Steroid Use in DMD

current recommendations and future research

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Duchenne muscular dystrophy (DMD)

Background

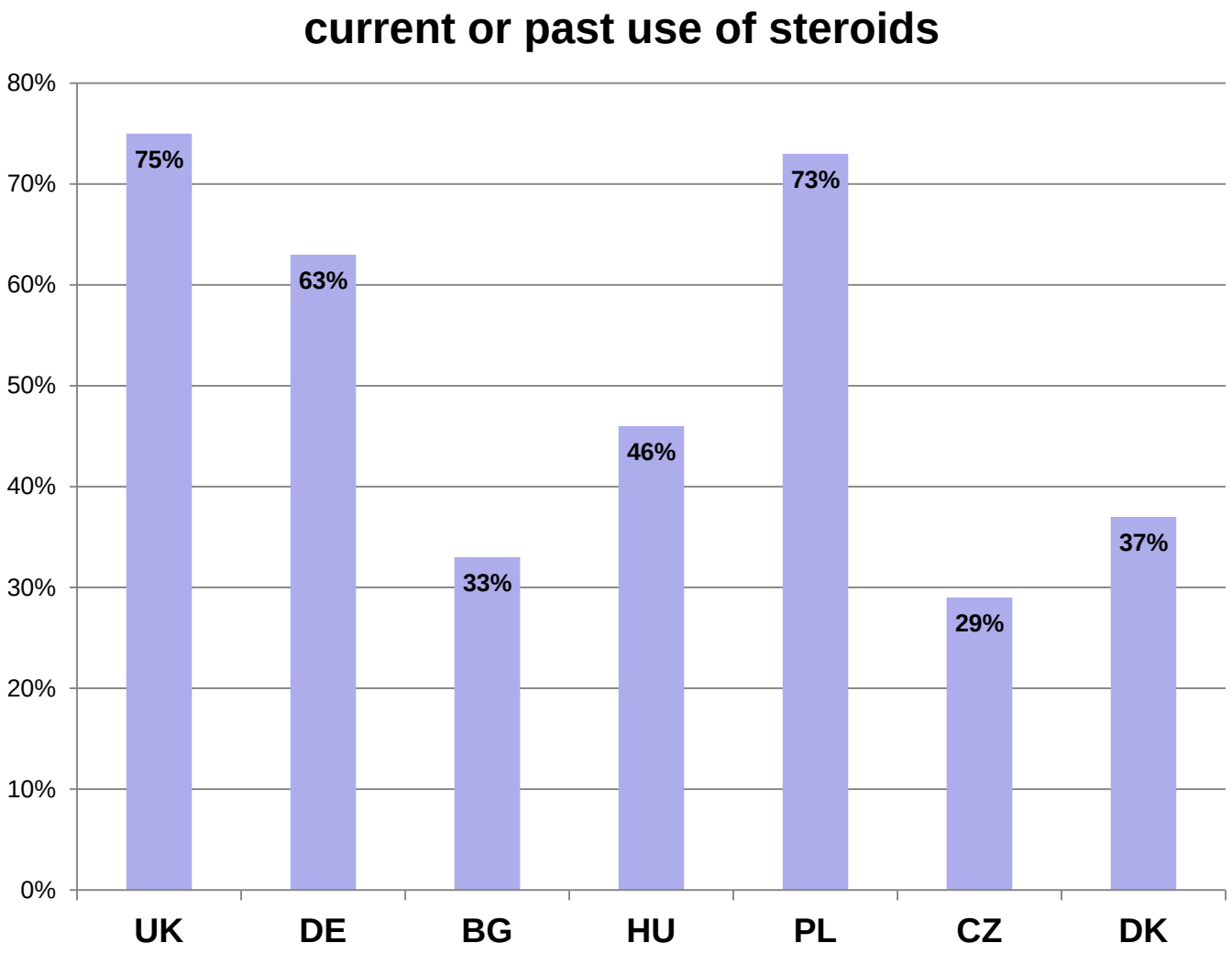
- X-chromosomal recessive muscular dystrophy
- Incidence 1 : 5000 male newborns: rare disorder
- Manifesting in infancy and following a progressive clinical course
- There is no causal therapy yet
- Major therapeutic options: steroid use, non-invasive ventilation, early appropriate cardioprotective medication and spinal surgery
- Cardiac dysfunction is observed to be the limiting factor for life expectancy

Steroid Use in DMD

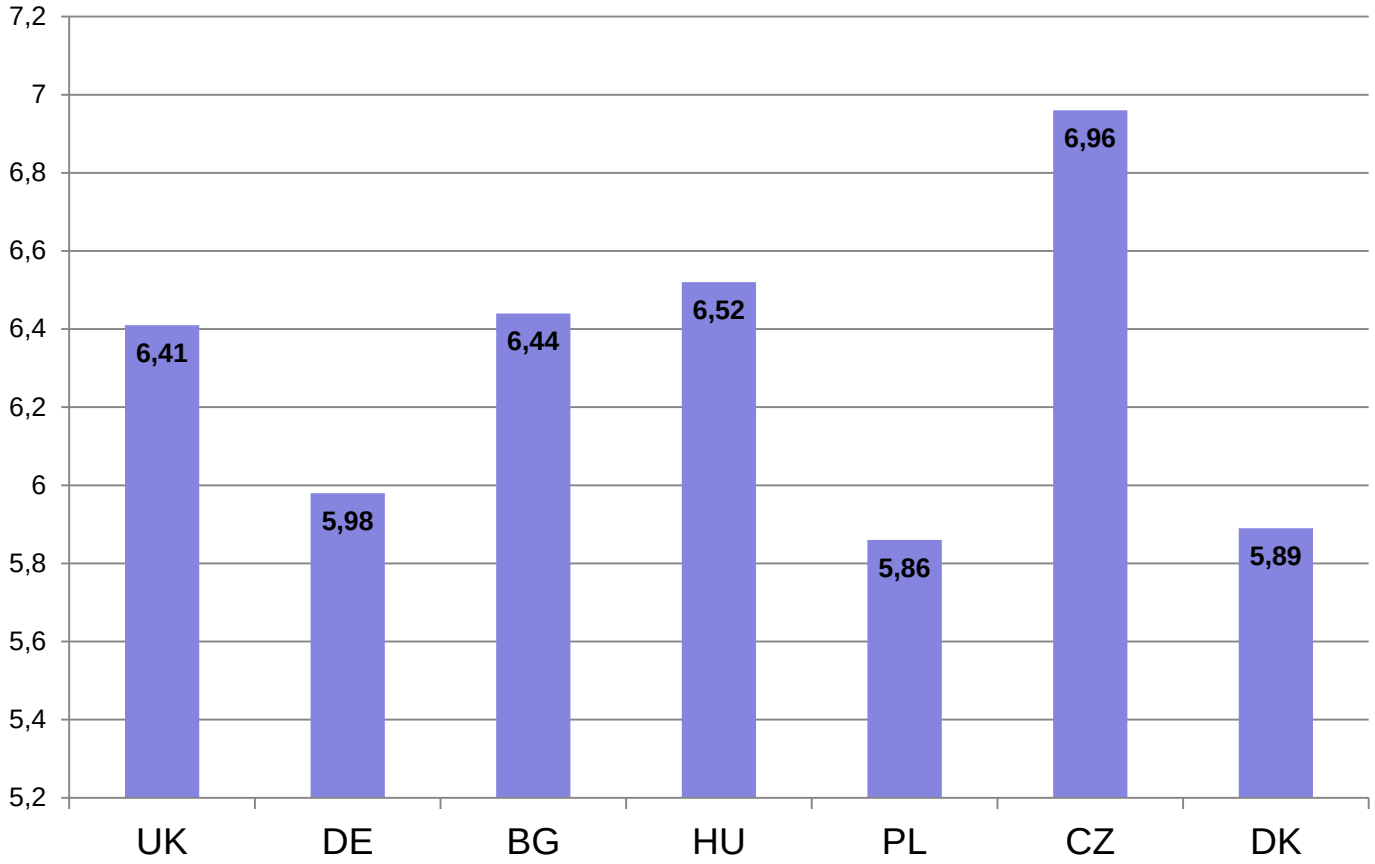
Background

- Steroid use in DMD is reported since 1974
- **Manzur et al., Cochrane Database Syst Rev. 2008**

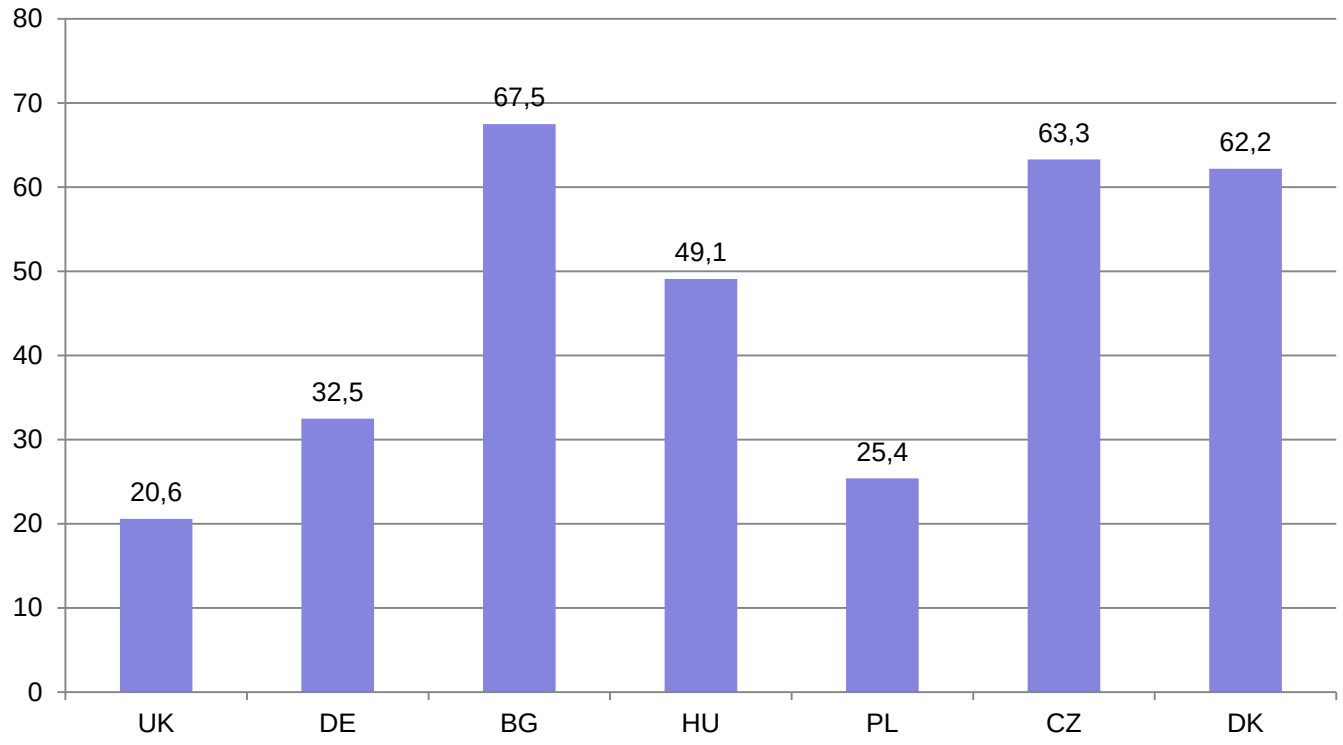
- Different regimens are used
  - Prednisone, Prednisolone 0.75 mg/KgBW/day or 10 days on / off
  - Deflazacort 0.9 mg/KgBW/day or 1.-20. day/month
  - Prednisone on weekends 10 mg/KgBW/2 days
- There is strong evidence for positive effects
- Side effects have to be considered
- The „best regimen“ is not evaluated so far!
- Long-term benefits and hazards cannot clearly be evaluated today


current or past use of steroids
80%
70%
60%
50%
40%
30%
20%
10%
0%
75%
63%
33%
46%
73%
29%
37%
UK
DE
BG
HU
PL
CZ
DK

Mean age at start of steroids (yrs)



Percentage of patients that have never taken steroids



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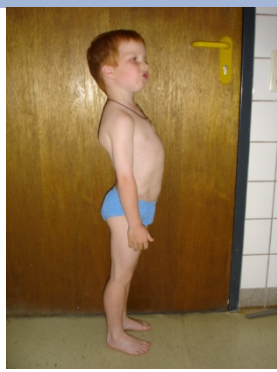

Positive effects – recommendations for steroid use

- Improvement of muscle strength and function over 6 months, stabilizing for up to 2 years
- Extended ambulant walking for 2-5 years
- Delay of cardiac dysfunction
- Delay of respiratory muscle involvement and of VC decline
- Delay of spinal surgery
- Increase of life span (1960: mean 14,4 years, today: mean 24,5 years)
- Improvement of quality of life

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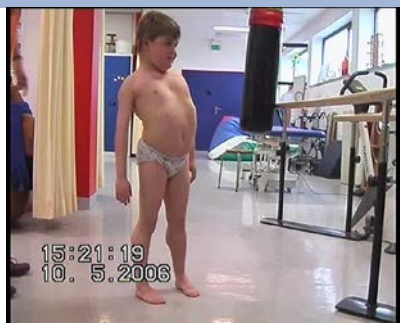
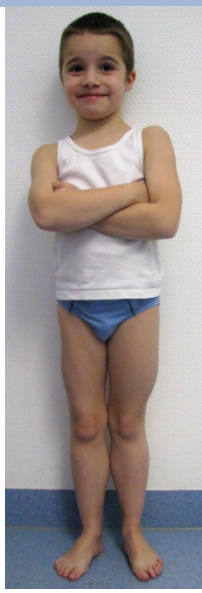


Side effects – appropriate monitoring necessary

- Excessive weight gain, decreased height
- Cushingoid appearance
- Cataracts
- Excessive hair growth
- Delayed puberty
- Glucose intolerance
- Increased arterial blood pressure
- Gastro-esophageal reflux, gastric ulcer
- Osteoporosis / pathologic fractures
- Behavioural abnormalities

Steroid Use in DMD



Own experiences

- We usually recommend deflazacort 0.9 mg/KgBW/day since the age of 5 years
- In case of side effects we suggest to switch to prednisone 10 days on / off

- Excessive weight gain îs not observed in all patients
- Decreased linear growth becomes a problem in boys elder than 10 years
- Vertebral and other pathologic fractures are not very often in our cohort
- Depressive mood is observed in many patients since the age around ten years, not only depending on steroid use
- Variable CNS – dysfunction needs early standardized testing
- Psychological care has to be started early during the clinical course
- Puberty and sexuality are becoming more important for the boys
- Many patients also use complementary medicine

Steroid Use in DMD

Open questions for future research

- What are the exact pathophysiological mechanisms of steroid therapy?
- What steroid regimen is the best addressing positive and negative effects?
- Can synergistic medication improve positive effects and reduce side effects?
- Complementary medicine: Is there an evident interaction with steroids?

  Does it play a role for study design and results?
- Cardiac dysfunction as a life limiting factor? Appropriate investigations, start and kind of medication?

Steroid Use in DMD

Open questions for future research

- Steroid-related adverse events or natural history?

- How can endocrinological aspects (growth, weight gain, puberty, sexuality and bone health) be monitored and treated?
- Is incontinence a common feature? What is the appropriate monitoring and treatment?
- What about renal function? Can long-term steroid therapy influence tubular function?

  Impact on bone density?
- Variable CNS dysfunction in DMD. Cerebellar affection and motor learning? In elder patients psychiatric symptoms like depression, anxiety and/or personality disorders
- **What can be improved for inclusion and transition??**

FOR-DMD

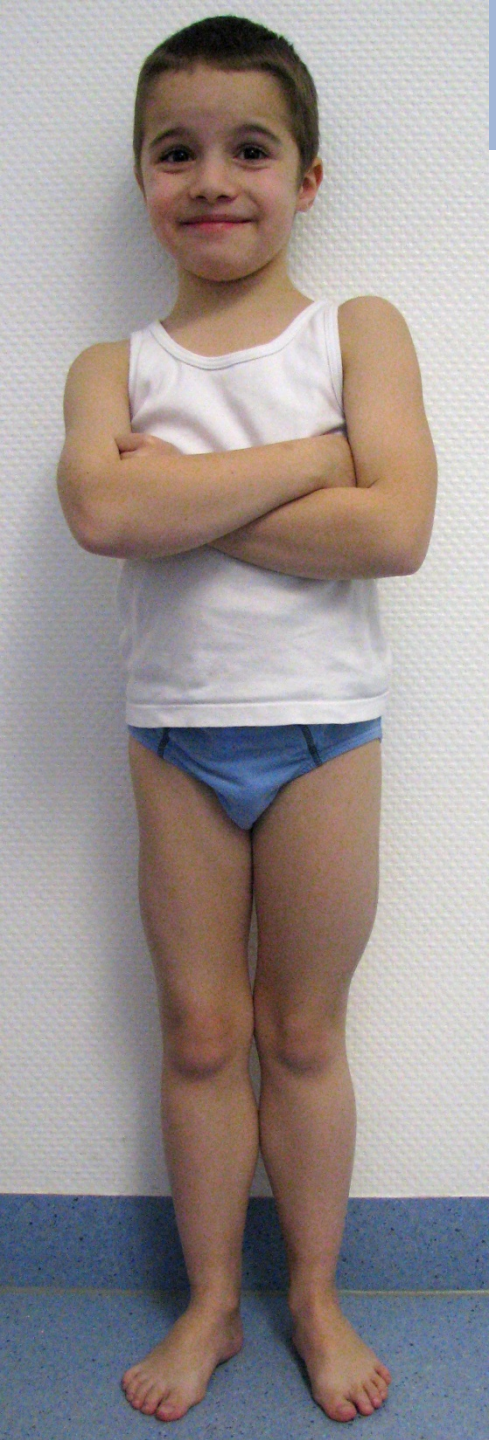
International, multi-centre study (in at least 39 muscle clinics in the US, Canada, UK, Germany, Italy) which will compare benefits and side effects of the three most widely used steroid treatments in DMD

- Daily prednisone (0.75 mg/KgBW/day)
- Intermittent prednisone (0.75 mg/KgBW/day 10 days on / 10 days off)
- Daily deflazacort (0.9 mg/KgBW/day)

- **1. Hypothesis:** Daily prednisone or deflazacort will be of greater benefit in terms of function and subject / parent satisfaction than intermittent prednisone
- **2. Hypothesis:** Daily deflazacort will be associated with a better side effect profile than daily prednisone

- **300 boys aged 4-7 years, not previously treated with steroids,** will be randomized into the three groups
- All boys will complete a minimum of 3 years (36 months)
- All boys will remain on study drug until the last boy completes the 36 months, may be up to 60 months

- **Primary outcome:** Time to stand from lying, forced vital capacity, subject/parent satisfaction with treatment
- **Secondary outcome:** Regimen tolerance, adverse event profile, secondary functional outcomes including the 6-minute walk test, quality of life, and cardiac function.



Thanks!