Het syndroom van Klinefelter: Screening en opvolging van metabole afwijkingen

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KLINEFELTER KLINIEK

Achtergrond

Fenotype = grote variabiliteit

- Niet alle symptomen komen samen voor

Achtergrond

- Klinefelter syndroom (KS)
  - primair testiculair falen **hypergonadotroof hypogonadisme**
  - voornaamste symptomen bij KS patiënten verbonden aan een **lage testosteronspiegel**
    - verminderde libido
    - gynaecomastie
    - fertiliteitproblemen

Table 1
Clinical features (%) of adult patients with Klinefelter syndrome.[3,38,81]

Small testes (<4–6 mL)	>95
Infertility	>99
Azoospermia	>95
Decreased facial hair	60–80
Decreased pubic hair	30–60
Abdominal adiposity	50
Gynecomastia	38–75
Varicose veins	40
Decreased libido and potency	70
Decreased muscle strength	70
The metabolic syndrome	46
Type 2 diabetes	10–39
Osteopenia and osteoporosis	40 + 10
Mitral valve prolapse	<55

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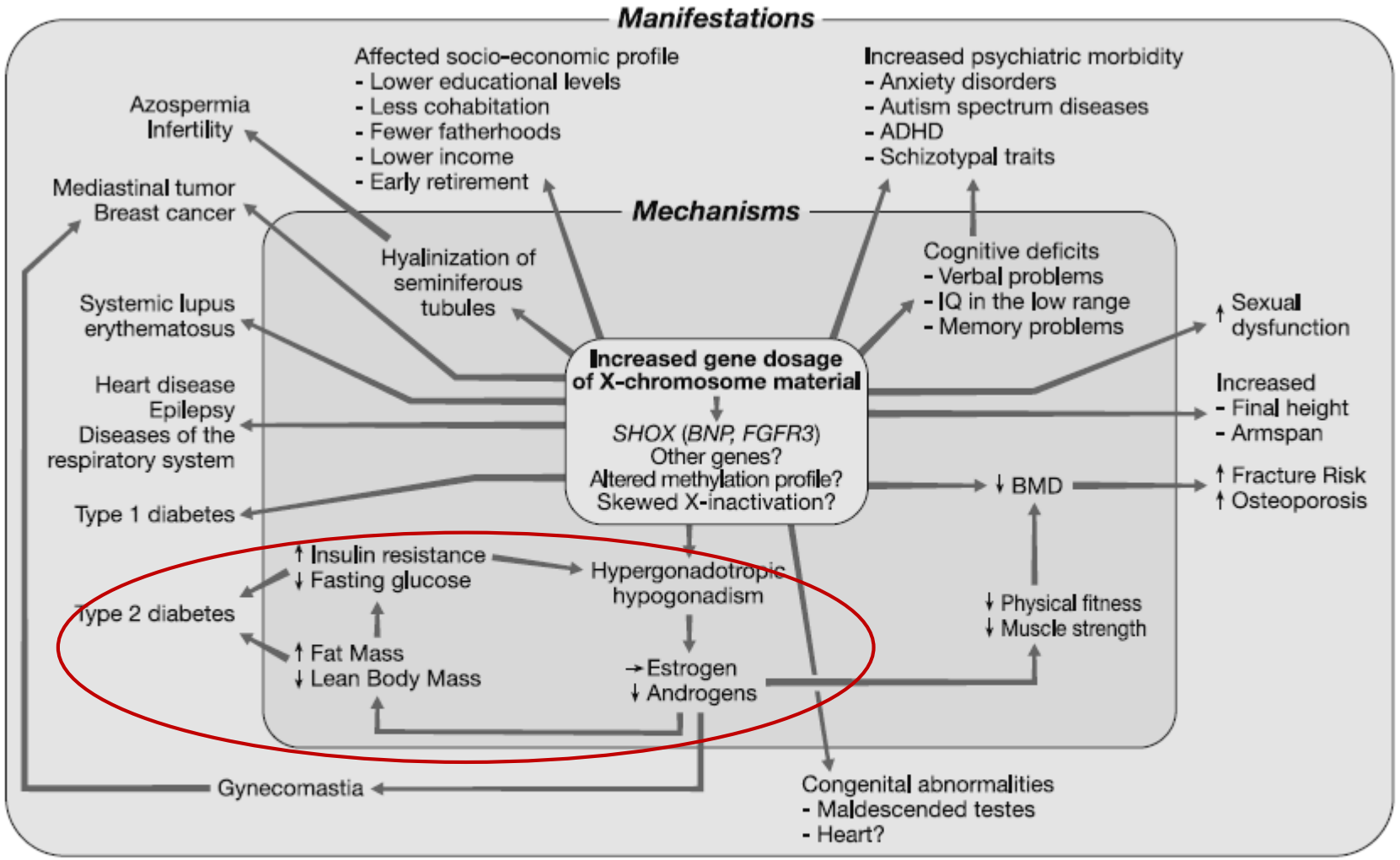
Pathofysiologie



Figuur 1. Het effect van verhoogde genexpressie op het extra X-chromosoom (en eventueel andere genetische mechanismen, zoals epigenetische en verminderde X-inactivatie) zijn de sleutelmechanismen, die de pathofysiologie zouden kunnen verklaren bij KS-patiënten. [1]

Groth KA et al. Klinefelter Syndrome-A Clinical Update. JCEM 2012

Co-morbiditeiten

- Wat is het belang van co-morbiditeiten die gepaard kunnen gaan met het Klinefelter syndroom (KS)?

Increased Mortality in Klinefelter Syndrome

ANDERS BOJESEN, SVEND JUUL, NIELS BIRKEBÆK, AND CLAUS H. GRAVHOLT

Medical Department M. (Diabetes and Endocrinology), Aarhus Sygehus, Aarhus University Hospital (A.B., C.H.G.); Department of Epidemiology and Social Medicine, Aarhus University (S.J.); and Department of Pediatrics, Skejby Hospital, Aarhus University Hospital (N.B.), DK-8000 Aarhus C, Denmark

Bojesen et al JCEM 2004

- Verhoogde mortaliteit van 40%
- Median “survival” KS= 71,4 jaar
  vs 73,5 (controle group)
  → Daling in **median “survival” of 2.1 jaar**

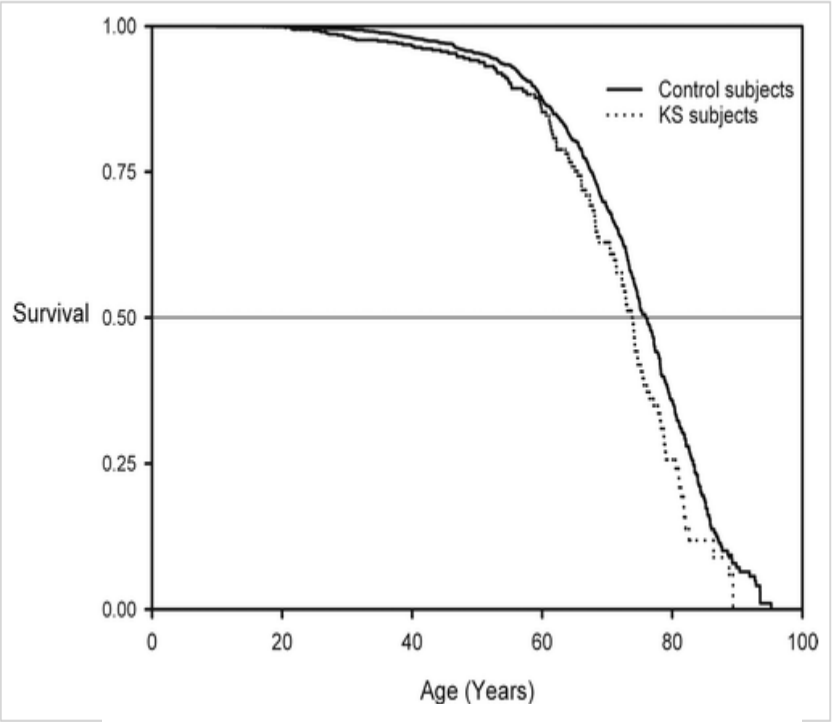


FIG. 1. Survival of KS subjects *vs.* control subjects (hazard ratio, 1.40; 95% CI, 1.13–1.74; $P = 0.002$). KS subjects lost 2.1 yr (95% CI, 0.3–3.9 yr; median survival) compared with control subjects.

Bojesen et al JCEM 2004

TABLE 2. Cause-specific mortality in patients with Klinefelter syndrome overall

ICD9 code	Cause	No. of deaths	SMR (95% CI)	AER per 100,000 per annum
140–208	All malignant neoplasms	99	1.2 (1.0–1.4)	27.7
240–279	Endocrine, metabolic, and nutritional	20	4.8 (2.9–7.4)[a]	29.9
250	Diabetes mellitus	17	5.8 (3.4–9.3)[a]	26.6
290–319	Mental disorders	14	3.7 (2.0–6.2)[c]	19.3
320–389	Diseases of the nervous system	15	2.8 (1.6–4.6)[b]	18.1
345	Epilepsy	8	7.2 (3.1–14.1)[a]	13.0
390–459	Diseases of the circulatory system	163	1.3 (1.1–1.5)[b]	70.4
410–414	Ischemic heart disease	60	0.7 (0.5–0.9)[b]	−48.7
415.1	Pulmonary embolism	8	5.7 (2.5–11.3)[a]	12.5
420–429	Other heart disease	16	2.2 (1.3–3.6)[b]	16.7
424.1	Aortic valve disease	2	2.0 (0.2–7.2)	1.9
430–437	Cerebrovascular disease	46	2.2 (1.6–3.0)[a]	48.0
430	Subarachnoid hemorrhage	6	3.1 (1.2–6.8)[c]	7.7
443.9	Peripheral vascular disease, unspecified	6	7.9 (2.9–17.2)[a]	9.9
460–519	Diseases of the respiratory system	65	2.3 (1.8–2.9)[a]	68.7
480–486	Pneumonia	25	2.3 (1.5–3.4)[a]	26.9
490–494, 496	Chronic lower respiratory disease	31	2.1 (1.4–3.0)[a]	31.0
520–579	Diseases of the digestive system	19	1.6 (1.0–2.6)	14.0
557	Vascular insufficiency of the intestine	5	12.3 (4.0–28.8)[a]	8.7
580–629	Diseases of the genitourinary system	9	3.6 (1.6–6.8)[b]	12.3
580–593	Renal and ureteric disease	7	5.0 (2.0–10.3)[b]	10.6
740–759	Congenital anomalies	9	6.8 (3.1–13.0)[a]	14.5
745–747	Cardiovascular congenital anomalies	5	7.3 (2.4–17.1)[b]	8.2
800–999	Accidents and violence	32	1.3 (0.9–1.8)	12.8
800–829	Fracture of bones	3	0.4 (0.1–1.3)	−7.2
820–821	Fracture of femur	2	39.4 (4.8–142.3)[b]	3.7
000–999	All causes	461[d]	1.5 (1.4–1.7)[a]	303.4

AER, Absolute excess risk.
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] Including, as well as the above, 14 deaths from various other specified causes and two from ill-defined causes.

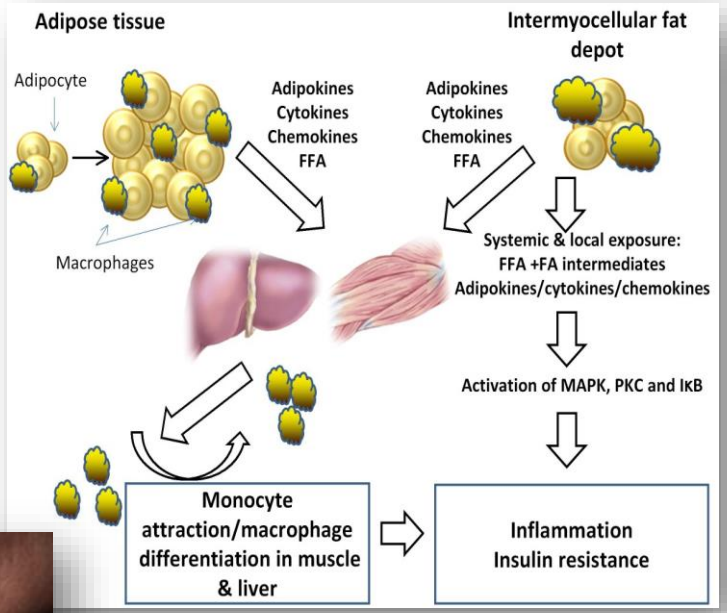
Swerdlow et al; JCEM 2005

Wat zijn metabole afwijkingen?

Insuline resistentie

- **Insuline resistentie** = ↓ biologisch effect van insuline (resistentie aan insuline gemedieerde glucose opname; ↓ de sensitiviteit beta-cellen aan glucose)

- **Insuline resistentie** is het gevolg van:
  → Adipokines/Cytokines, metabole brandstoffen (vvz) uit **vetcellen** welke insuline activiteit veranderen.



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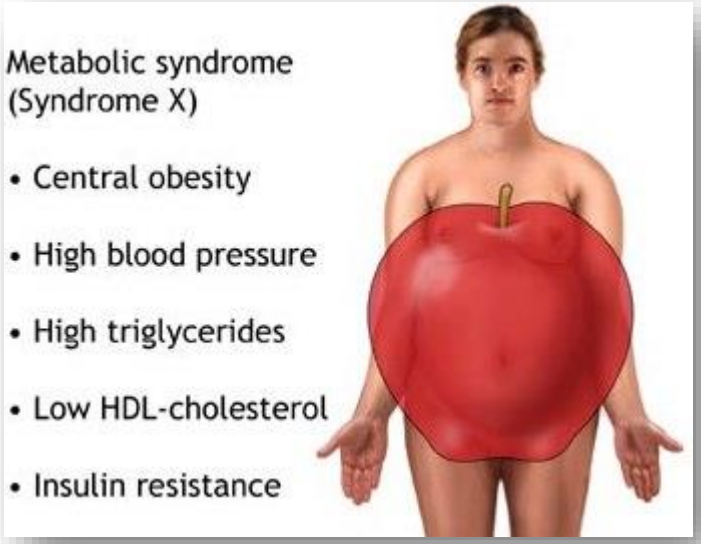
Insuline resistentie

- **Hyperinsulinemia**

  → verhoogd VLDL syntheses,
  → aktivatie sympathisch zenuwstelsel,
  → Na+ reabsorptie →



hyperlipidemie, hypertensie (metabool syndroom)

Diabetes en Obesitas

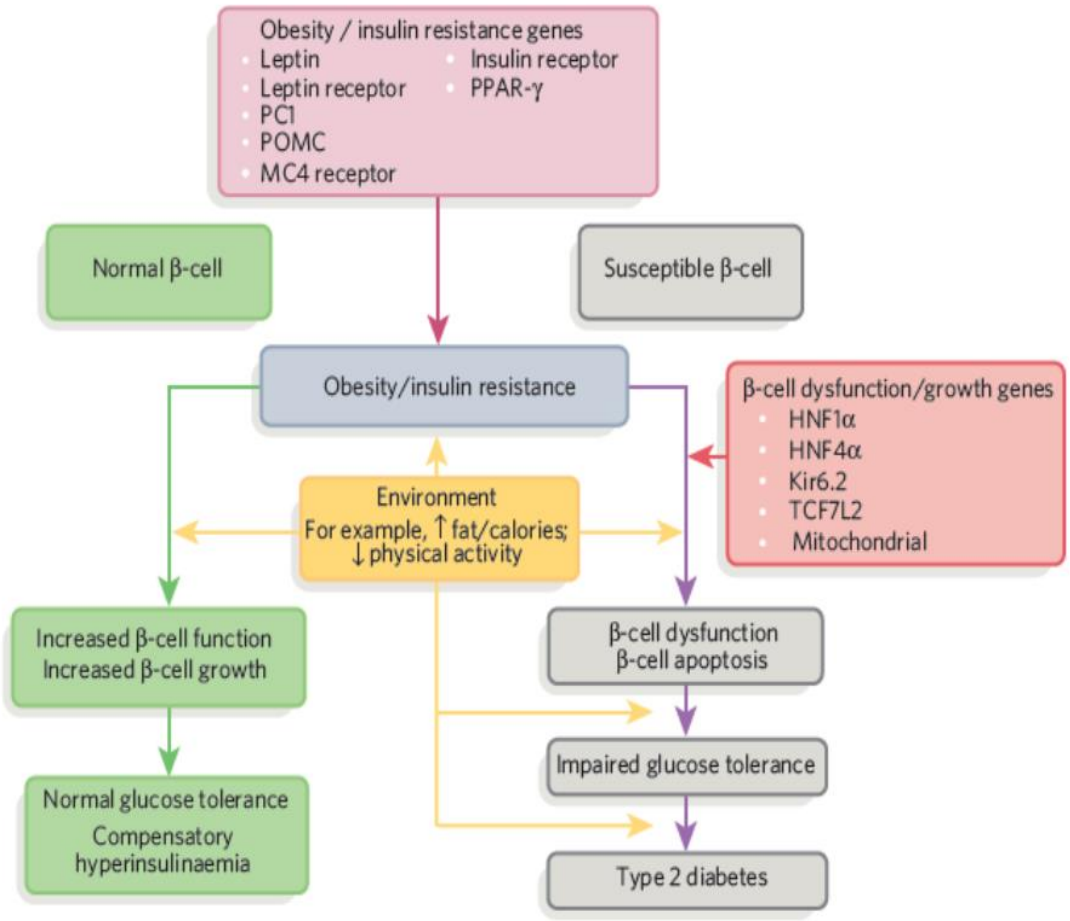
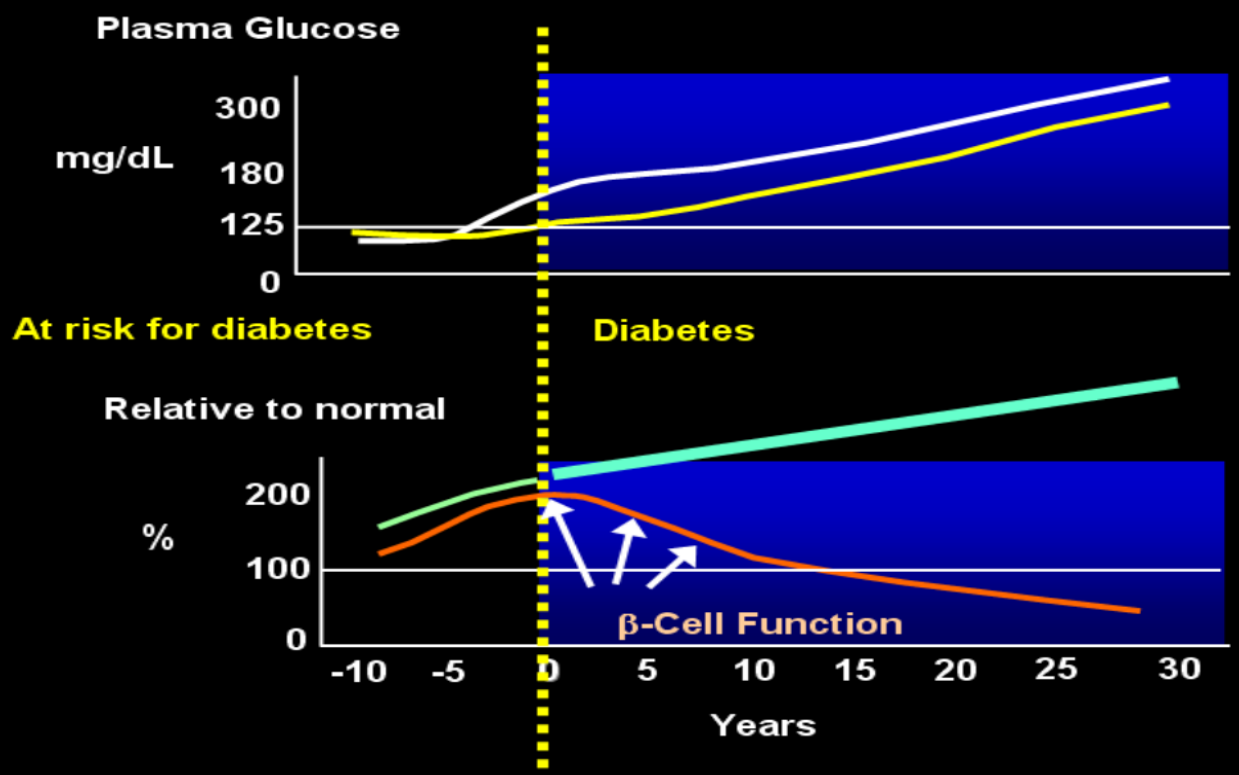


Figure 3 | Interaction of genes and the environment in individuals who maintain normal glucose tolerance and those who develop type 2 diabetes. Genes responsible for obesity and insulin resistance interact with environmental factors (increased fat/caloric intake and decreased physical activity), resulting in the development of obesity and insulin resistance. These increase secretory demand on β-cells. If the β-cells are normal, their function and mass increase in response to this increased secretory demand, leading to compensatory hyperinsulinaemia and the maintenance of normal glucose tolerance. By contrast, susceptible β-cells have a genetically determined risk, and the combination of increased secretory demand and detrimental environment result in β-cell dysfunction and decreased β-cell mass, resulting in progression to impaired glucose tolerance, followed, ultimately, by the development of type 2 diabetes. HNF, hepatocyte nuclear factor.

Kahn et al Nature 2006

Type 2 Diabetes: A Natural History



Metabole afwijkingen bij patiënten met het Klinefelter syndroom

Body composition, metabolic syndrome and type 2 diabetes in Klinefelter syndrome

Claus H Gravholt (ch.gravholt@dadlnet.dk)[1], Anne S Jensen[1], Christian Høst[1], Anders Bojesen[2]

1.Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus Sygehus NBG, Aarhus C, Denmark
2.Department of Clinical Genetics, Vejle Hospital, Sygehus Lillebaelt, Vejle, Denmark

Gravholt et al.
Acta Pediatrica 2011

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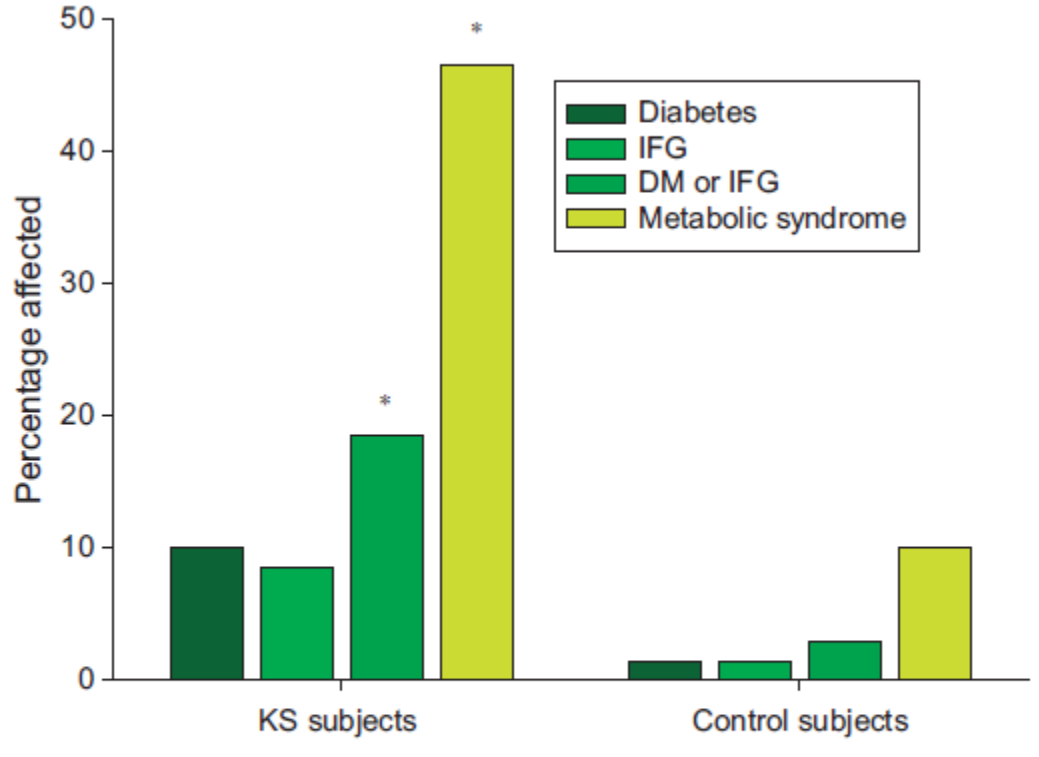

Figure 1 Distribution of 70 Klinefelter syndrome (KS) and 70 age-matched controls with regard to frequency of diabetes (DM), impaired fasting glucose (IFG) or the metabolic syndrome. * indicates $p < 0.05$ (16).

Gravholt et al.
Acta Pediatrica 2011

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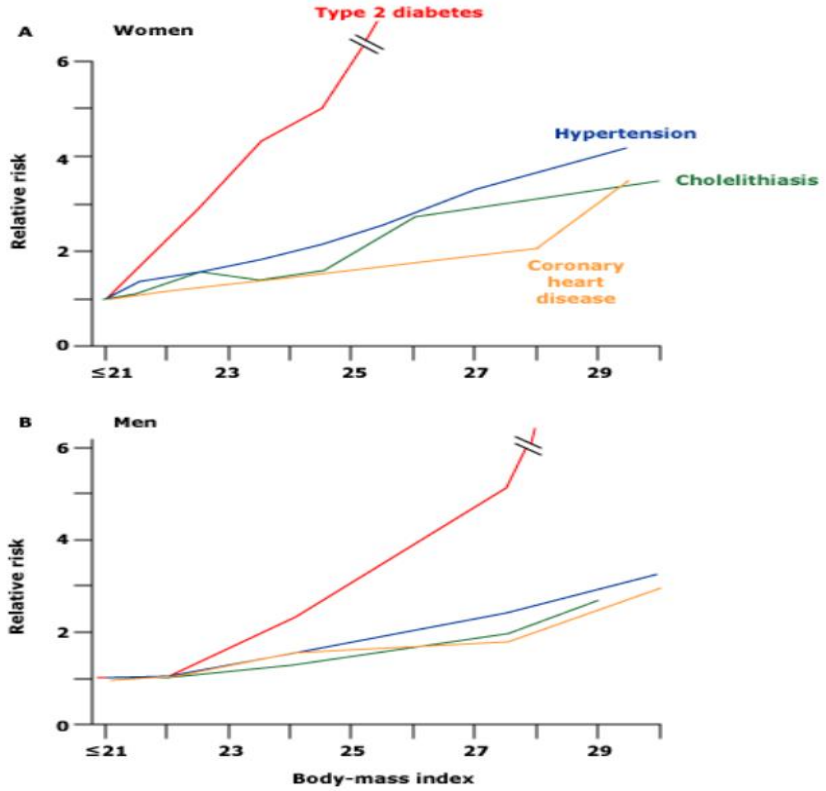
Type 2 Diabetes



Increasing body-mass index (BMI kg/m2), even within the normal range of BMI (21 to 24.9), is associated with an increased risk of type 2 diabetes, hypertension, coronary heart disease, and cholelithiasis. Panel A shows data for women in the Nurses' Health Study, initially 30 to 55 years of age, who were followed for up to 18 years. Panel B shows data for men in the Health Professionals Follow-up Study, initially 40 to 65 years of age, who were followed for up to 10 years.

Data from Willett, WC, Dietz, WH, Colditz, GA. Guidelines for healthy weight. N Engl J Med 1999; 341:427.

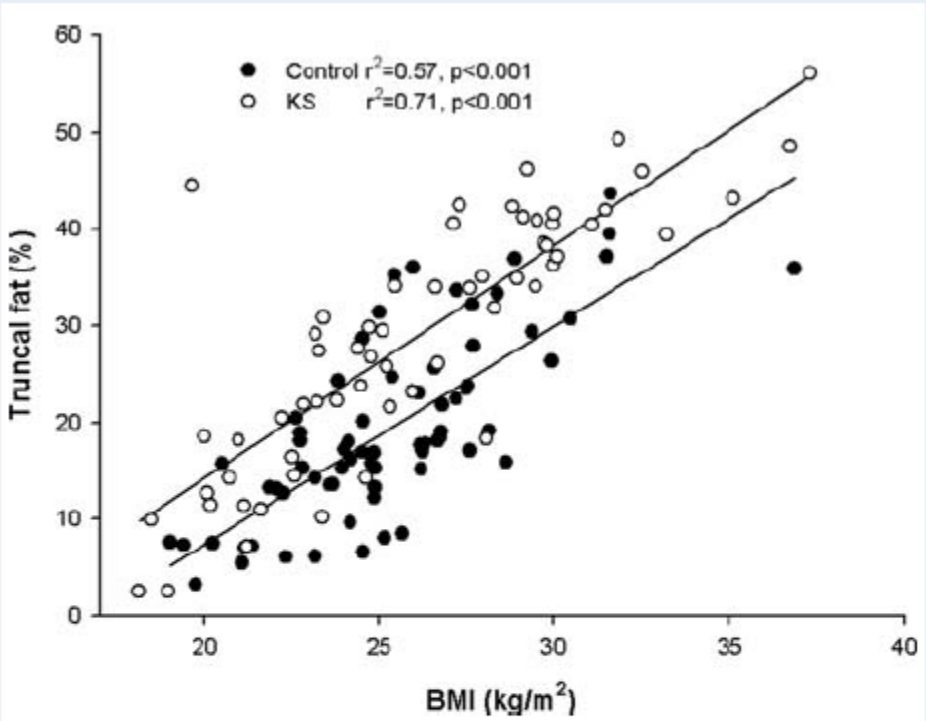


Figure 2 Truncal fat in correlation with BMI. KS patients (open circles) have on average ~8% more fat on the trunk compared with controls (filled circles), independent of BMI. No formal testing for differences between the two regression lines was made, but confidence intervals for the two lines were not overlapping. Truncal fat was determined by DXA scans using a Hologic 2000 (Bojesen *et al.*, 2006a, b).

IMAT-free SM (kg)

Bojessn et al.
Diabetes Care 2006

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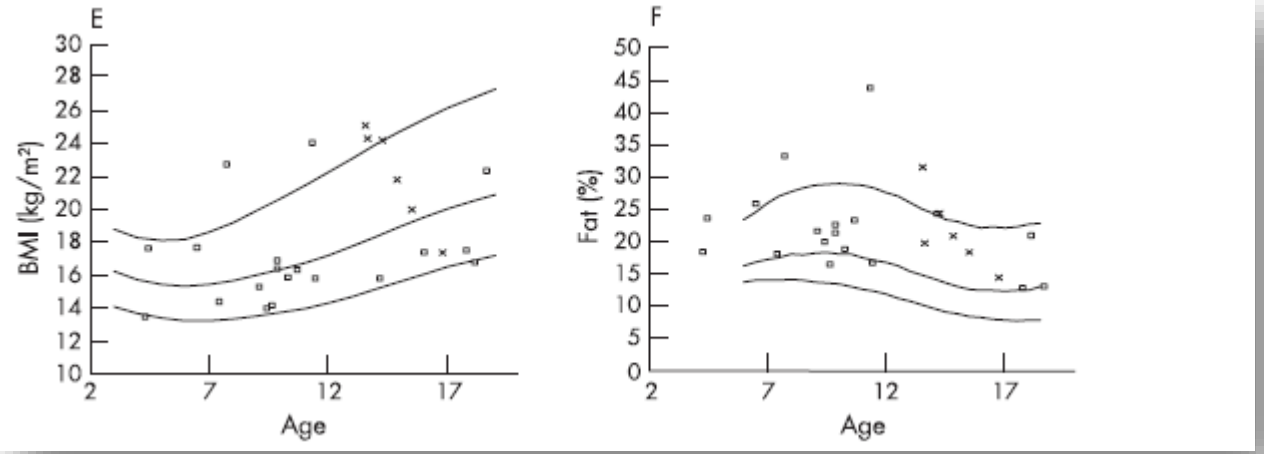
Normal bone mineral content but unfavourable muscle/fat ratio in Klinefelter syndrome

L Aksglaede,[1] C Molgaard,[2,3] N E Skakkebæk,[1] A Juul[1]

- Retrospectieve crossectionele studie
- **Lichaamssamenstelling** in 24 KS patiënten met mediane **leeftijd 11 jaar**.



- Significant verhoogde “body fat mass” ondanks normaal “lean body mass” en BMI in vergelijking met de algemene bevolking
- Vermoedelijk al een ongunstige spier/vet ratio in kinderjaren

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KLINEFELTER KLINIEK

→ Motorische stoornissen

- Snelle vermoeidheid (langdurige fysieke inspanning)
  - Veranderde lichaamssamenstelling (↑ vetmassa, ↓ actieve celmassa)
  - ↓ aeroob vermogen
  - ↓ spierkracht

Sokol et al; Fertil Steril 2012

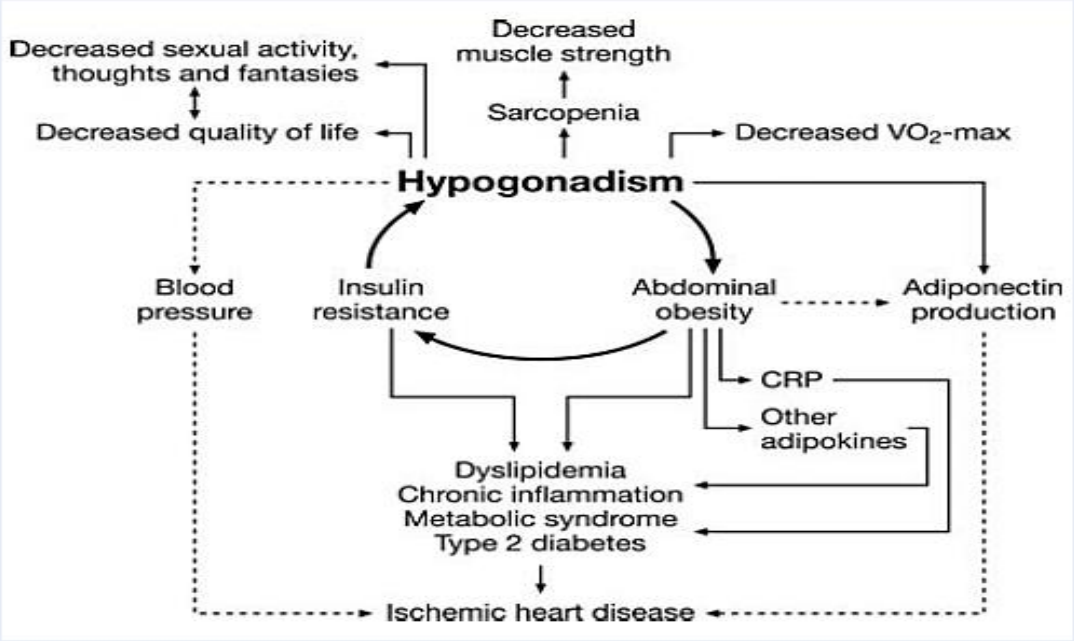


Figure 3 The vicious circle of hypogonadism, abdominal adiposity and insulin resistance has direct and indirect consequences in KS. Although speculative, it seems that normal blood pressure and perhaps normal adiponectin levels counterbalance the detrimental effect of hypogonadism-abdominal obesity-insulin resistance on cardiovascular risk factors. Solid arrows indicate promotion, dotted arrows indicate inhibition. VO_2-max, the maximum capacity to transport and utilize oxygen during incremental exercise (Bojesen and Gravholt, 2007).

Effect testosteron substitutie therapie ?

Table 1 Characterization and effects of testosterone replacement therapy on cardiovascular risk factors in Klinefelter syndrome.

References	No of patients	Findings	Effect of testosterone treatment (TST)
Metabolic syndrome			
(9)	71	42% KS vs 10% in controls	–
(10)	60	34%	–
(11)	69	50% KS vs 10% in controls	No effect
(12)	89	7% in young KS; 24% HOMA >2.5	–
Diabetes mellitus			
(20)	Rev	12%	–
(21)	50	10%	–
(23)	895	6.5% in Japan	No effect
(22)	Rev	15–50% in Western countries 3.9–4.1% in Japan	–
(5)	781	DM hazard ratio1.64	–
(7)	3518	DM cause-specific mortality ratio 7.07; standardized mortality ratio: 5.8; Hazard Ratio: 1.6	–
Dyslipidemia			
(9) (29) (12)	71 Rev 89	Increased total cholesterol, LDL cholesterol, Triglycerides and decreased levels of HDL	Contrasting data on the effect of TT on improving lipidic profile
Hormones and biomarkers			
(9)	71	**CRP** levels increased at baseline compared with controls	Reduction in CRP levels
(31)	19 untreated, 20 treated		
(9)	71	Increased levels of **Leptin** at baseline compared with controls	No effect
(31) (11)	19 untreated, 20 treated 69	KS with MS display normal levels of **adiponectin** compared with MS controls	No effect
(35) (38)	68 36	Reduced concentration of **EPCs** KS compared with age-matched controls and hypogonadal patients	No effect

Rev, review of literature.

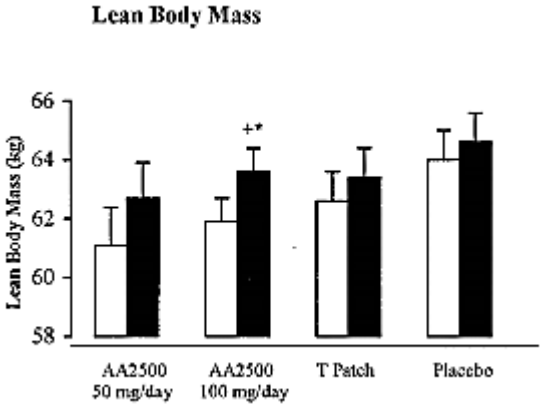
European Journal of Endocrinology

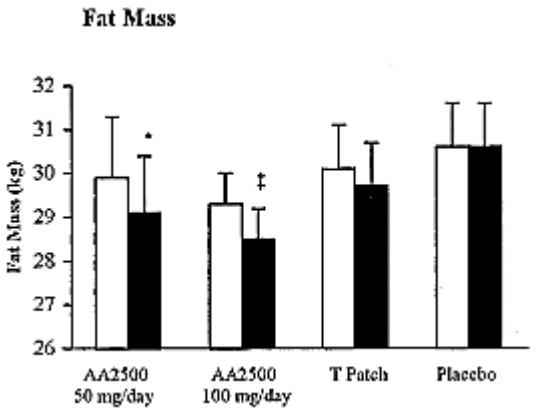
Salzano et al; EJE 2016

AA2500 Testosterone Gel Normalizes Androgen Levels in Aging Males with Improvements in Body Composition and Sexual Function

C. STEIDLE, S. SCHWARTZ, K. JACOBY, T. SEBREE, T. SMITH, R. BACHAND, AND THE NORTH AMERICAN AA2500 T GEL STUDY GROUP

Steidle et al; JCEM 2003





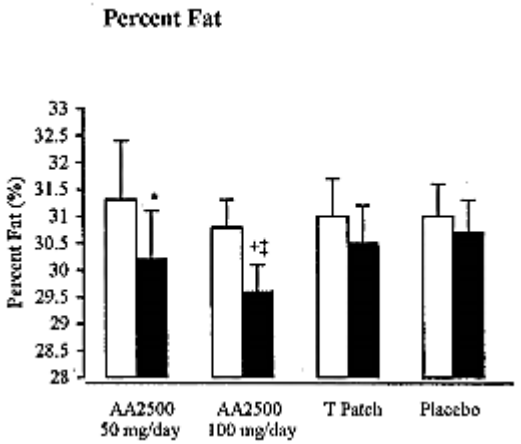


FIG. 3. Values are expressed as means ± 1 SE in LBM, FM, %F, and TBM after treatment with 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo. □, Baseline; ■, d 90; *, Significant *vs.* placebo: $P < 0.05$; +, significant *vs.* T patch: $P < 0.05$; ‡, significant *vs.* placebo: $P < 0.01$.

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European Journal of Endocrinology (2006) 154 899–906 ISSN 0804-4643

CLINICAL STUDY

Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes

D Kapoor[1,3], E Goodwin[1], K S Channer[2] and T H Jones[1,3]

[1]Centre for Diabetes and Endocrinology, Barnsley NHS Foundation Trust Hospital, Gawber Road, Barnsley S75 2EP, UK and [2]Department of Cardiology, Royal Hallamshire Hospital, Sheffield, UK and [3]Academic Unit of Endocrinology, Division of Genomic Medicine, University of Sheffield, UK

(Correspondence should be addressed to T H Jones; Email: hugh.jones@bdgh-tr.trent.nhs.uk)

- double-blind placebo-controlled crossover study
- 24 hypogonadale mannen met type 2 diabetes
- Testosteron 200 mg om de 2 weken of placebo voor 3 maanden

Kapoor et al; EJE 2006

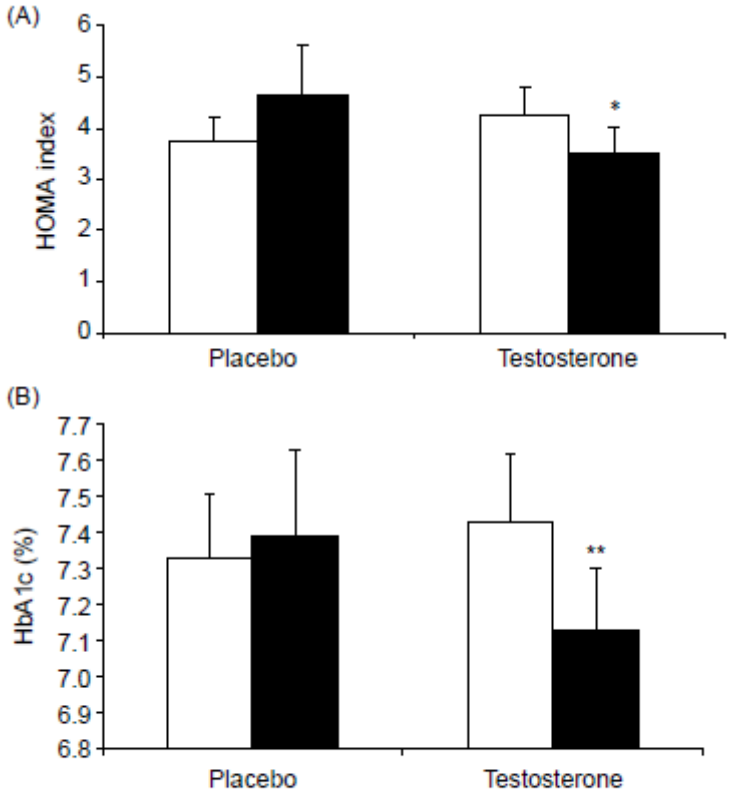

Figure 1 Effect of testosterone replacement compared to placebo on (A) HOMA index and (B) HbA1c. White, baseline; black, after 3 months of treatment (mean ± S.E.M.) *P=0.02, **P=0.03.

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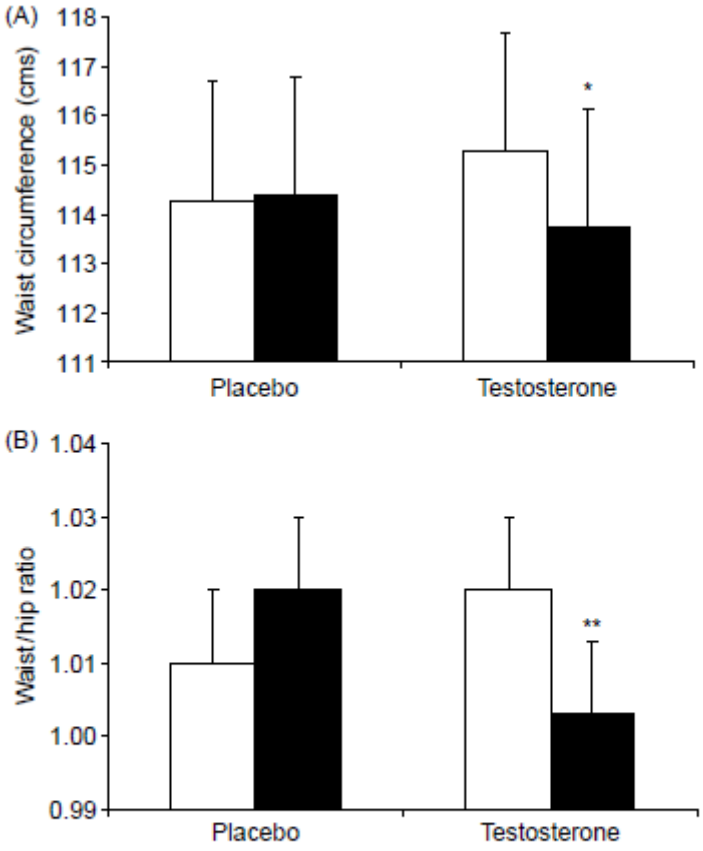

Figure 2 Effect of testosterone replacement compared to placebo on (A) waist circumference and (B) waist/hip ratio (mean ± S.E.M.) *P=0.03, **P= 0.01 vs placebo.

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Screening en opvolgen van metabole afwijkingen

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KLINEFELTER KLINIEK

Screening en opvolging

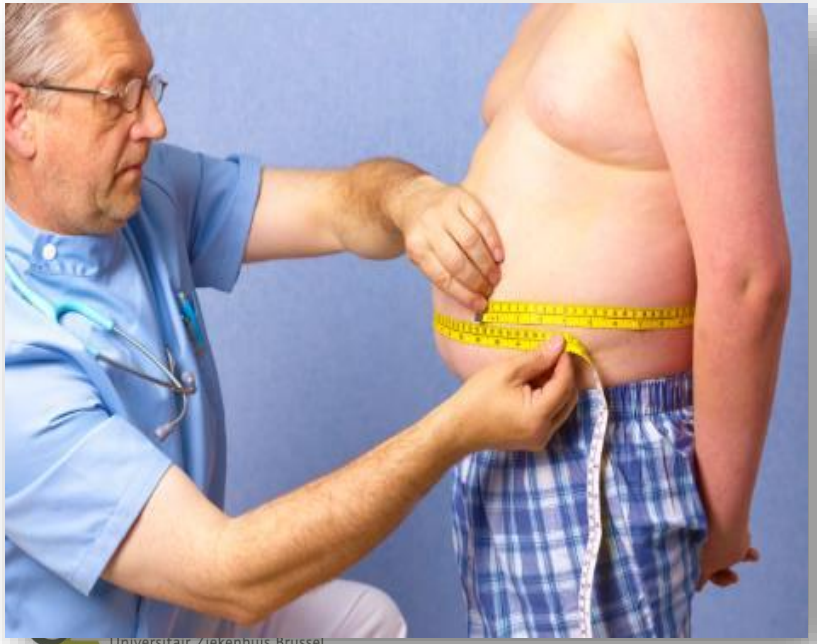
Medische opvolging bij volwassen mannen met het syndroom van Klinefelter.

EERSTE CONTACT	
Informatie patiënt	Vragen (vragenlijst) over welzijnsgevoel, fysieke activiteit, energie, libido, enz.
Nazicht bij eerste contact	
Algemeen fysiek onderzoek met aandacht voor	– Bloeddruk – Gewicht en gestalte – Buikomtrek – Palpatie en volumemeting van de testes – Gynaecomastie – Tekenen van veneuze insufficiëntie – Spierkracht – Tandproblemen
Biologie	– Testosteron, oestradiol, SHBG, LH en FSH – Nuchtere glucose en lipiden – 25-OH-vitamine D en PTH – Schildklierfunctie – PSA en bèta-hCG
Beeldvorming	– Botdensitometrie – (Thoraxfoto (F/P))* – (Echografie borsten/testis)* – (Echocardiografie)*
Bijkomende analysen	– Sperma – Psychologische evaluatie
Initiële therapie	– Dieet en aanpassingen levensstijl – Start testosteronsubstitutietherapie (intramusculair, transdermaal) – Calcium/vitamine D-toediening

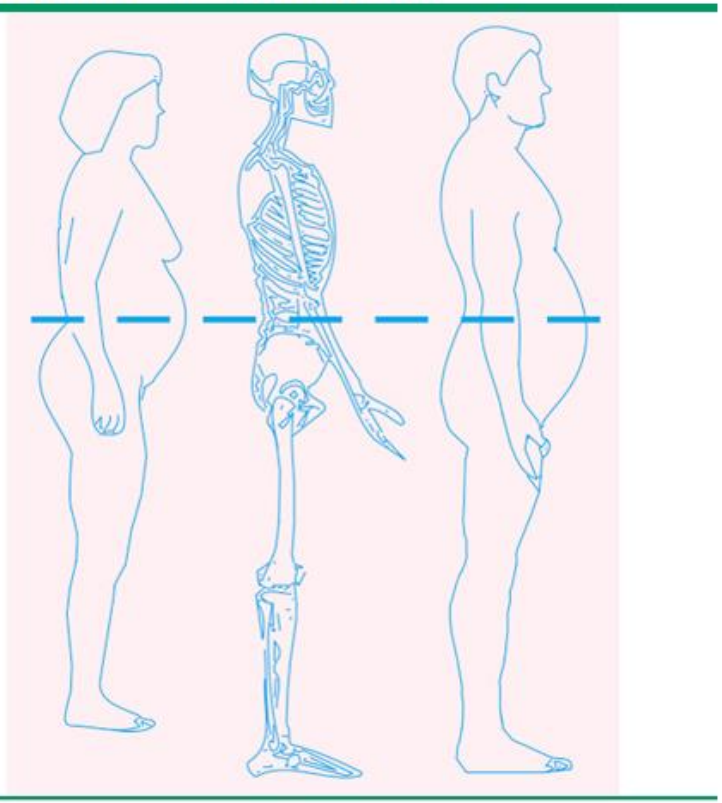
Unuane D. Tijdschr. voor Geneeskunde 2015

- Mannen: ≥ 102 cm
- Vrouwen:≥ 88 cm

  - Verhoogd cardiovasculair risiko



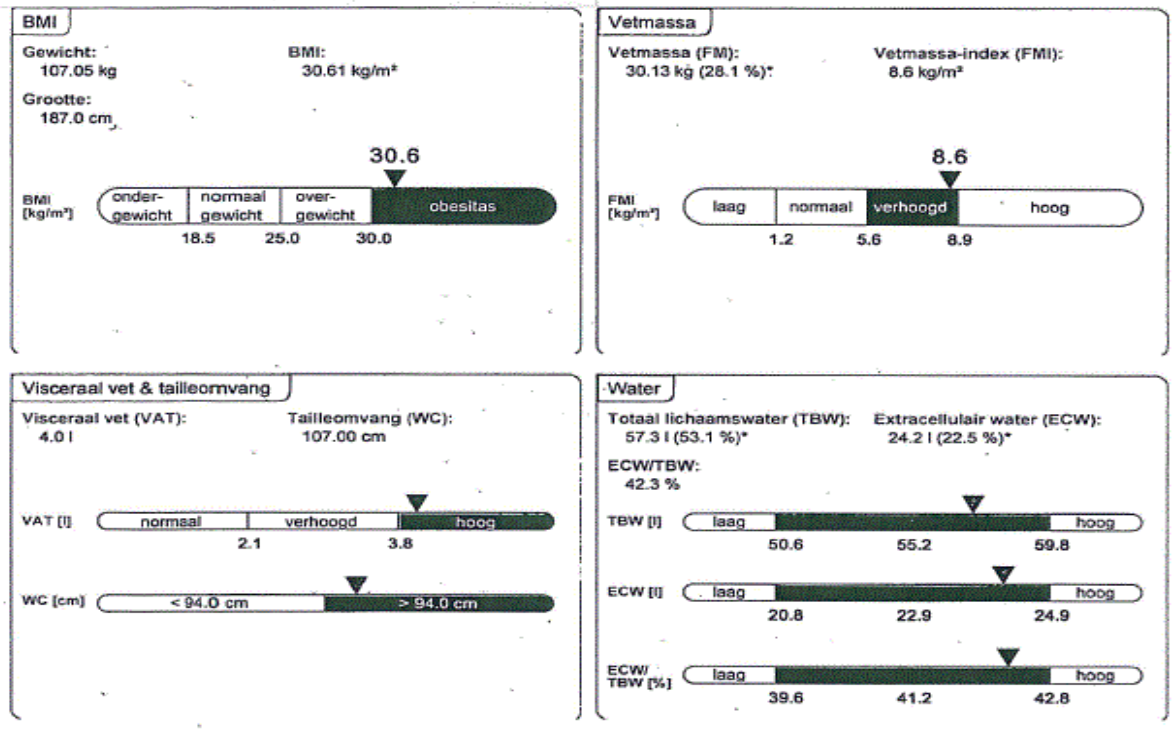
Waist circumference measurement



Measuring-tape position for waist (abdominal) circumference in adults. To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.

Impendantie meting

seca
Resultaten



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Screening en opvolging

VERDERE OPVOLGING (INITIEEL NA DRIE MAANDEN, NADIEN JAARLIJKS)	
Algemeen fysiek onderzoek met aandacht voor	– Bloeddruk – Gewicht en gestalte – Buikomtrek – Palpatie en volumemeting van de testes – Gynaecomastie – Tekenen van veneuze insufficiëntie – Spierkracht – Tandproblemen
Biologie	– Testosteron, oestradiol, SHBG, LH en FSH – Nuchtere glucose en lipiden – Vitamine D-status – Schildklierfunctie – PSA – Hemoglobine, hematocriet
Beeldvorming (om de twee jaar)	– Botdensitometrie – (Thoraxfoto (F/P))* – (Echografie borsten/testis)* – (Echocardiografie)*

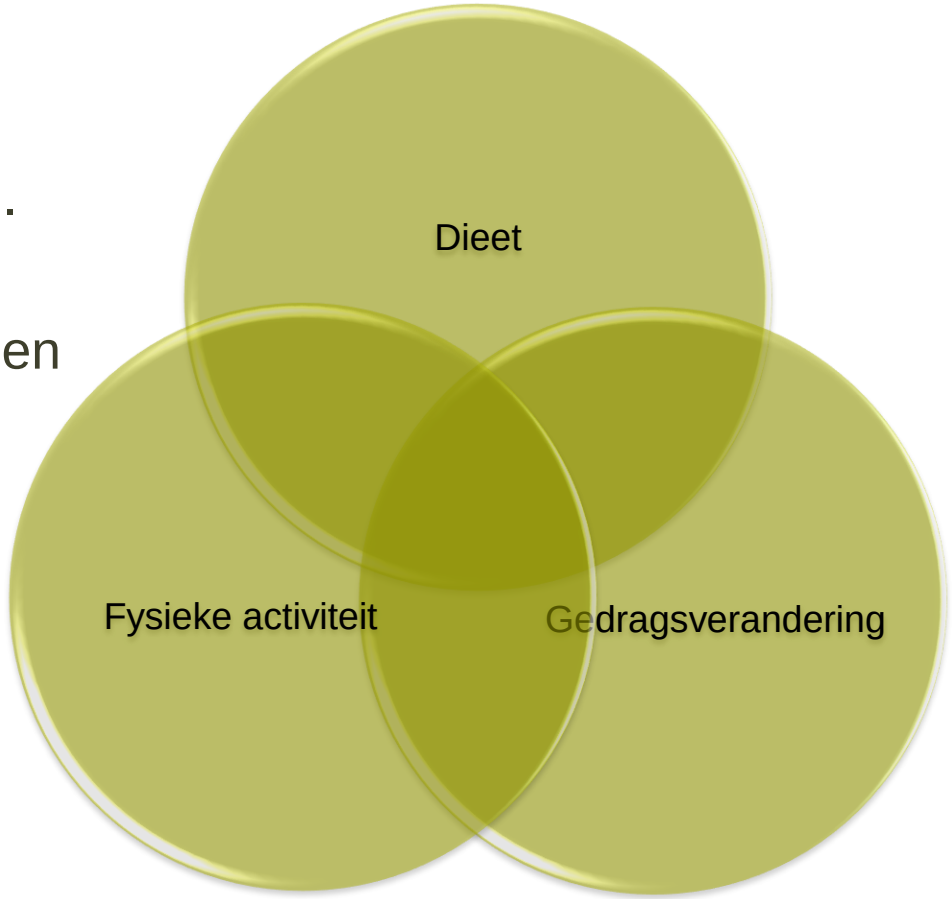
* Bij klinisch vermoeden.
25-OH-vitamine D: 25-hydroxyvitamine D; FSH: follikelstimulerend hormoon; hCG: humaan choriongonadotrofine; LH: luteïniserend hormoon; PSA: prostaatspecifiek antigeen; PTH: parathormoon; SHBG: sekshormoonbindend globuline.

Unuane D. Tijdschr. voor Geneeskunde 2015

Behandeling metabool syndroom

- **Levensstijl aanpassingen**
- ↳**Multidisciplinaire** aanpak ((psycholoog, diëtiste, kinesitherapie, endocrinoloog).

- Medicamenteuze therapie indien noodzakelijk.



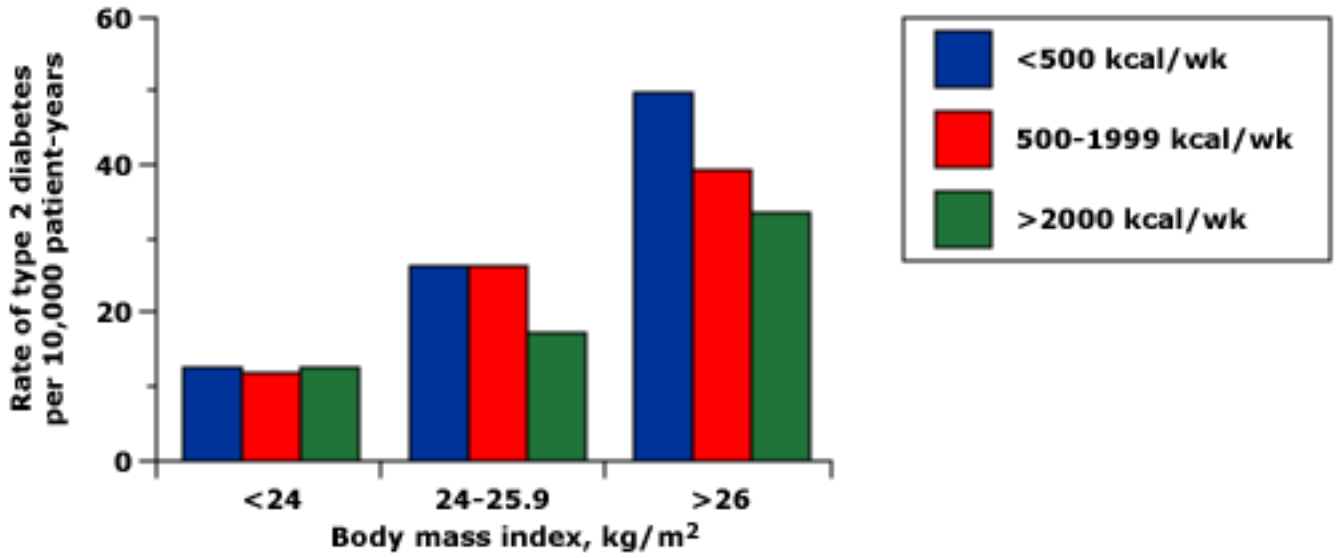
Dieet

- Doelen:

- Haalbare doeleinden →initieel 5-7% gewicht reductie.
- Behouden van gewichtsreductie!

Fysieke activiteit

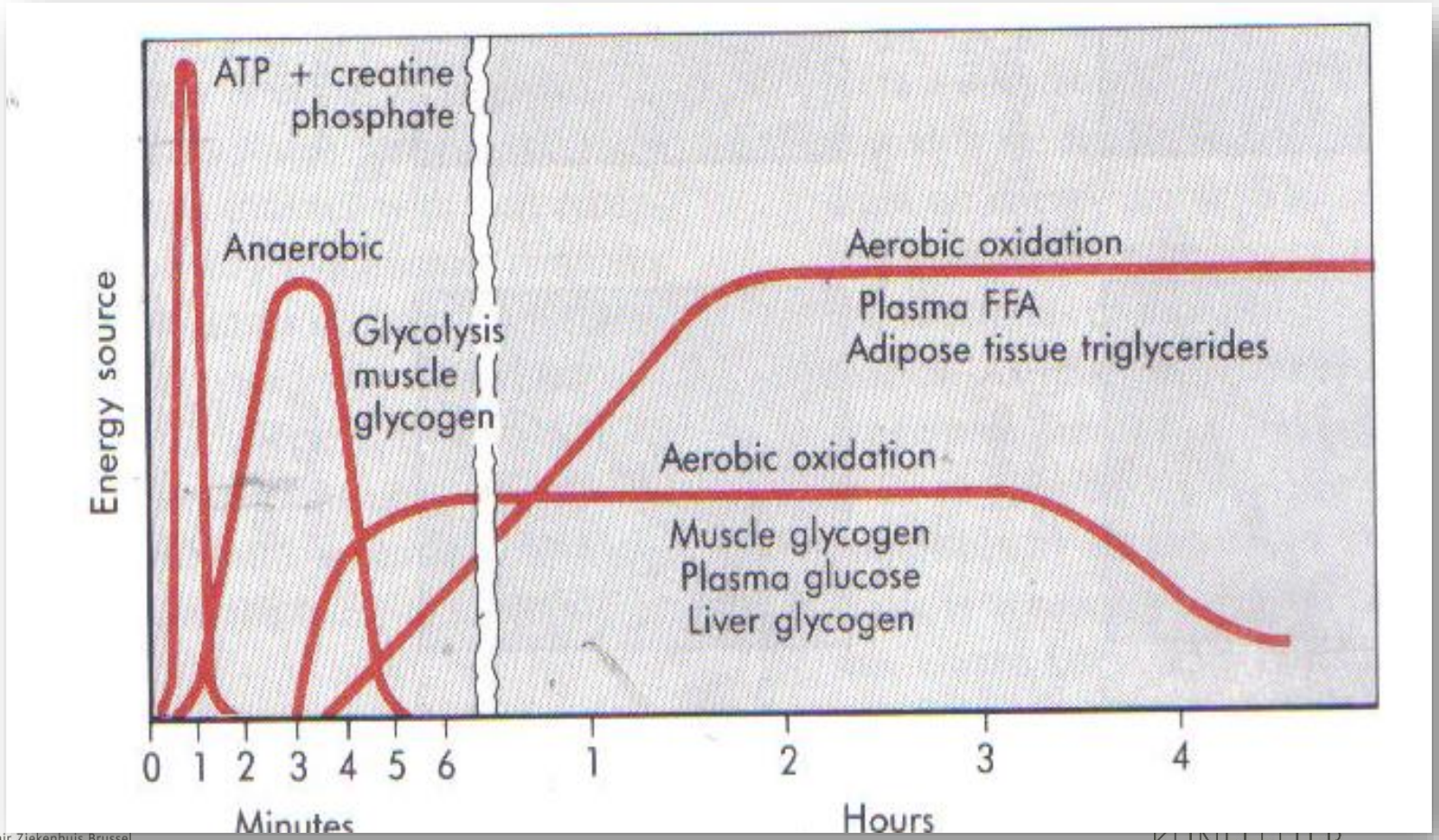
Importance of body weight and exercise on development of type 2 diabetes



Adjusted incidence of type 2 diabetes mellitus in 5990 men in relation to body mass index (BMI, in kg/m^2) and the level of physical activity (in kcal/wk). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for men with a BMI below 24.

Data from: Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991; 325:147.

Energy sources during exercise




UNDER ARMOUR

Figure 2. Predicted weight change over time by PAL change category among men in the Aerobic Center Longitudinal Study (ACLS) cohort. PAL=average daily physical activity level expressed as the ratio of total energy expenditure to the resting metabolic rate (TEE/RMR). Models adjusted for age, sex, height, baseline weight, and smoking. DiPietro, et al. Int J Obesity. 28:1541-1547,2004.

Public Health Strategy for Obesity Prevention and Control

Level	State	Intervention
Primary	Normal weight (BMI 20-24.9)	**30 min or more** of *moderate* intensity activity on most days
Secondary	Overweight (BMI 25-29.9)	**45 to 60 min** of *moderate* intensity activity on most days
Tertiary	Obese (BMI ≥30)	**60 to 90 min** of *moderate* intensity or **35 min** of *vigorous* activity on most days

Saris, et al., Obesity Reviews. 4:101 -114, 2003

Body composition changes in obese adults following diet, exercise or diet plus exercise intervention

Variable	Diet	Exercise	Diet and exercise
Weight lost, kg	10.7 ± 0.5	2.9 ± 0.4	11.0 ± 0.6
Percentage body fat decrease	6.0 ± 1.0	3.5 ± 0.5	7.3 ± 0.8
Weight loss maintained at one year	6.6 ± 0.5	6.1 ± 2.1	8.6 ± 0.8

Values are means (± SE).
Adapted from Tremblay, A, Despres, J, Maheux, J, et al, Med Sci Sports Exerc 1991; 23:1326.

UpToDate

Conclusie en “take home message”

- De prevalentie van metabool syndroom (MS) en diabetes mellitus type 2 (DM 2) ligt hoger bij patiënten met het Klinefelter syndroom (KS).
- MS en DM 2 kunnen bijdragen tot verhoogde morbiditeit en mortaliteit bij patiënten met het KS.
- Er is een sterke associatie van vetcel massa met MS en DM 2 (insulineresistentie).

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KLINEFELTER KLINIEK

Conclusie en “take home message”

- Bij patiënten met KS is er een hogere vetcelmassa in vergelijking met de algemene bevolkingen dit al vanaf de kinderjaren.
- Regelmatige opvolging van metabole parameters is dus wenselijk.
- Levensstijlaanpassingen staat centraal in de preventie en behandeling (indien nodig medicamenteuze therapie).

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KLINEFELTER KLINIEK


The End