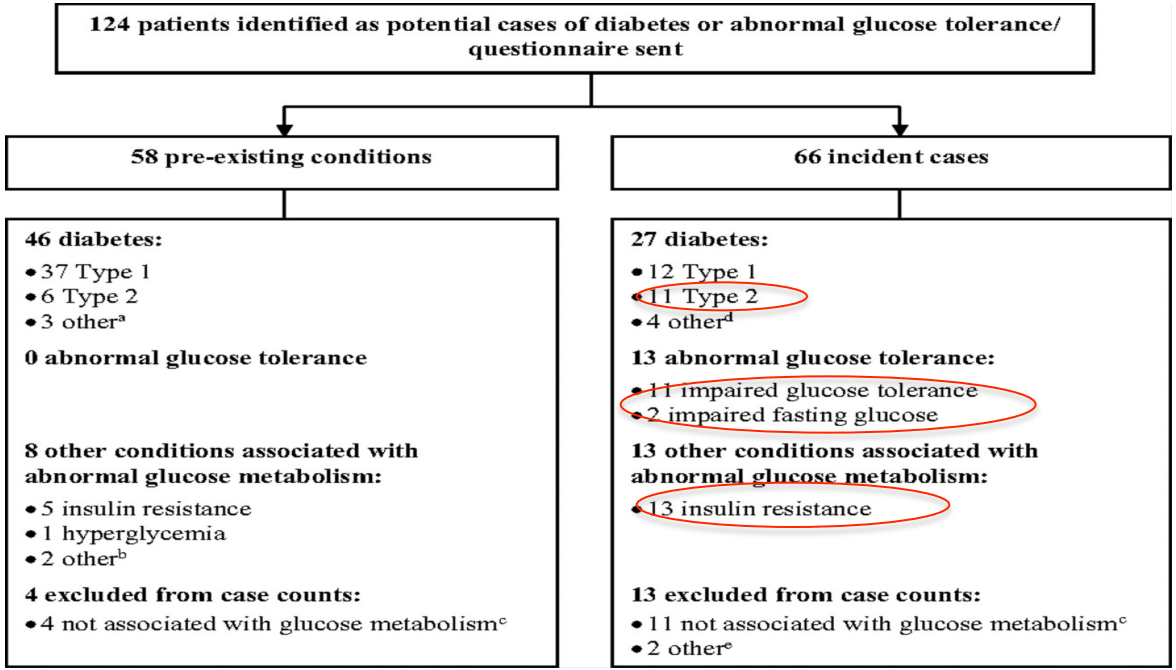

Data from 11.686 GH-treated patients in the GeNeSIS.

- There were no GeNeSIS cases of type 2 diabetes before GH initiation.
- **Among the 11 patients with incident type 2 diabetes, risk factors for diabetes were identified in 10 patients.**
- Glucose concentrations normalized for seven of nine patients for whom glycemic status could be determined (three of whom continued GH therapy and four who discontinued).

From: Prevalence and Incidence of Diabetes Mellitus in GH-Treated Children and Adolescents: Analysis from the GeNeSIS Observational Research Program

J Clin Endocrinol Metab. 2011;96(6):E1025-E1034. doi:10.1210/jc.2010-3023

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Diabetes Care. 2012 Jan; 35(1): 57–62.
Published online 2011 Dec 9. doi: [10.2337/dc11-0449]
PMCID: PMC3241307

Incidence of Diabetes Mellitus and Evolution of Glu
Growth Hormone–Deficient Subjects During Grov
Therapy

A long-term observational study

Anton Luger, MD,[1] Anders F. Mattsson, PHD,[2] Maria Kołtowska-Häg
PHD,[3,4] Miklos Góth, MD, PHD,[5] Johan Verhelst, MD, PHD,[6] and Rog

Glucose homeostasis parameters should be monitored carefully in these patients!

Out of the 13,294 patients in KIMS, only patients with severe adult-onset GH deficiency selected, confirmed with an accepted GH stimulatory test and naïve to GH treatment were

iabetes incidence was not associated with the GH dose or with the IGF-I concentrations reached after 1 year, and diabetes incidence decreased with increasing duration of GHRT. **These observations might be interpreted either as an indication that GH does not play a causative role in the development of diabetes or, alternatively, that diabetes develops above a GH threshold dose and IGF-I concentrations and that patients at risk for developing diabetes do so early after initiation of GHRT.**

- Small but significant increase of fasting glucose concentrations of 0.7 mg/dL/year and HbA1c levels of 0.036%/year.

The GH-deficient patients exhibited at baseline a substantial adverse risk profile for developing diabetes. Indeed, the patients developing diabetes were significantly older; had significantly higher BMI, waist circumference, triglyceride concentrations, and blood pressure; and had significantly lower HDL-cholesterol concentrations when compared with those who did not develop diabetes.

DM e GH: impatto e correlazione

apem Annals of Pediatric Endocrinology & Metabolism
https://e-apem.org/

Ann Pediatr Endocrinol Metab. 2017 Sep; 22(3): 145–152.
Published online 2017 Sep 28. doi: [10.6065/apem.2017.22.3.145]

PMCID: PMC5642081
PMID: 29025199

Effects of growth hormone on glucose metabolism and insulin resistance in human

Shin-Hye Kim, MD, PhD and Mi-Jung Park, MD, PhD

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Relatively few studies have been conducted examining the change of glucose metabolism after GH treatment in the pediatric population. Most of these studies have demonstrated that increased insulin resistance, indicated by increased fasting insulin and homeostasis model assessment of insulin resistance levels, was observed during GH therapy in GH-deficient children and adolescents, but their fasting/postprandial glucose and HbA1c levels remained within in normal range.

Table 3.

Effects of recombinant human GH treatment on glucose metabolism in children and adolescents with GH deficiency

Study	Number of cases	Age (yr)	Daily GH dose	Duration of GHT	Findings
Saenger et al. [49]	GHD=70	-	0.05 mg/kg	5 Years	↔Fasting/postprandial glucose, ↑fasting/postprandial insulin, ↔HbA_{1c}
Heptulla et al. [29]	GHD=6, ISS=2	12±1	0.05 mg/kg	6 Months	↔Fasting glucose, ↑insulin, ↓IS (HC)
Radetti et al. [50]	GHD=128, Healthy control=40	8.9±3.2	0.04–0.05 mg/kg	6 Years	↓QUICK, no cases with IGT, DM at 6 year
Salerno et al. [51]	GHD=30, Healthy control=30	9.3±0.5	0.03 mg/kg	2 Years	↔Fasting glucose, ↑insulin, ↑HOMA-IR
Metwalley et al. [52]	GHD=30, Healthy control=20	4–10	1 mg/m^2	1 Year	↑Fasting glucose, ↑insulin, ↑HOMA-IR
Meazza et al. [53]	GHD=16, Healthy control=20	3.4–14.7	0.025 mg/kg	1 Year	↑Fasting glucose, ↑insulin
Ramistella et al. [54]	GHD=32, Healthy control=33	8.9±3.6	0.03 mg/kg	2 Years	↔Fasting glucose, ↑insulin, ↑HOMA-IR
Ciresi et al. [30]	GHD=73, Healthy control=50	10.3±2.8	0.025–0.033 mg/kg	1 Year	↔Fasting glucose, ↔insulin, ↑HOMA-IR, ↓QUICKI, ↔AUC gluc, ↓AUC insulin (OGTT),↓IS (HC)

Participant's age was presented in mean±standard deviation or range.

GH, growth hormone; GHT, growth hormone treatment; GHD, growth hormone deficiency; HbA_{1c}, glycosylated hemoglobin; IS, insulin sensitivity; HC, hyperglycemic clamp; QUICKI, quantitative insulin check index; IGT, impaired glucose tolerance; DM, diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; AUC gluc, the area under the curve for glucose; AUC insulin, the area under the curve for insulin; OGTT, oral glucose tolerance test.

Effects of growth hormone on glucose metabolism and insulin resistance in human. APEM 2017

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Table 4.

Effects of recombinant human GH treatment on the development of DM in children and adolescents

Study	Number of cases	Age (yr)	Daily GH dose	Duration of GHT	Findings
Blethen et al. [31]	>19,000 NCGS cohort	7.2–12.9 (at enrollment)	-	-	↑DM incidence in subjects with identifiable risk factors
Cutfield et al. [32]	23,333 KIGS cohort	10.3 (7.2–12.7)	0.03 mg/kg (0.02–0.04)	2.9 Years	↑T2DM incidence in subjects with identifiable risk factors, ↔T1DM incidence
Child et al. [33]	11,686 GeNeSIS cohort	10.2 (6.5–12.7)	0.04 mg/kg (0.03–0.05)	2.5 Years	↑T2DM incidence in subjects with identifiable risk factors, ↔T1DM incidence
Poidvin et al. [34]	5,100 French SAGhE cohort (iGHD, ISS, SGA)	20–44	0.03±0.01 mg/kg	4 Years	↔DM prevalence

Participant's age was presented in mean±standard deviation, median (interquartile range), or range.

GH, growth hormone; DM, diabetes mellitus; GHT, growth hormone treatment; NCGS, National Cooperative Growth Study; KIGS, Pharmacia and Upjohn International Growth Study; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; GeNeSIS, GH-treated patients in the Genetics and Neuroendocrinology of Short Stature International Study; SAGhE, Safety and Appropriateness of Growth Hormone Treatments in Europe; iGHD, isolated growth hormone deficiency; ISS, idiopathic short stature; SGA, small-for-gestational age.

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Casistica personale

- 67 pz IGHD – 43M, 24F
- Età media alla diagnosi: 11.6 ± 2.2
- Età media al retesting: 16.7 ± 1.3
- Valutazione pre-terapia (t0): BMI, glicemia, insulinemia, HOMA-IR
- Ogni 6 mesi sono stati rivalutati: BMI, glicemia, insulinemia, HOMA-IR

DM e GH: impatto e correlazione

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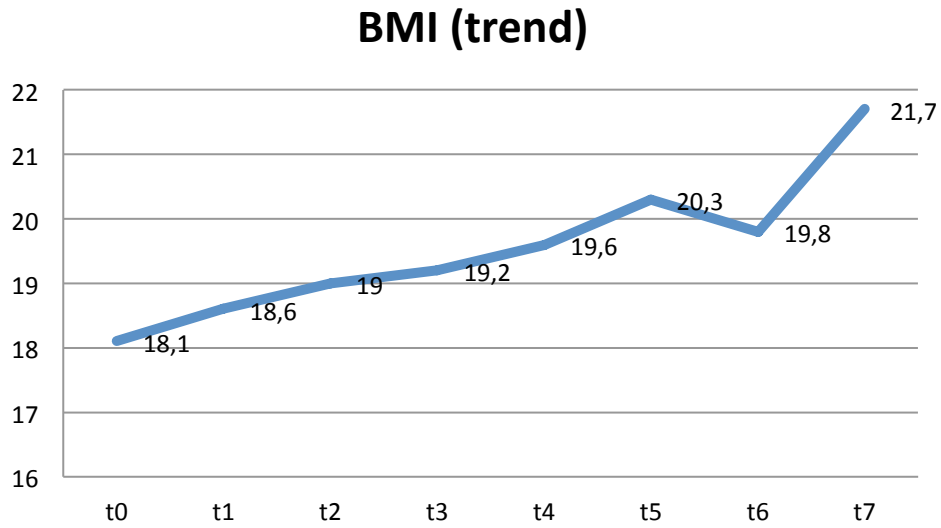
Casistica personale

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
36 mesi (t5)
48 mesi (t6)
Retesting (t7)



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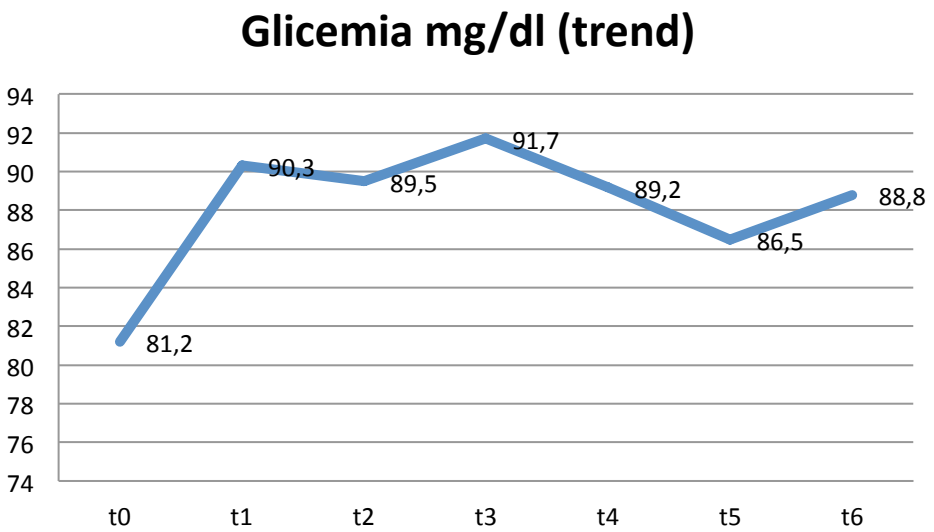
Casistica personale

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
36 mesi (t5)
48 mesi (t6)



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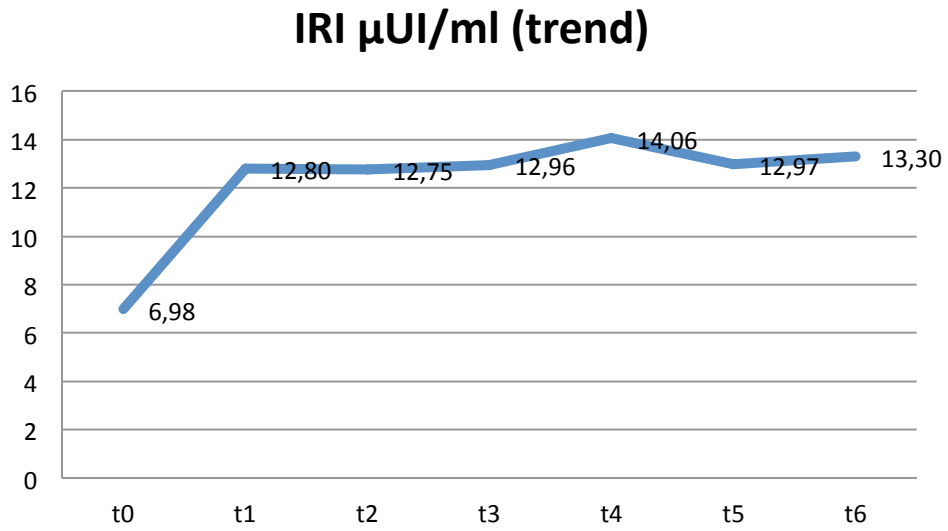
Casistica personale

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
36 mesi (t5)
48 mesi (t6)



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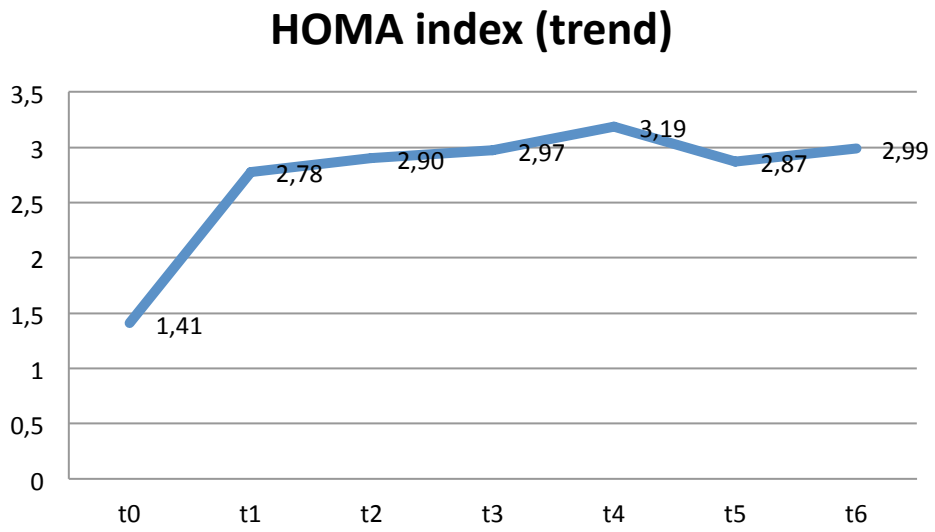
Casistica personale

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
36 mesi (t5)
48 mesi (t6)



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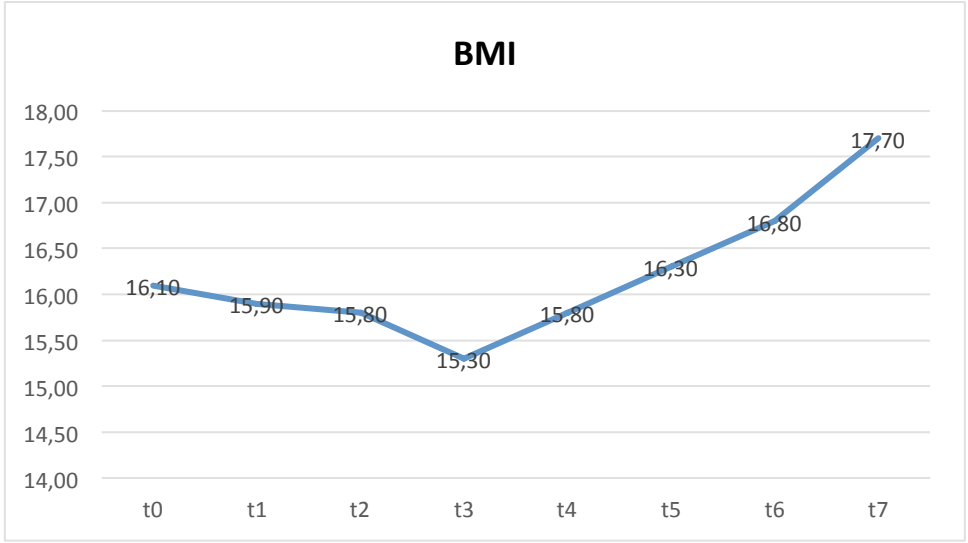
Case Report

Sofia anni 10.3 IGHD

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
30 mesi (t5)
36 mesi (t6)
48 mesi (t7)



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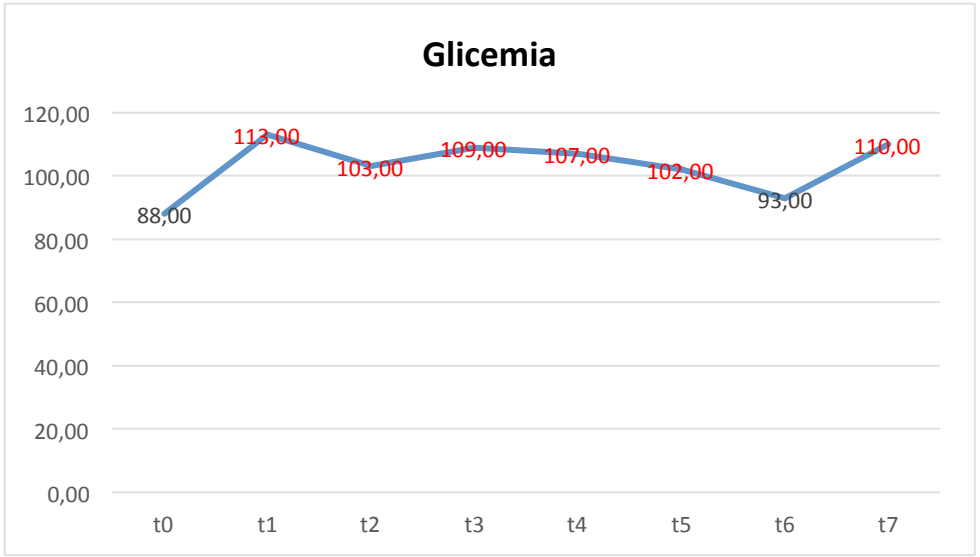
Case Report

Sofia IGHD

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
30 mesi (t5)
36 mesi (t6)
48 mesi (t7)



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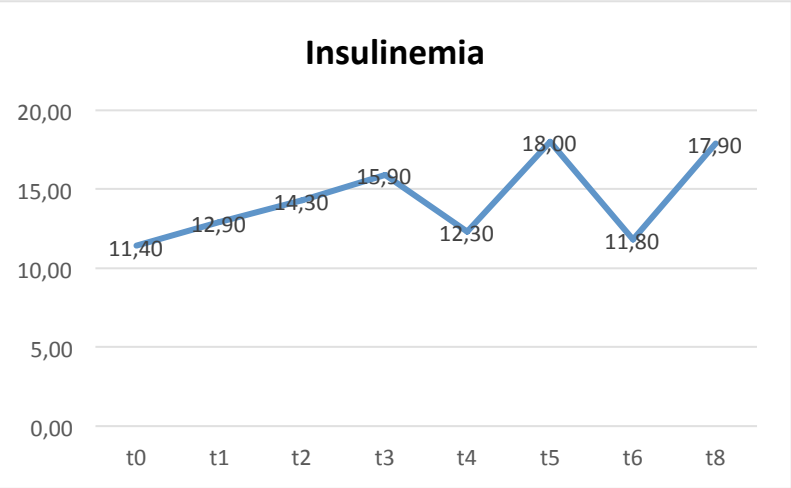
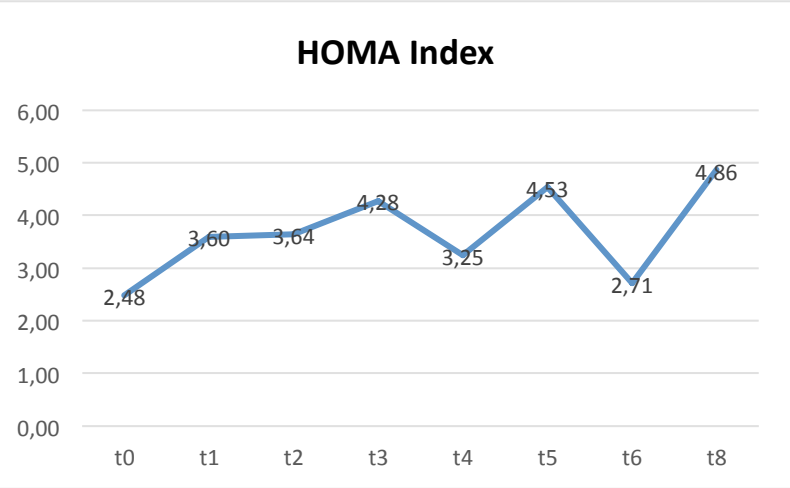
Case Report

Sofia IGHD

Preterapia (t0)
6 mesi (t1)
12 mesi (t2)
18 mesi (t3)
24 mesi (t4)
30 mesi (t5)
36 mesi (t6)
48 mesi (t7)





DM e GH: impatto e correlazione

THM

1) Nei pazienti trattati con GH non vi è incremento del DM tipo 1.
2) La terapia con GH può determinare un aumento della glicemia e della insulinemia basali e dell'HOMA-ir index.
3) Nei soggetti predisposti può esservi un lieve aumento del diabete tipo 2.
4) L'azione sembra essere transitoria.
5) Opportunità di misure sullo stile di vita nei pazienti a rischio di sviluppare DM2 che avviano GHRT