Studierna som förändrat mitt kliniska arbete

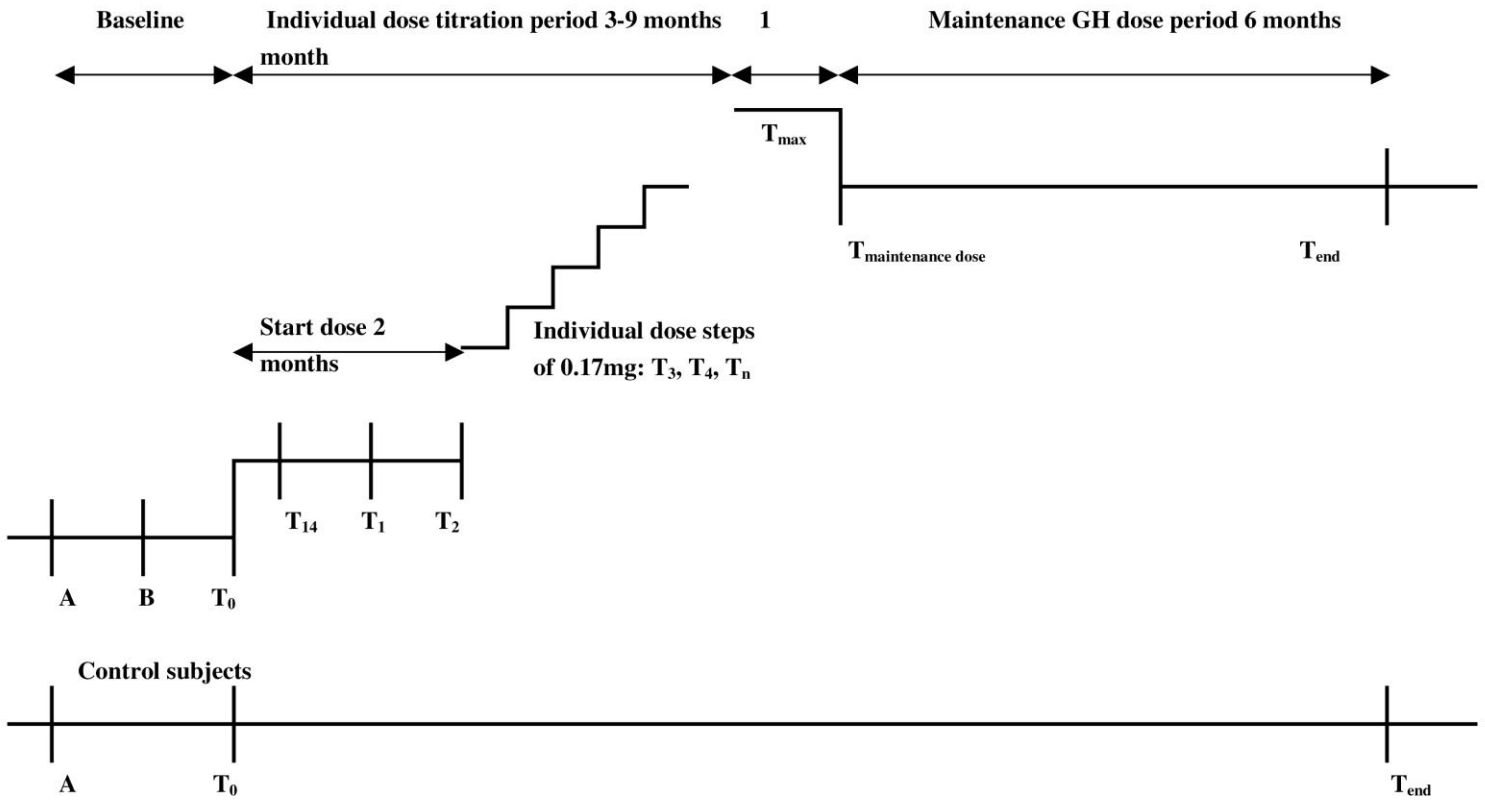
Bertil Ekman
Endodiabetes Linköping
2025-03-28

Första läkarstämman 1992

Chou YH, Brown EM, Levi T, Crowe G, Atkinson AB, Arnqvist HJ, Toss G, Fuleihan GE, Seidman JG, Seidman CE.
The gene responsible for familial hypocalciuric hypercalcemia maps to chromosome 3q in four unrelated families. Nat Genet. 1992 Jul;1(4):295-300.

Winqvist O, Karlsson FA, Kämpe O.
21-Hydroxylase, a major autoantigen in
idiopathic Addison's disease. Lancet. 1992 Jun 27;339(8809):1559-62.

GH substitution



Ekman B, Lindström T, Nyström F, Olsson AG, Toss G, Arnqvist HJ. A dose titration model for recombinant GH substitution aiming at normal plasma concentrations of IGF-I in hypopituitary adults. Eur J Endocrinol. 2002 Jul;147(1):49-57.

IGF-I vuxen ålder

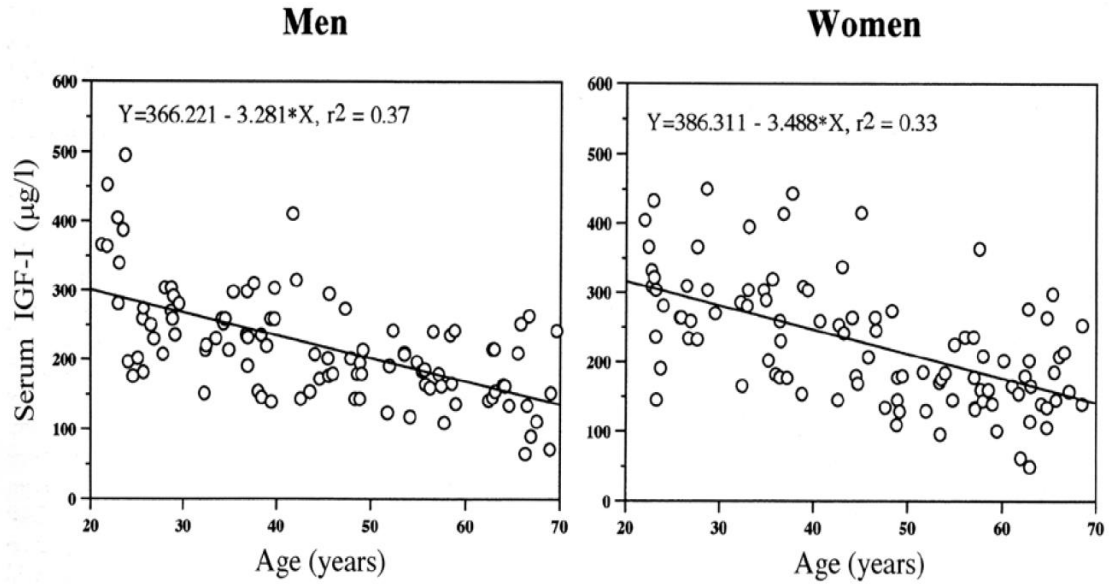
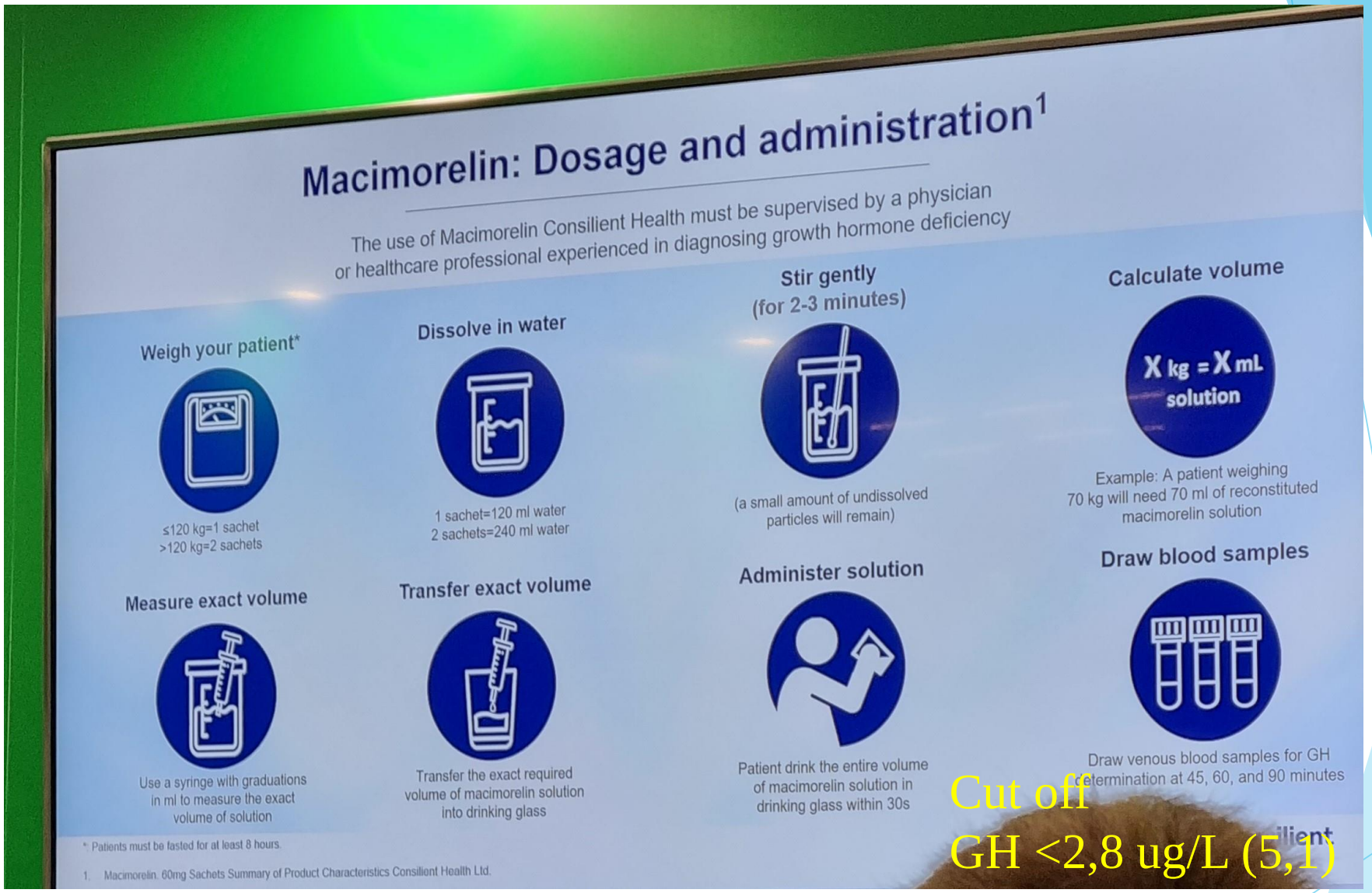


Fig 3. IGF-I in relation to age

Nyström FH, Ohman PK, Ekman BA, Osterlund MK, Karlberg BE, Arnqvist HJ. Population-based reference values for IGF-I and IGF-binding protein-1: relations with metabolic and anthropometric variables. Eur J Endocrinol. 1997 Feb;136(2):165-72.



Garcia JM, Biller BMK, Korbonits M, Popovic V, Luger A, Strasburger CJ, Chanson P, Medic-Stojanoska M, Schopohl J, Zakrzewska A, Pekic S, Bolanowski M, Swerdloff R, Wang C, Blevins T, Marcelli M, Ammer N, Sachse R, Yuen KCJ. Macimorelin as a Diagnostic Test for Adult GH Deficiency. J Clin Endocrinol Metab. 2018 Aug 1;103(8):3083-3093.

Maintenance dose of GH

The median GH dose was significantly affected by gender, males 0.33 mg/day (0.17-1.17) vs. females 0.83 mg/day (0.33-1.33) (*P*= 0.017), and negatively correlated with age in both genders (Fig 8). The 3 women with childhood onset of GH deficiency had higher median maintenance GH dose, 1.0 mg (0.83-1.33), then the 4 women with adulthood onset, 0.6 mg (0.33-1.0) (*P*=0.15).

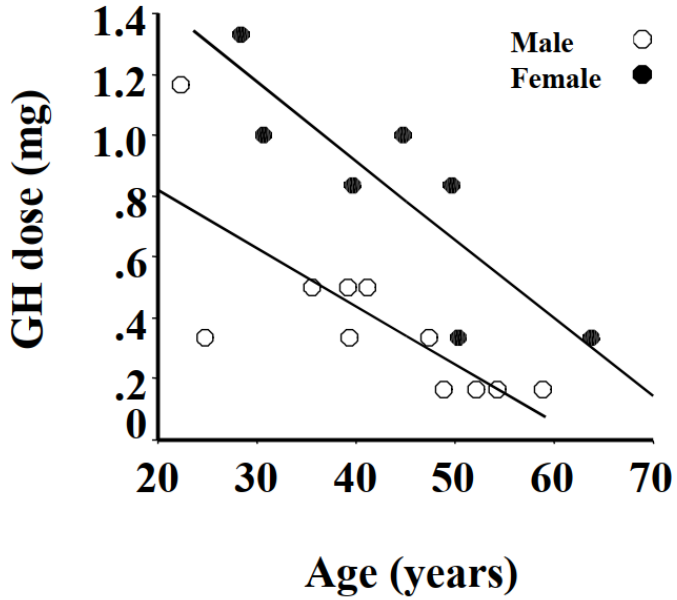


Fig 8. The GH-dose in relation to age.

Ekman B, Lindström T, Nyström F, Olsson AG, Toss G, Arnqvist HJ. A dose titration model for recombinant GH substitution aiming at normal plasma concentrations of IGF-I in hypopituitary adults. Eur J Endocrinol. 2002 Jul;147(1):49-57.

Timing och Könsskillnader

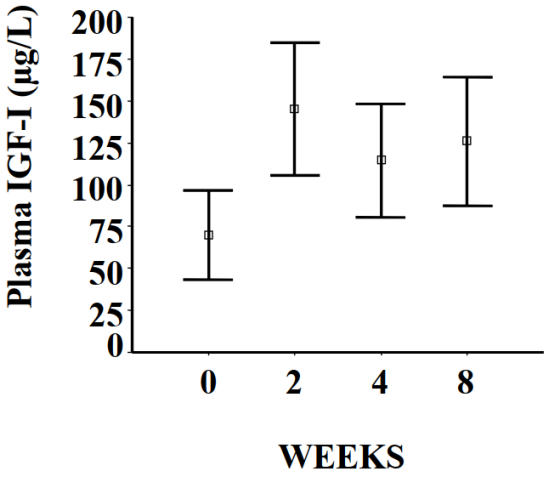


Fig 5. Mean IGF-I levels in 14 patients (7 males and 7 females) at baseline and after 2, 4 and 8 weeks on the startdose of 0.17 mg/day

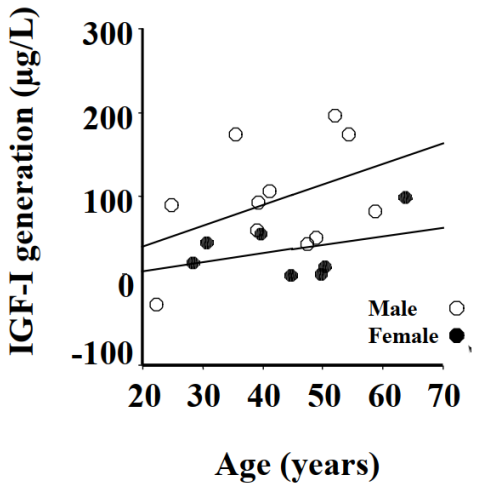


Fig 6. Net increment of circulating IGF-I after 2 months on the start dose in relation to age. All 18 patients had a GH-dose of 0.17 mg/day.

Ekman B, Lindström T, Nyström F, Olsson AG, Toss G, Arnqvist HJ. A dose titration model for recombinant GH substitution aiming at normal plasma concentrations of IGF-I in hypopituitary adults. Eur J Endocrinol. 2002 Jul;147(1):49-57.

Effekter av titrerad GH substitution

- Ingen aktivering av RAAS
- LDL-Cholestrol sjunker 0,5 mmol/L
- Dynamisk muskelstyrka ökar kopplat till IGF-I ökning
- Fasteglukos och fasteinsulin ökar (normalisering?)
- Fritt T4 sjunker och fritt T3 ökar
- Benmassan minskar första året för att sedan öka

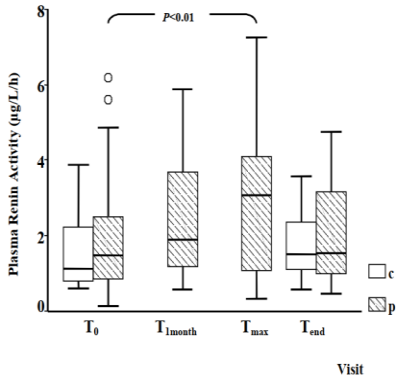


Figure 10. Plasma renin activity during GH-substitution and in control subjects. The boxes represent median and 25th to 75th percentiles. c=control subjects and p= patients.

Ekman B, Lindström T, Nyström F, Olsson AG, Toss G, Arnqvist HJ. A dose titration model for recombinant GH substitution aiming at normal plasma concentrations of IGF-I in hypopituitary adults. Eur J Endocrinol. 2002 Jul;147(1):49-57.

Typ 1 diabetes och GH-IGF-I axeln

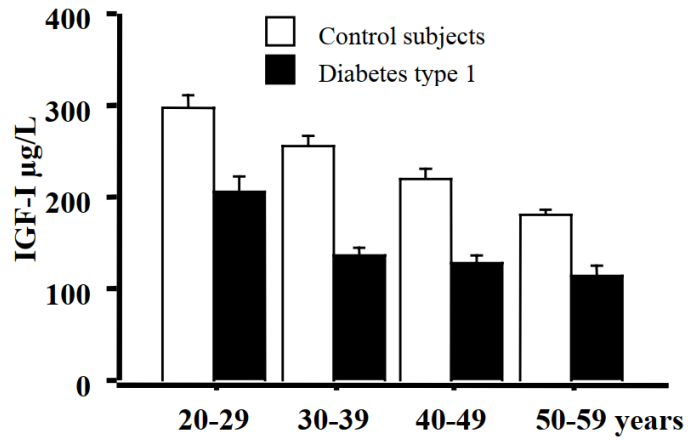


Fig 15. Mean plasma levels of IGF-I in patients with type 1 diabetes (black bars) compared to an age and sex matched reference population (white bars) Age distribution of controls/patients: 20-29 years n=41/28, 30-39 years n=42/54, 40-49 n=36/35 and 50-60 years n=44/17

Ekman B, Nyström F, Arnqvist HJ. Circulating IGF-I concentrations are low and not correlated to glycaemic control in adults with type 1 diabetes. Eur J Endocrinol. 2000 Oct;143(4):505-10.

The GH-IGF-I-insulin-system in insulin deficiency

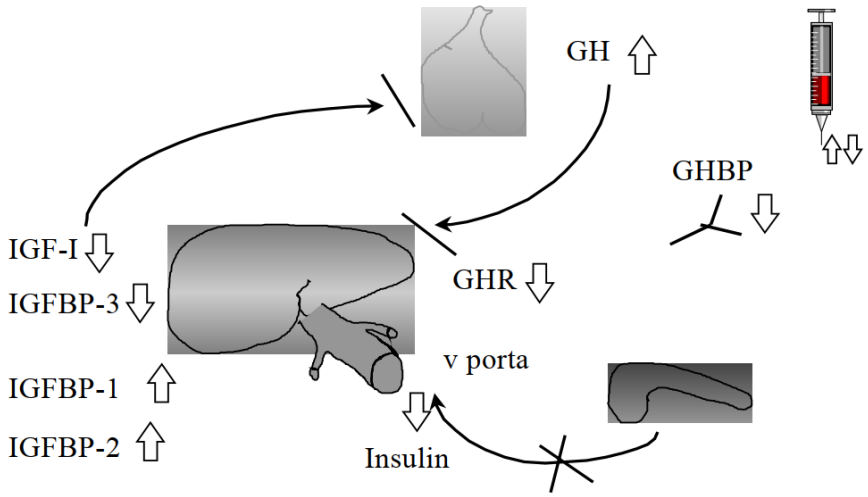


Fig 18. Despite normal peripheral insulin concentrations by subcutaneous injections, the intraportal concentrations are much less in type 1 diabetes. This probably causes down regulation of the growth hromone receptor (GHR), and the corresponding growth hormone binding hormone (GHBP), and the stimulation of GH on IGF-I expression in the liver declines. The lowered levels of IGF-I induce increased levels of GH because of decreased neagative feedback on the pituitary level. In addition IGFBP-1, which decreases the free fraction of IGF-I, is increased due to the portal hypo-insulinemia.

Thesis Bertil Ekman 2002

IGFBP-1

(Unpublished data). IGFBP-1 was increased at baseline in the patients and decreased significantly after GH-substitution, *P*=0.014. The difference in baseline levels of IGFBP-1 was nearly significant between patients and controls *P*=0.051. Fasting insulin levels were negatively correlated with IGFBP-1 levels before GH-substitution r = -0.58, *P*=0.016, an association which was weaker after GH-substitution, r = -0.45, *P*=0.083 (unpublished data)

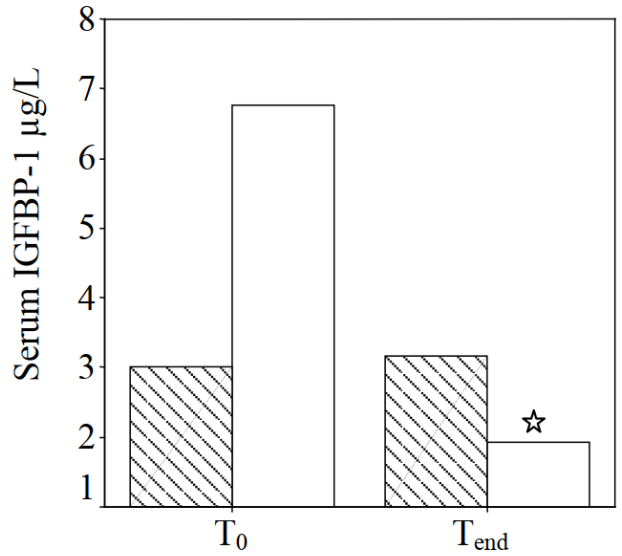


Fig 9. IGFBP-1 levels before GH-substitution (T_0) and at the end of the study (T_{end}). ☆ indicates P<0.05 compared with baseline. Shaded bars = controls. White bars = patients.

Thesis Bertil Ekman 2002

GDISS

Table 4. Multiple logistic regression of risk of developing diabetes. Odds ratios (OR, 95% CI) for developing diabetes mellitus postpartum at increasing levels of fasting blood glucose and 2-h OGTT blood glucose levels found at diagnosis of GDM.

Blood glucose at diagnosis (mmol/l)	Number of women at follow-up with		OR (95% CI)
	Diabetes	No diabetes	
Fasting			
≤4.5	42	263	1
4.6–5.0	51	188	1.7 (1.1–2.7)
5.1–5.5	49	160	1.9 (1.2–3.0)
5.6–6.0	40	78	3.2 (1.9–5.3)
≥6.1	79	56	8.8 (5.5–14)
2 h OGTT			
9.0–9.5	85	456	1
9.6–10.0	57	222	1.4 (0.95–2.0)
10.1–10.5	47	121	2.1 (1.4–3.1)
10.6–11.0	42	74	3.0 (2.0–4.8)
≥11.1	93	98	5.1 (3.5–7.3)

Wahlberg J, Ekman B, Nyström L, Hanson U, Persson B, Arnqvist HJ. Gestational diabetes: Glycaemic predictors for fetal macrosomia and maternal risk of future diabetes. Diabetes Res Clin Pract. 2016 Apr;114:99-105.

Normal kortisol sekretion

- **8-15 mg/dygn**

- **5.7 mg/m2/dygn (18 män i sen pubertet).**

  Esteban et al JCEM 71 39-45, 1991.

- **5-7 mg/m2/dygn (5 män 7 kvinnor).**

  Kerrigan et al JCEM 76, 1505-1510, 1993

Lite siffror (som får tas med en viss nypa salt)

Förbehållet att CBG-nivåer inte är förhöjda:

”Under vilken kortisolnivå kan jag anse min misstanke vara bekräftad?”

101 nmol/L med 98% säkerhet
65 nmol/L med 99% säkerhet
41 nmol/L med 100% säkerhet

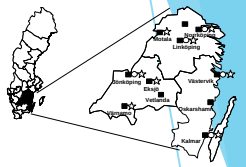
”Vid vilken nivå kan jag släppa misstanken?”

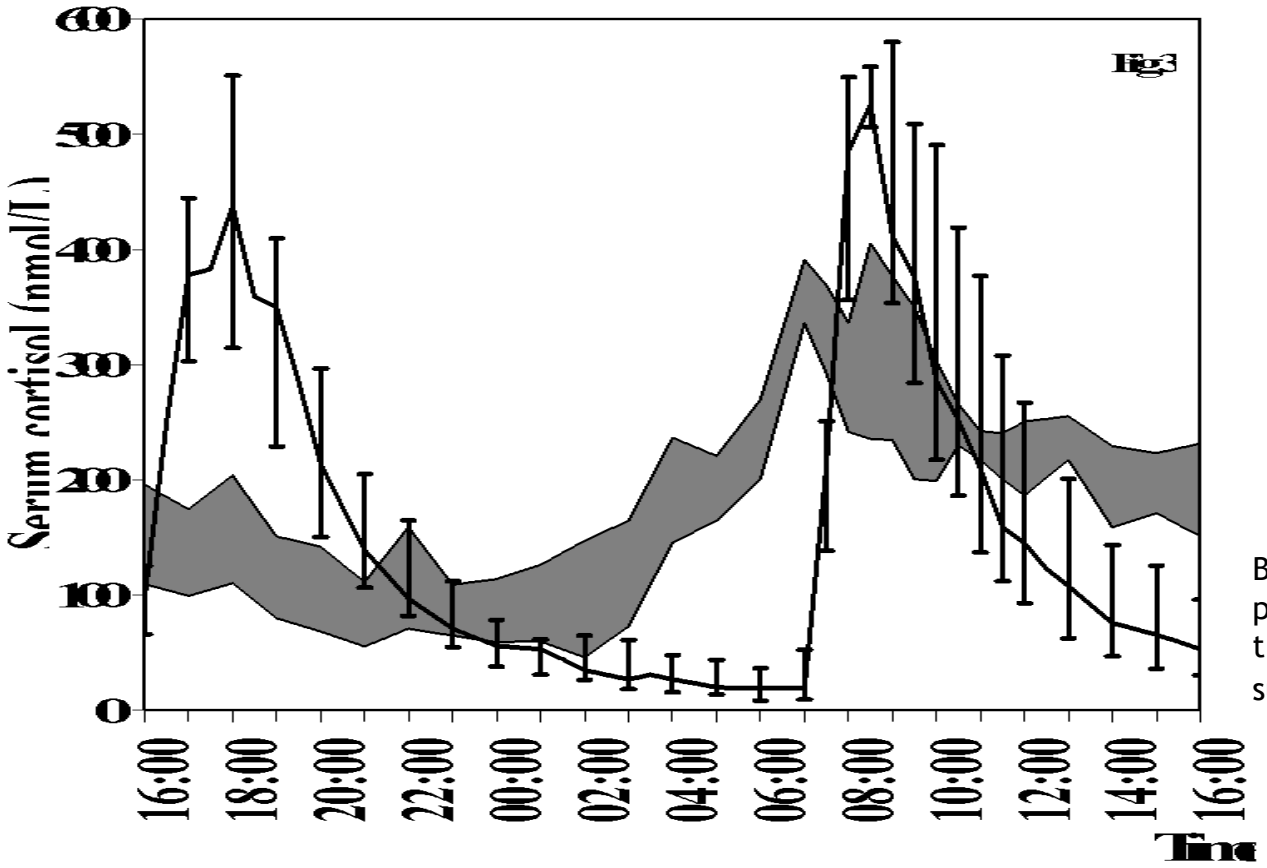
340 nmol/L med 98% säkerhet
392 nmol/L med 99% säkerhet
400 nmol/L med 100% säkerhet

Perozo et al. 2023 - Morning serum cortisol role in the adrenal insufficiency diagnosis with modern cortisol assays

Konventionell kortisonsubstitution till patienter med hypofysinsufficiens

Cortison acetat 25 mg +12.5 mg





Blomgren J, Ekman B, Andersson PO, Arnqvist HJ. Non-physiological levels of circulating cortisol in growth hormone-treated hypopituitary adults afterconventional cortisone substitution. Scand J Clin Lab Invest. 2004 Apr;64(2):132-9.

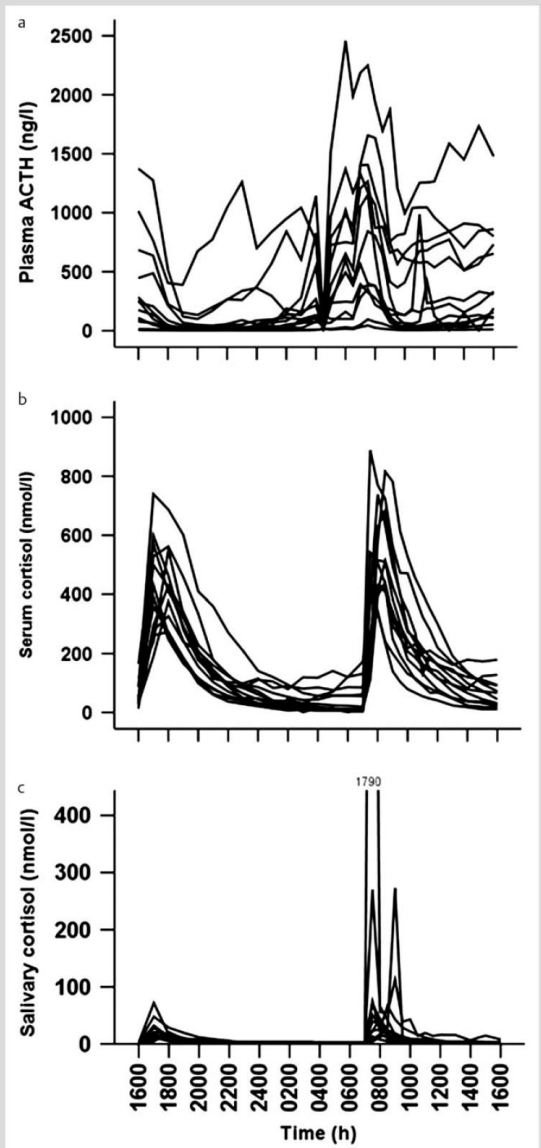
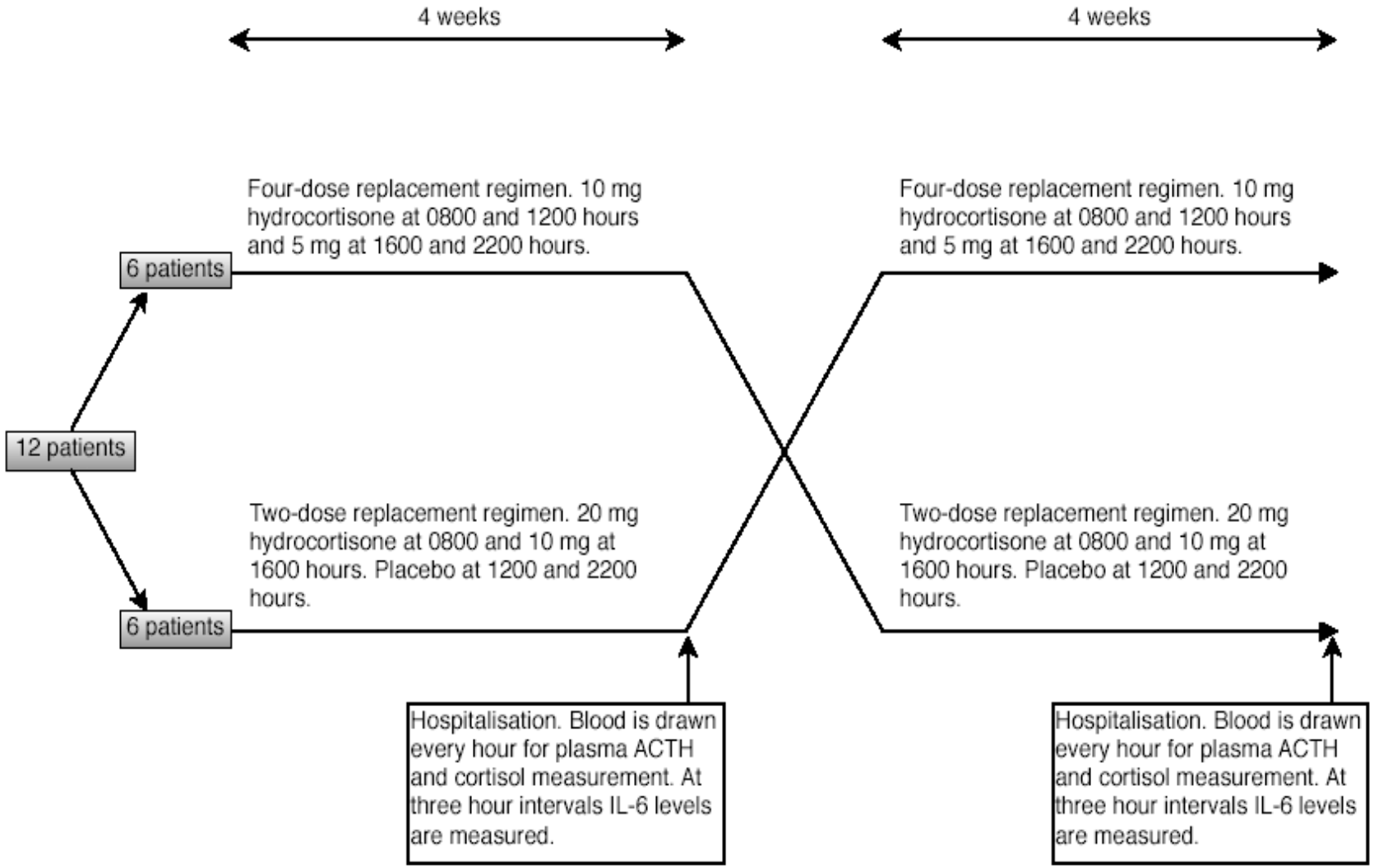


Fig. 1 Individual 24-h profiles of plasma ACTH (**a**) and plasma cortisol (**b**) and salivary cortisol (**c**) in 13 patients (8 females/5 males) with PAI treated with cortisone 12.5 mg cortisone acetate orally at 16:00 h and 25 mg at 07:00 h.

Ekman B, Blomgren J, Andersson PO, Carlsson M, Arnqvist HJ. Variable sensitivity to the glucocorticoid activity of cortisol in patients with primary adrenal insufficiency: assessment with ACTH profiles. Horm Metab Res. 2010 Dec;42(13):961-6.


4 weeks
4 weeks
Four-dose replacement regimen. 10 mg hydrocortisone at 0800 and 1200 hours and 5 mg at 1600 and 2200 hours.
Four-dose replacement regimen. 10 mg hydrocortisone at 0800 and 1200 hours and 5 mg at 1600 and 2200 hours.
6 patients
12 patients
Two-dose replacement regimen. 20 mg hydrocortisone at 0800 and 10 mg at 1600 hours. Placebo at 1200 and 2200 hours.
Two-dose replacement regimen. 20 mg hydrocortisone at 0800 and 10 mg at 1600 hours. Placebo at 1200 and 2200 hours.
6 patients
Hospitalisation. Blood is drawn every hour for plasma ACTH and cortisol measurement. At three hour intervals IL-6 levels are measured.
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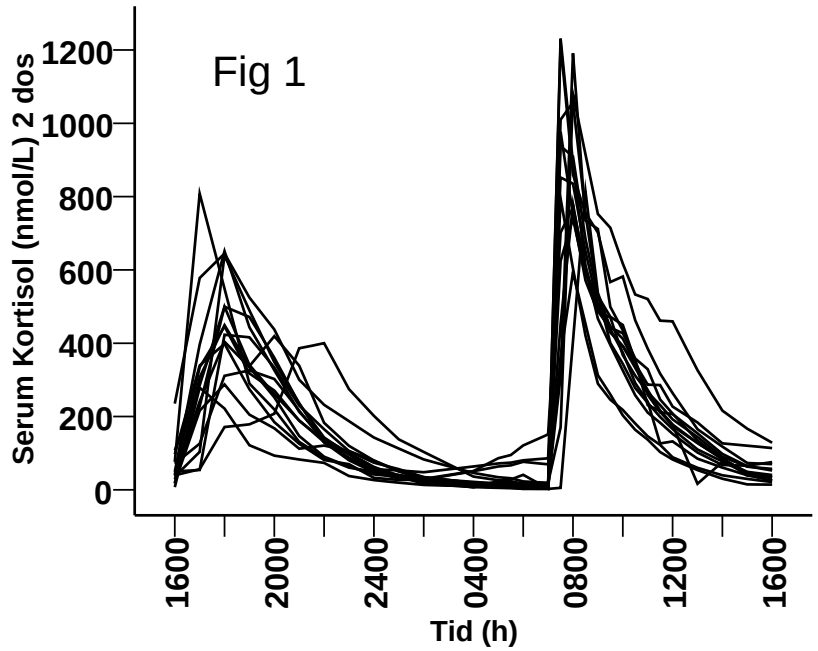
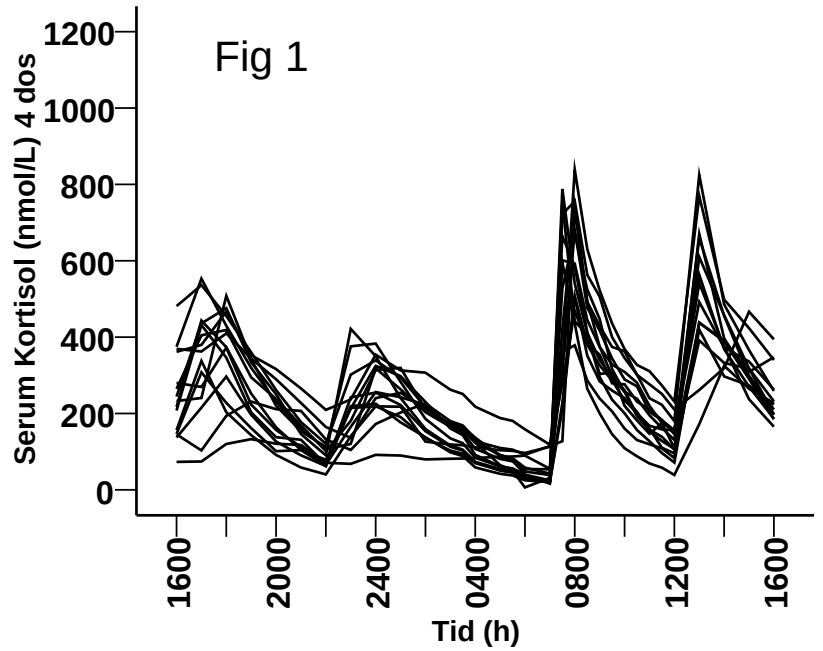
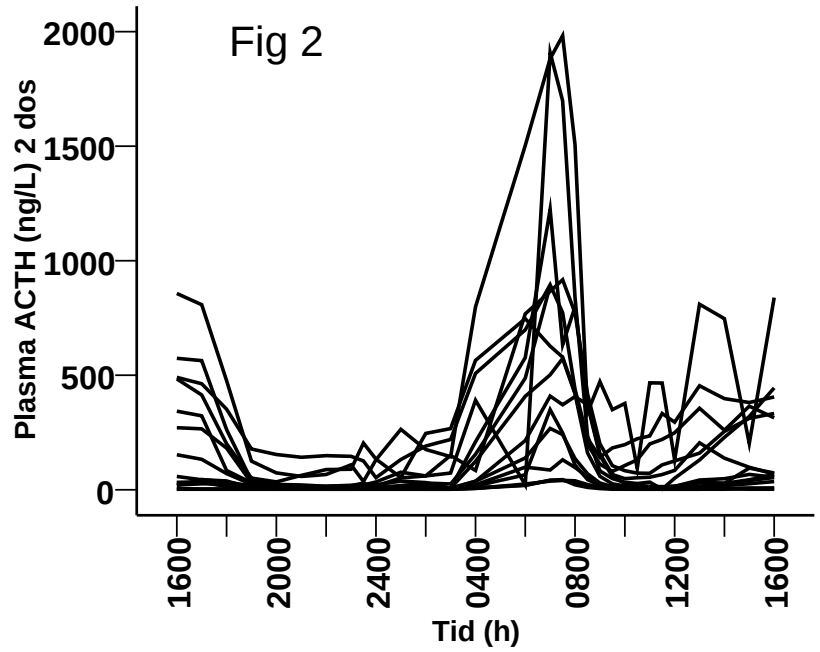
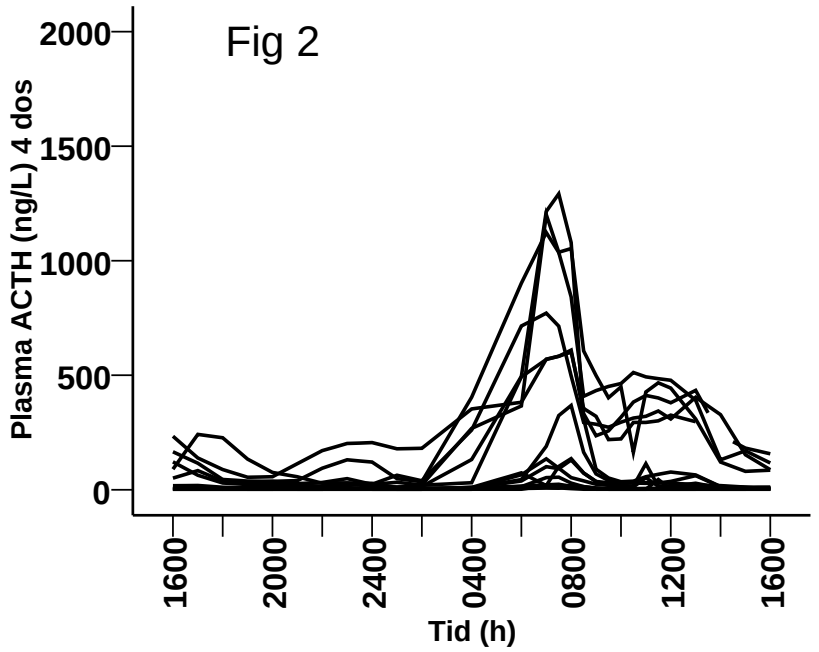




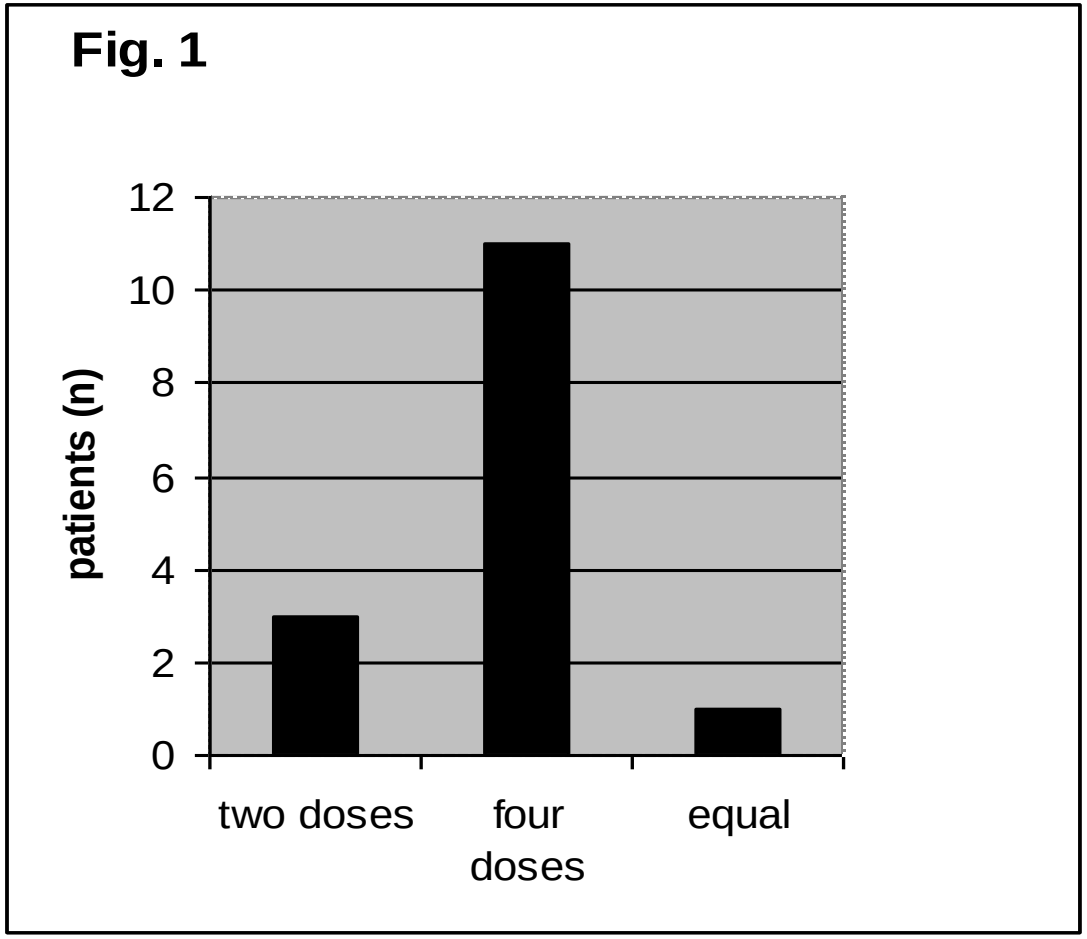
Ekman B, Bachrach-Lindström M, Lindström T, Wahlberg J, Blomgren J, ArnqvistHJ. A randomized, double-blind, crossover study comparing two- and four-dosehydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency. Clin Endocrinol (Oxf). 2012 Jul;77(1):18-25.



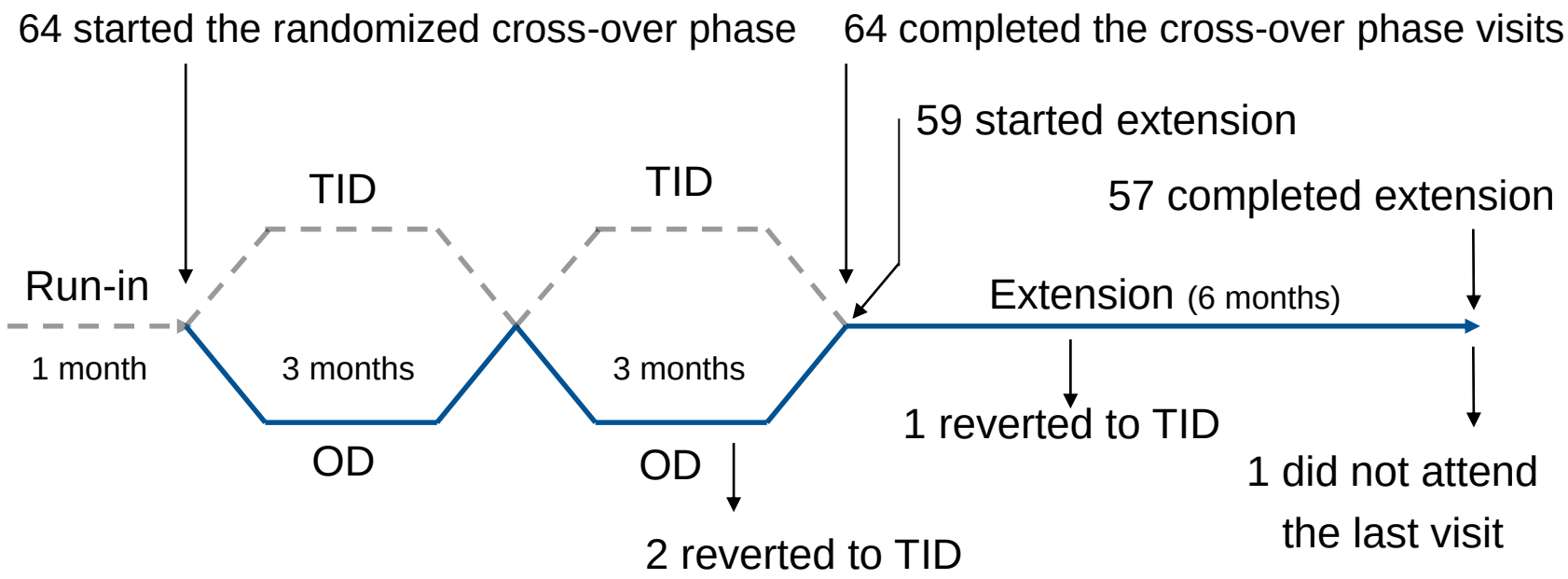


Ekman B, Bachrach-Lindström M, Lindström T, Wahlberg J, Blomgren J, ArnqvistHJ. A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency. Clin Endocrinol (Oxf). 2012 Jul;77(1):18-25.

Två elle 4 doser hydrokortison?

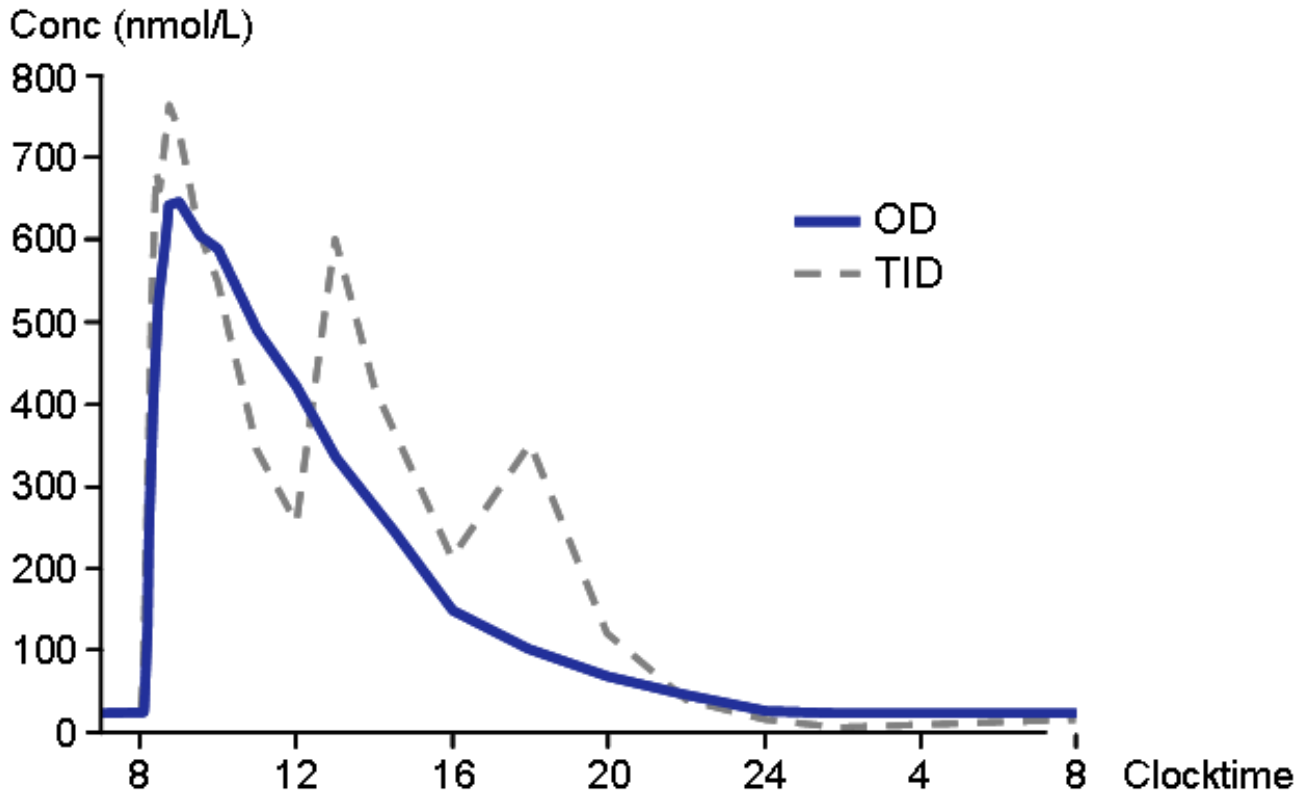


Duocort



Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engström BE, Olsson T, Ragnarsson O, Ryberg M, Wahlberg J, Biller BM, Monson JP, Stewart PM, Lennernäs H, Skrtic S. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab. 2012 Feb;97(2):473-81.

Duocort (Plenadren®)



Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B,Engström BE, Olsson T, Ragnarsson O, Ryberg M, Wahlberg J, Biller BM, Monson JP, Stewart PM, Lennernäs H, Skrtic S. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab. 2012 Feb;97(2):473-81.

Turnerakademin

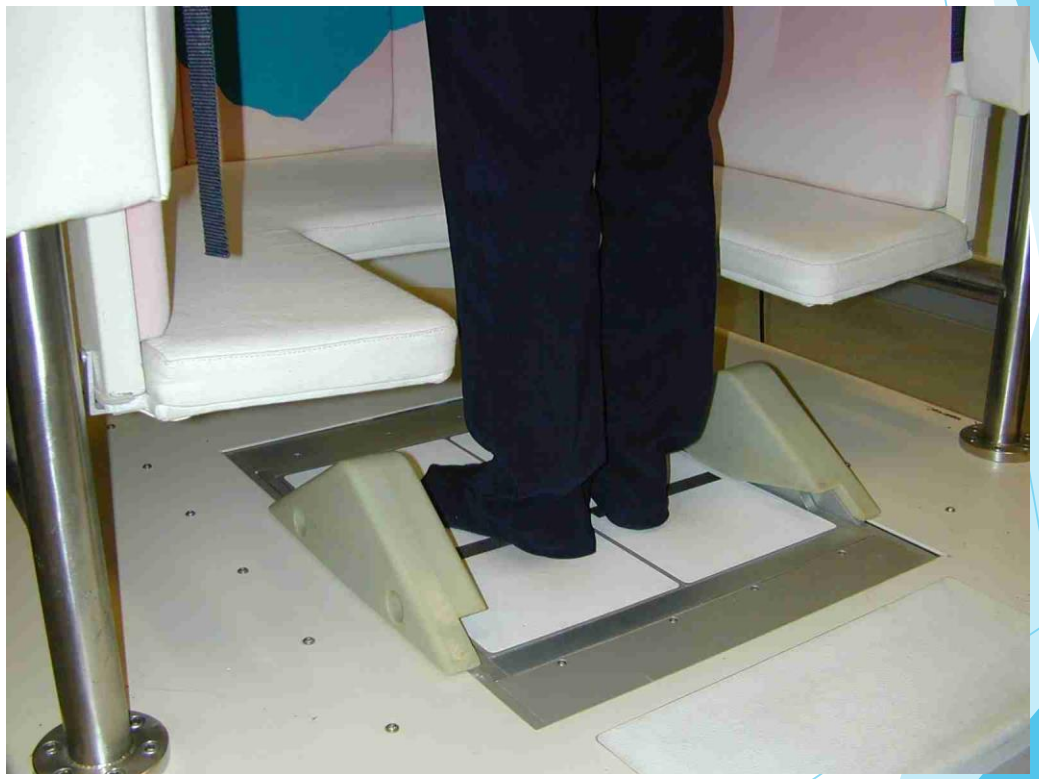
Aortic dissection was the single largest cause of death in TS, accounting for 23% (8/35) of total deaths.

Thunström Sofia, Wide U, Landin-Wilhelmsen K, Berntorp K, Bryman I, Krantz E, Wahlberg J, Ekman B, Isakson M, Karlsson A, Bergström I, Naessén S. Psychiatric disorders and comorbidity in women with Turner Syndrome: a retrospective national cohort study. Transl Psychiatry. 2024 Sep 4;14(1):355.

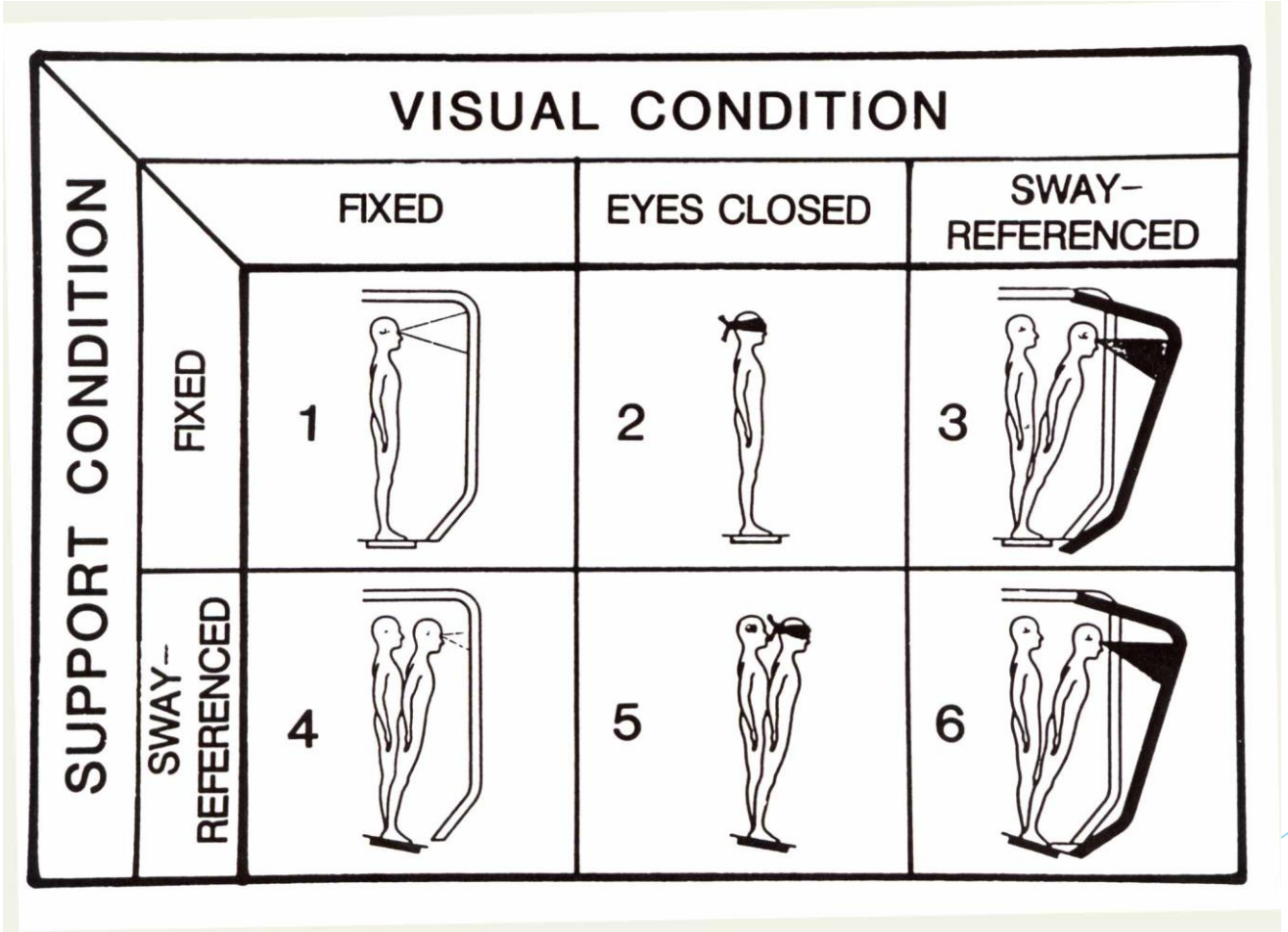
There was no increase in psychiatric diagnosis within the group with time, nor correlation to specific karyotype or somatic comorbidity as congenital heart disease and hypothyroidism, hormonal treatment, or childbirth. In addition, the frequency of psychiatric diagnosis in TS was lower than in the population-based data.

Thunström Sofia, Wide U, Landin-Wilhelmsen K, Berntorp K, Bryman I, Krantz E, Wahlberg J, Ekman B, Isakson M, Karlsson A, Bergström I, Naessén S. Psychiatricdisorders and comorbidity in women with Turner Syndrome: a retrospective national cohort study. Transl Psychiatry. 2024 Sep 4;14(1):355.

EquiTest

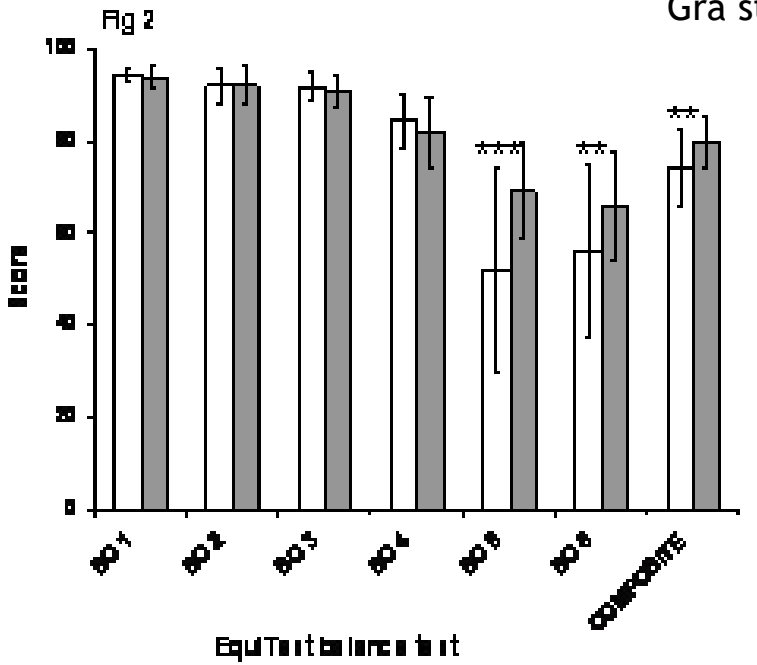


EquiTest


VISUAL CONDITION
SUPPORT CONDITION
FIXED
SWAY-REFERENCED
FIXED
EYES CLOSED
SWAY-REFERENCED
1
2
3
4
5
6

Vita staplar = Turner

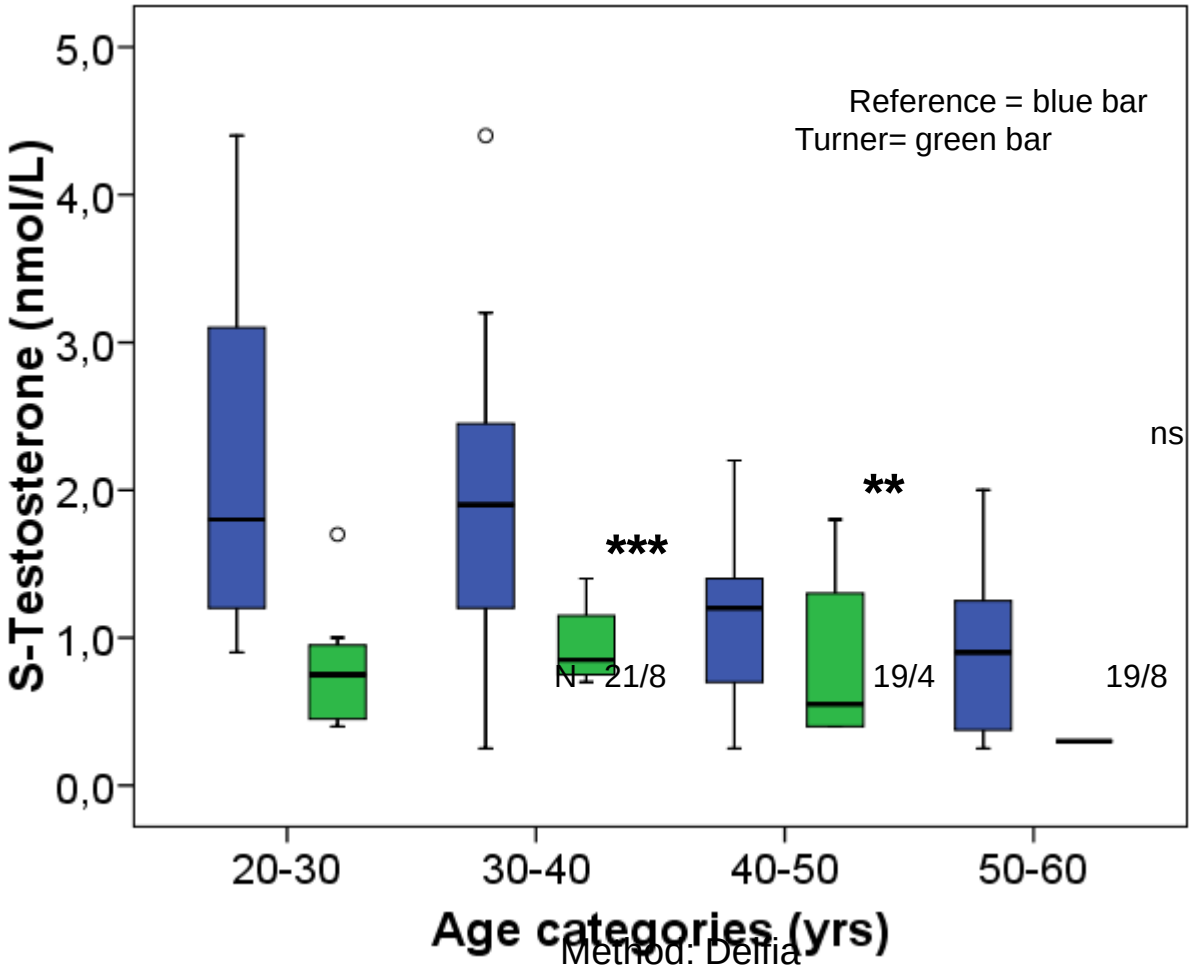
Grå staplar = kontroller



Composite (a merge of all six recordings) was significantly lower in the TS-group, $p<0.05$. In the TS group high total body weight was related to worse outcome on tests SO5, SO6, and composite, while total bone mass, age, height, or waist showed no significant association with balance scores. Our findings indicate that TS could have an increased risk for falling due to impaired ability to manage complex coordination tasks

Wahlberg J, Sydsjö G, Ledin T, Bågesund M, Ekman B. Impaired postural balance in turner syndrome. Horm Metab Res. 2013 Jul;45(7):537-40.

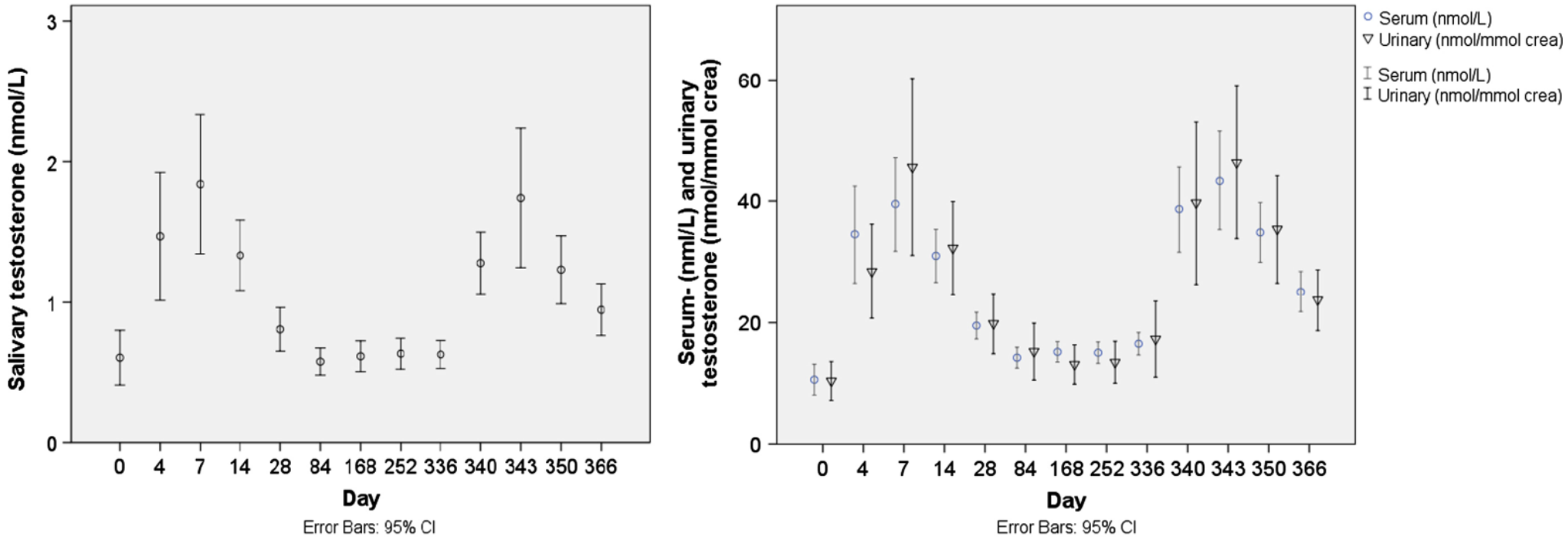
Referens population/Turner
S-Testosteron



N= 21/8 19/4 19/8 20/1

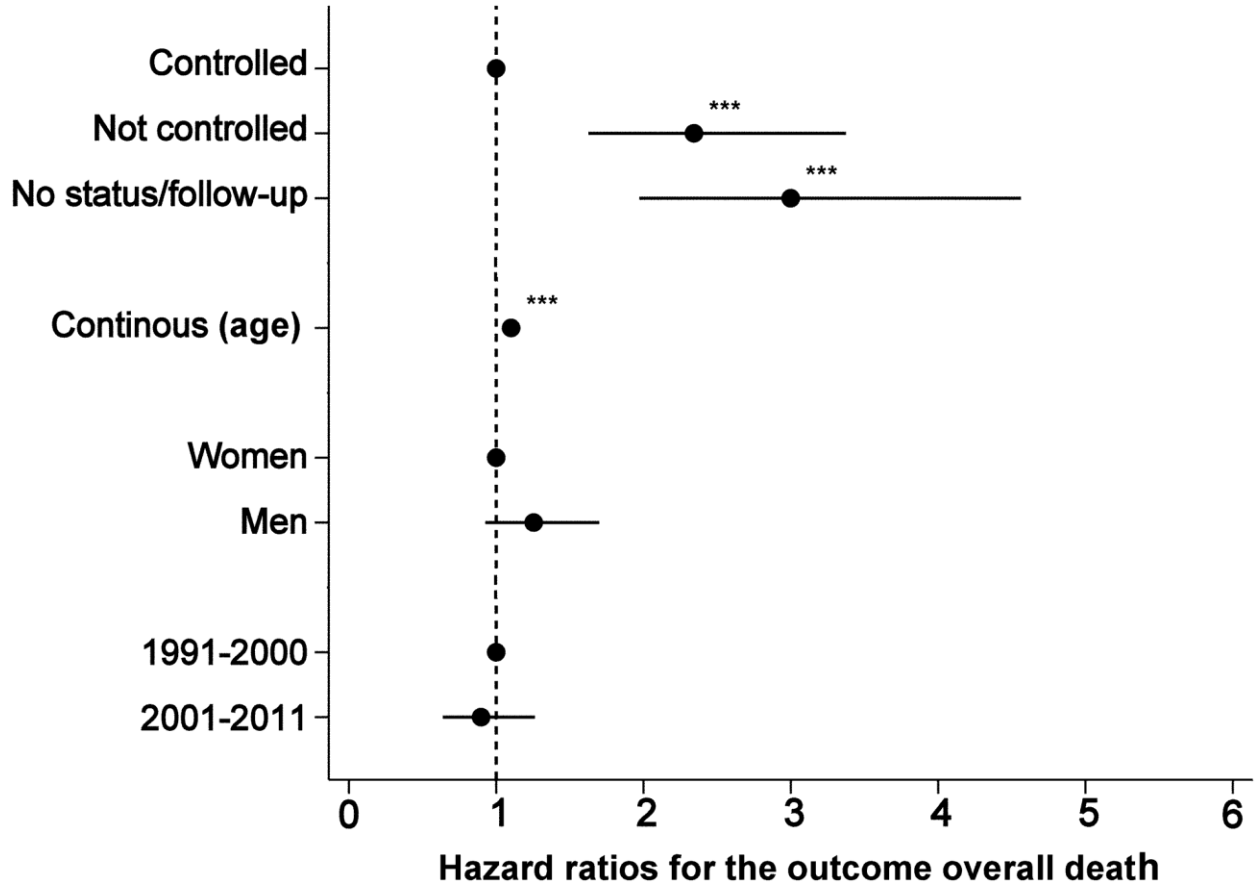
Method: Delfia

Figure 3 Testosterone concentrations (mean ± 95% CI) for all measured values in saliva (left) and serum and urine (right) in patients during intramuscular testosterone undecanoate injections every 12th week during 12 months and first and last injections.



Lood Y, Aardal-Eriksson E, Webe C, Ahlner J, Ekman B, Wahlberg J.
Relationship between testosterone in serum, saliva and urine during treatment with intramuscular testosterone undecanoate in gender dysphoria and male hypogonadism. Andrology. 2018 Jan;6(1):86-93.

Figure 3 Hazard ratios (HRs) with 95% CIs for the outcome of overall death in patients with acromegaly until June 30, ...



Eur J Endocrinol, Volume 186, Issue 3, Mar 2022, Pages 329–339, https://doi.org/10.1530/EJE-21-0729

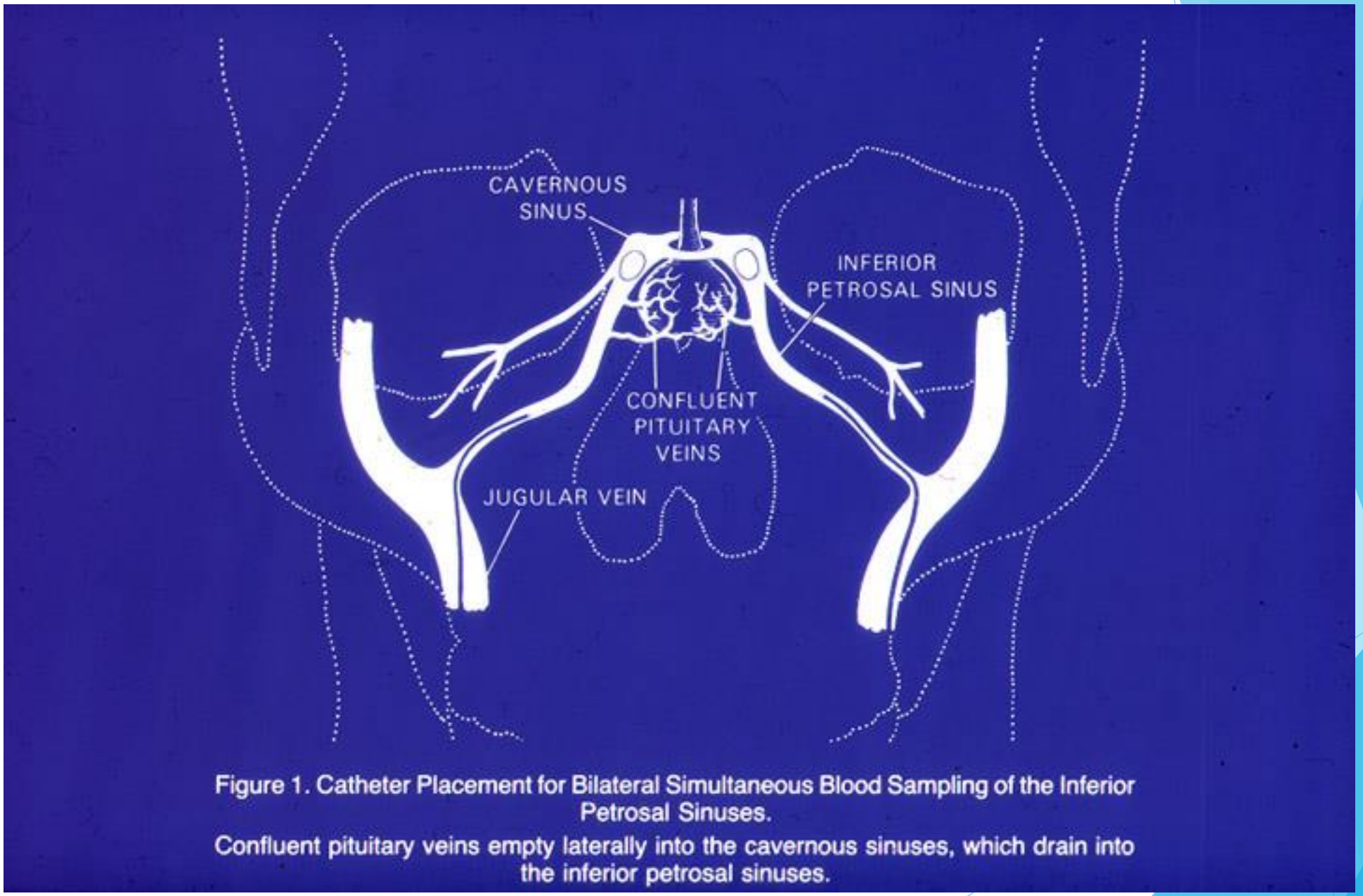


Figure 1. Catheter Placement for Bilateral Simultaneous Blood Sampling of the Inferior Petrosal Sinuses.

Confluent pituitary veins empty laterally into the cavernous sinuses, which drain into the inferior petrosal sinuses.

Sinus cavernosus kateterisering

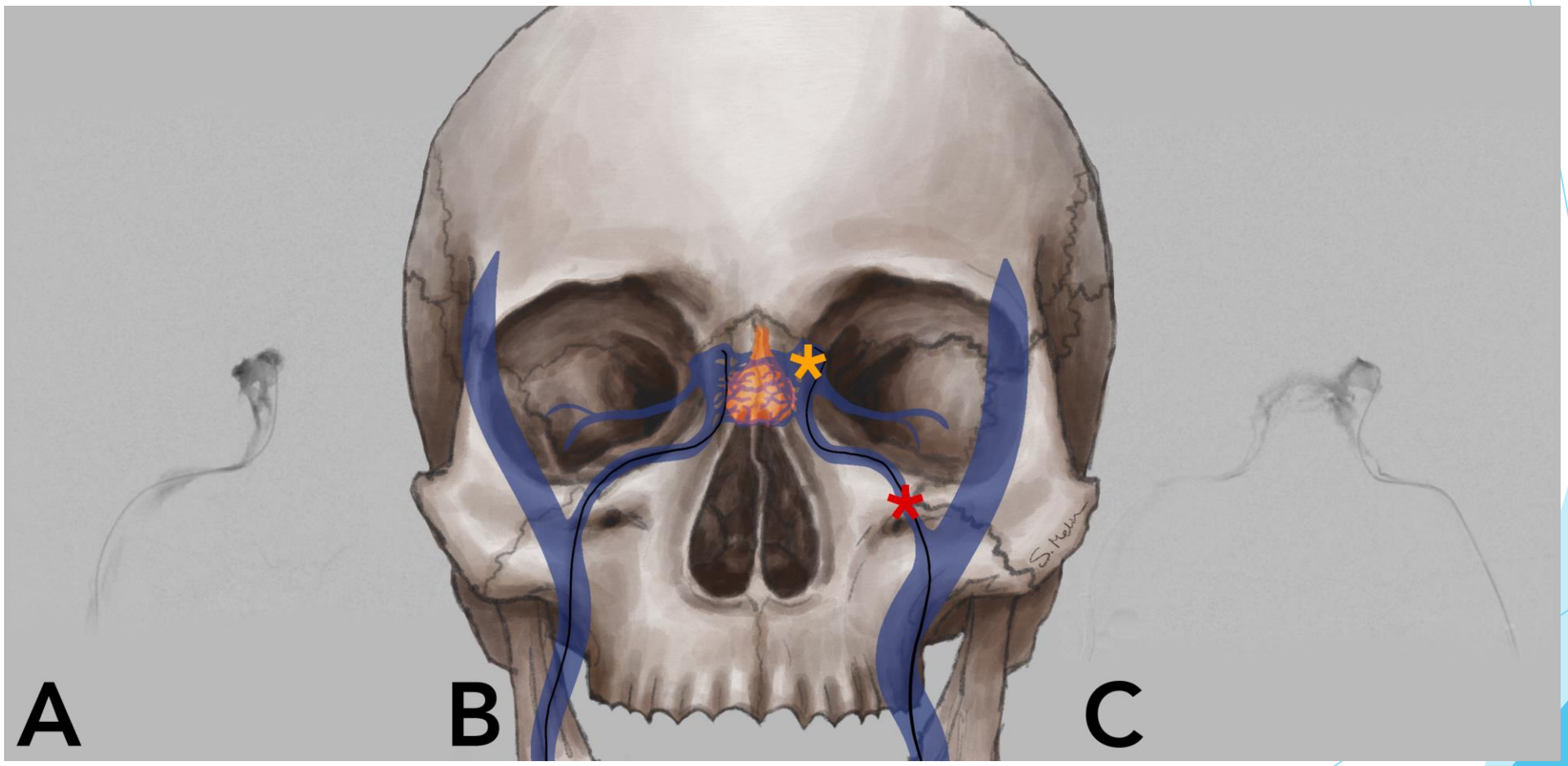
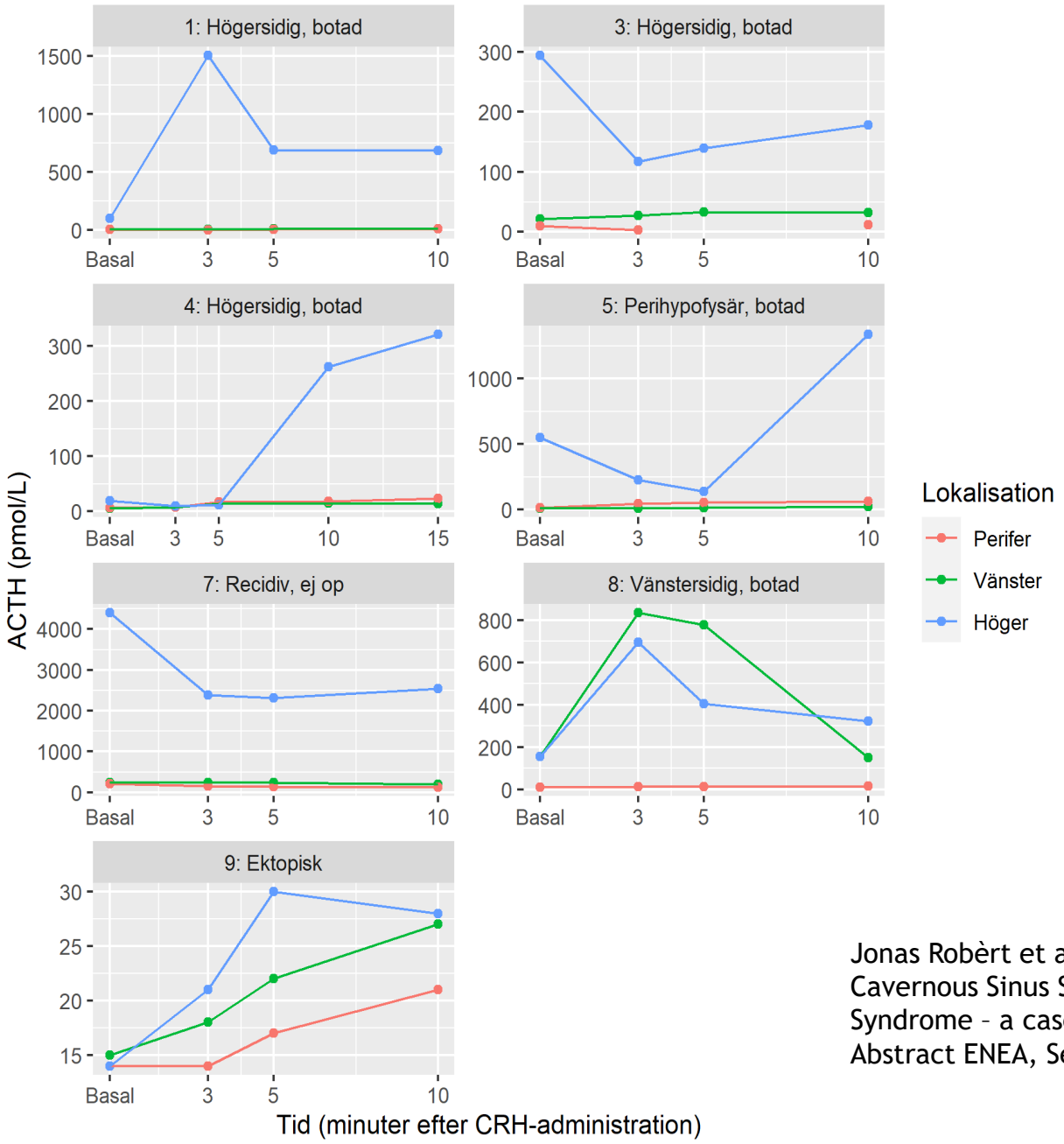
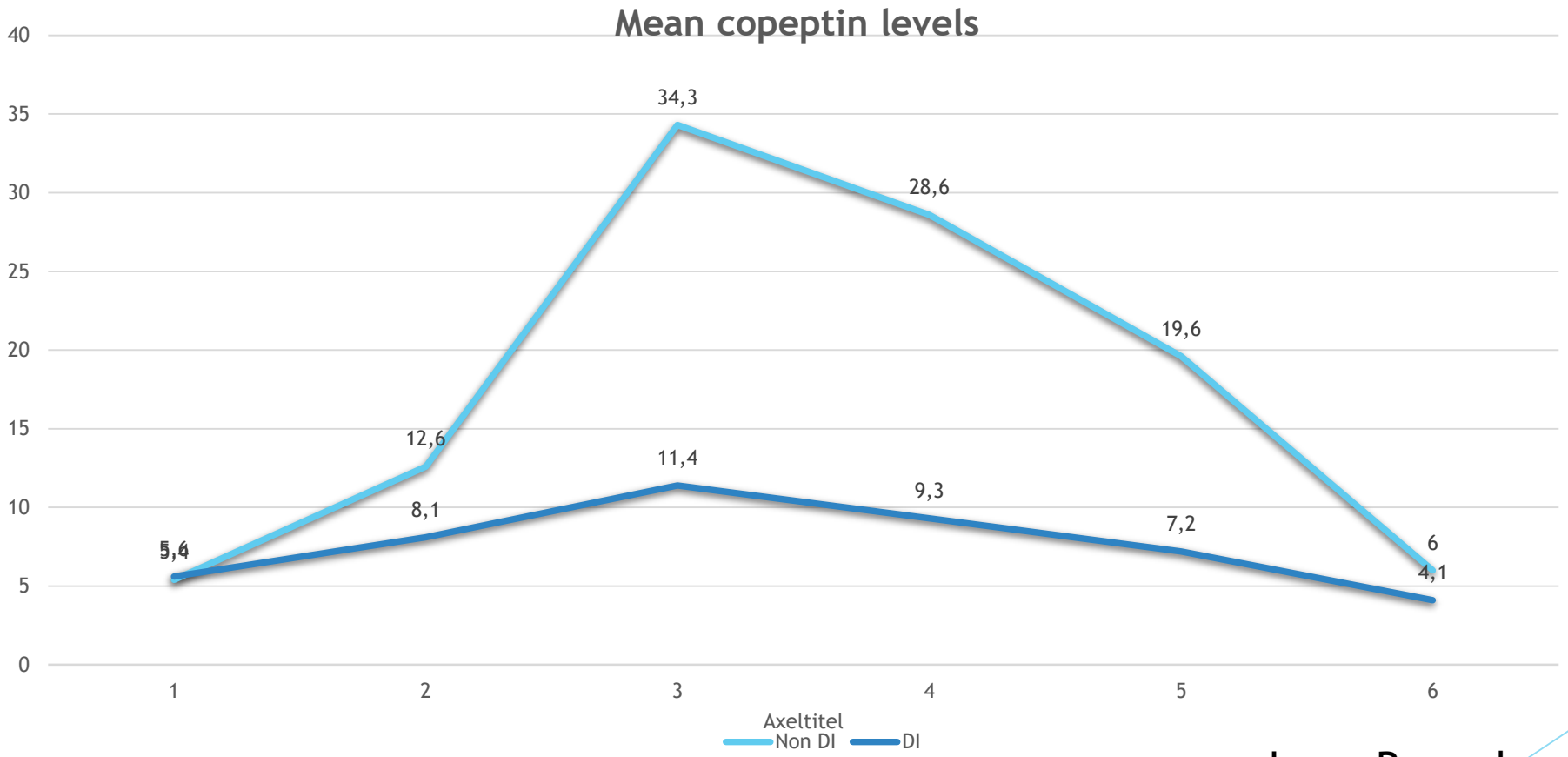


Bild Sofia Melin



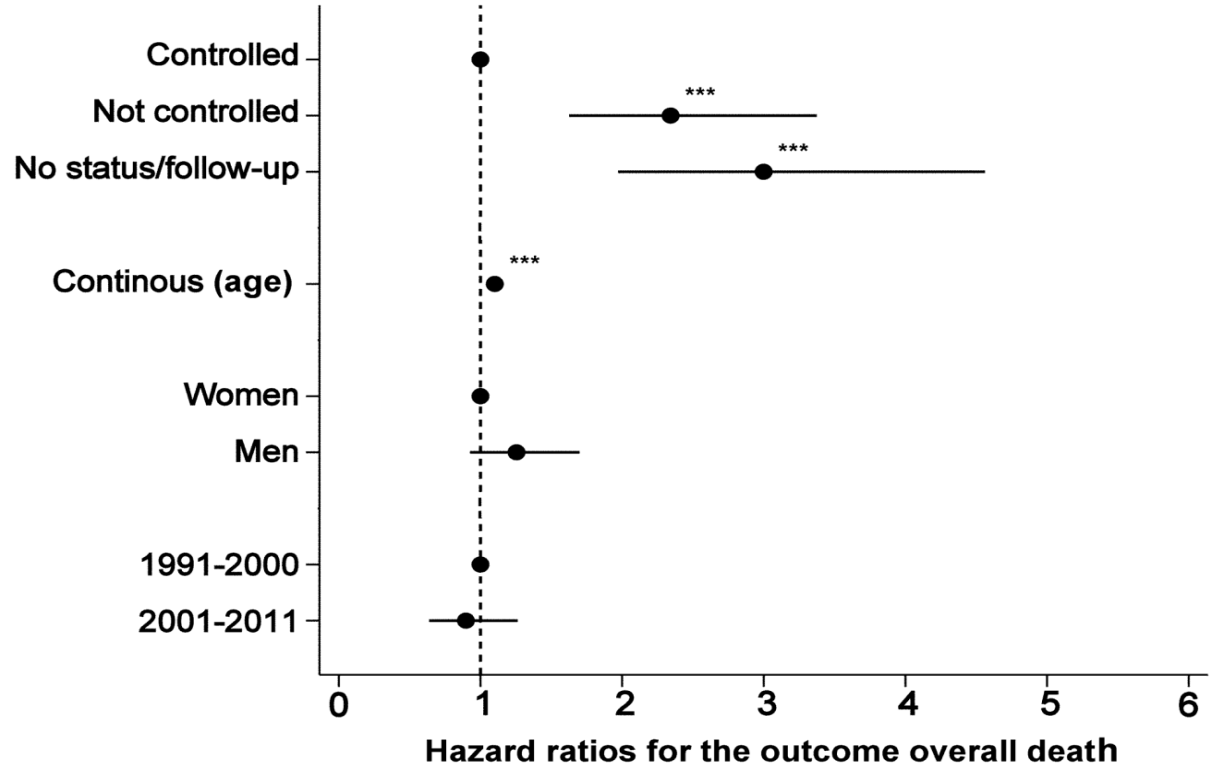
Jonas Robèrt et al
Cavernous Sinus Sampling in the Diagnosis of Endogenous Cushing Syndrome – a case series and methods description
Abstract ENEA, Sevilla sept 2024.

Copeptin vid hypofyskirurgi



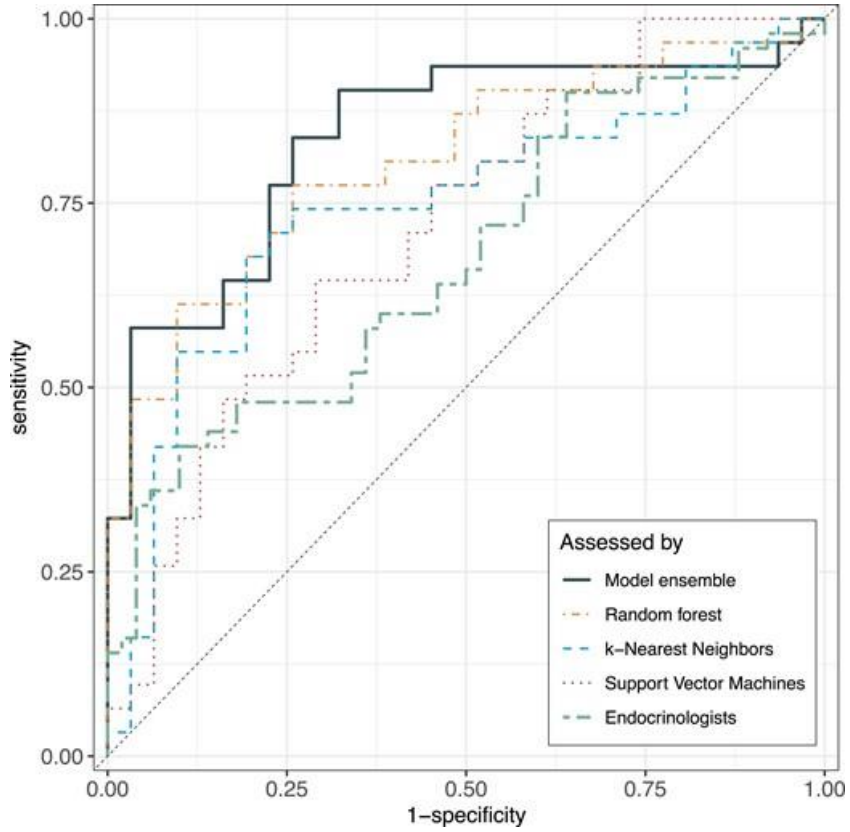
Jonas Rosander et al.
Under databearbetning

Akromegali



Arnardóttir S, Järås J, Burman P, Berinder K, Dahlqvist P, Erfurth EM, Höybye C, Larsson K, Ragnarsson O, Ekman B, Edén Engström B. Long-term outcomes of patients with acromegaly: a report from the Swedish Pituitary Register. Eur J Endocrinol. 2022 Feb 1;186(3):329-339.

Röstanalys vid akromegali



The machine learning model identified patients with acromegaly more accurately (area under the receiver operating curve [ROC AUC] 0.84) than experienced endocrinologists (ROC AUC 0.69).

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Några saker att arbeta vidare med.

- **Teknik**
- Nya diagnostiska verktyg
- AI stödda insulinpumpar och sensorer. Billigare teknik borde komma så även typ 2 diabetes får sensorer som via smarta appar som inkluderar kombinerad livsvanestöd kan leda till bättre egenvård.

- **Förebygga sjukdomsuppkomst eller lindra sjukdomsförloppet**
- Screening för Typ 1 diabetes.
- Immunologisk behandling av typ 1 diabetes och potentiellt även för andra autoimmuna endokrina sjukdomar.
- Skall man medicinskt behandla primär aldosteronism med aldosteronreceptorblockad?
- Samarbete med andra specialiteter som använder behandling som allvarligt skadar hormonkörtlarna eller ger hormonella funktionsstörningar.

- **Förbättrad hormonbehandling**
- Strukturerad obesitasbehandling med mättnadshormoner. Samarbete med kirurgiska obesitascentrum
- Utveckla mera fysiologiska hormonbehandlingar. Hormonpumpar utöver insulinpumpar?

Tack alla medarbetare från förr och framåt!