Duchenne Muscular Dystrophy: Steroids – A Growing Issue

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Duchenne ACTT Conference, 8-9 March 2020

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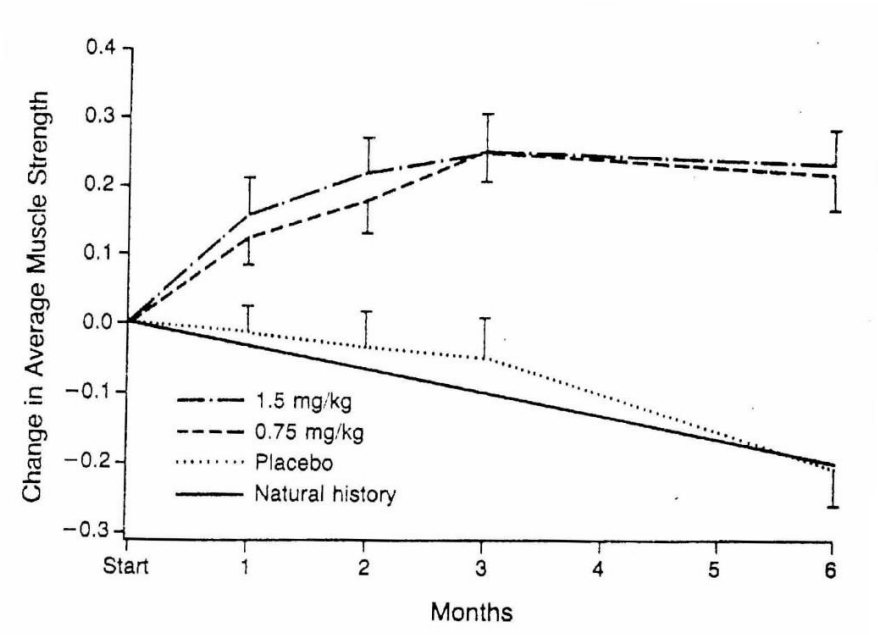
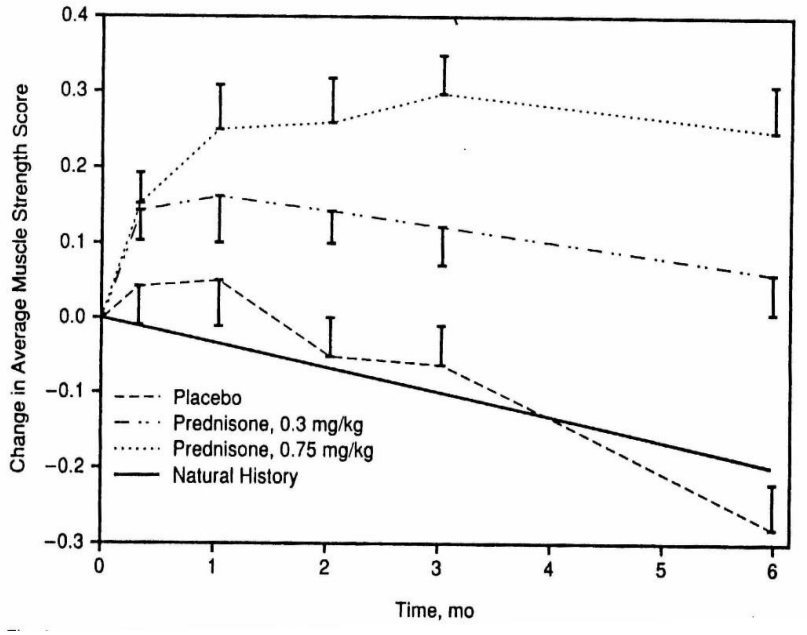
Glucocorticoids for DMD

- **Glucocorticoids: evidence based standard of care for treatment of DMD**
  - **Drachman et, Lancet 1974 – open label prednisone in 14 patients; ages 3-10, 1-28 months treatment**
  - **Brooke et al, Arch Neurol 1987 – RDBPC trials**





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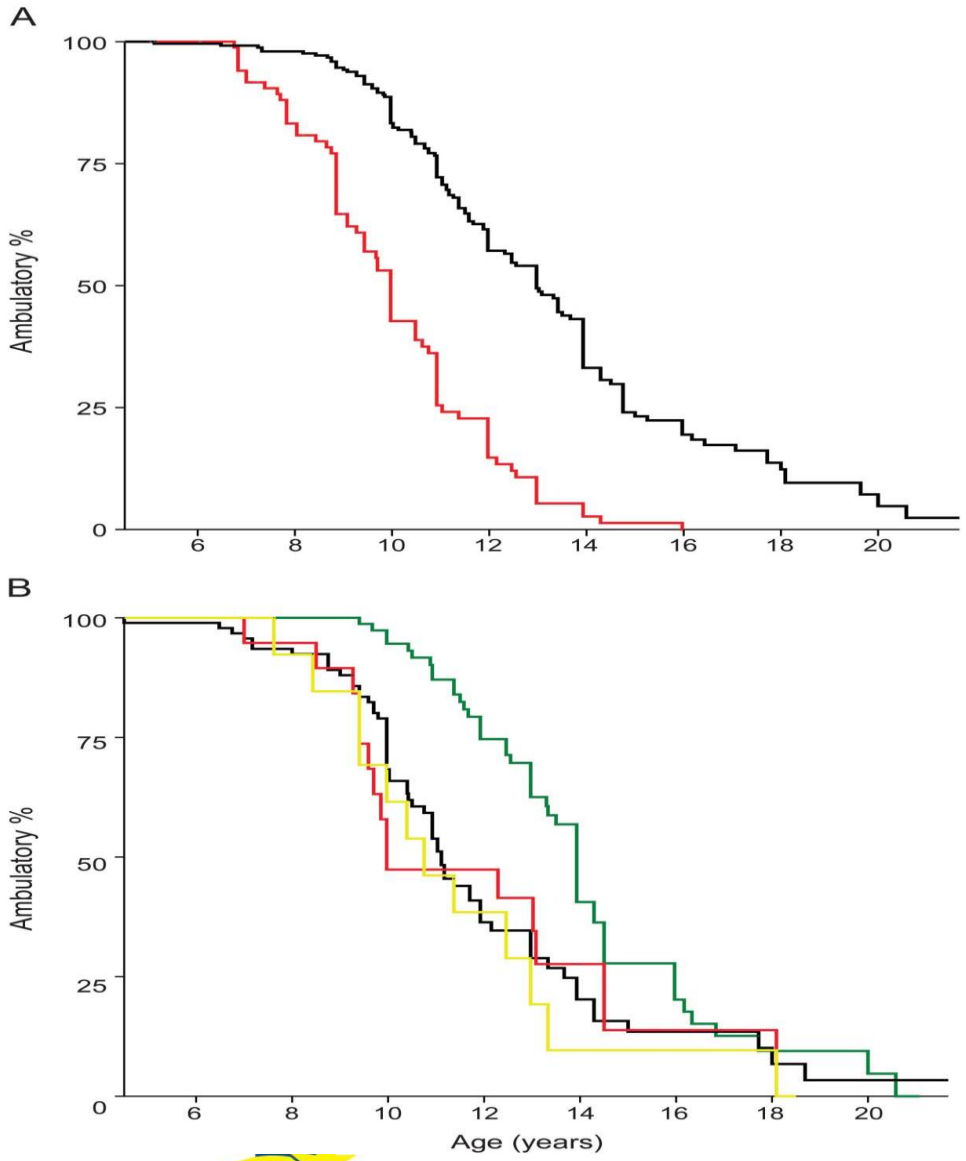
- ***Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy.*** *Ricotti V et al, NorthStar Clinical Network. J Neurol Neurosurg Psychiatry 2013;84:698–705*

- **"The median loss of ambulation was 12 years in intermittent and 14.5 years in daily treatment"**
- **Body mass index mean z score was higher in the daily regimen**



Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study.

Bello et al. Neurology 2015; 85: 1048-55

(A) Participants treated at least 1 year while ambulatory (n 5 252, black line) vs participants treated less or untreated (n 5 88, red line). (B) Participants treated with the most common drug-regimen combinations: daily PRED (n 5 94, black line), high-dose 2 days/week PRED (n 5 19, red line), low-dose intermittent PRED (n 5 14, yellow line), and daily deflazacort (n 5 80, green line). PRED 5 prednisone or prednisolone.

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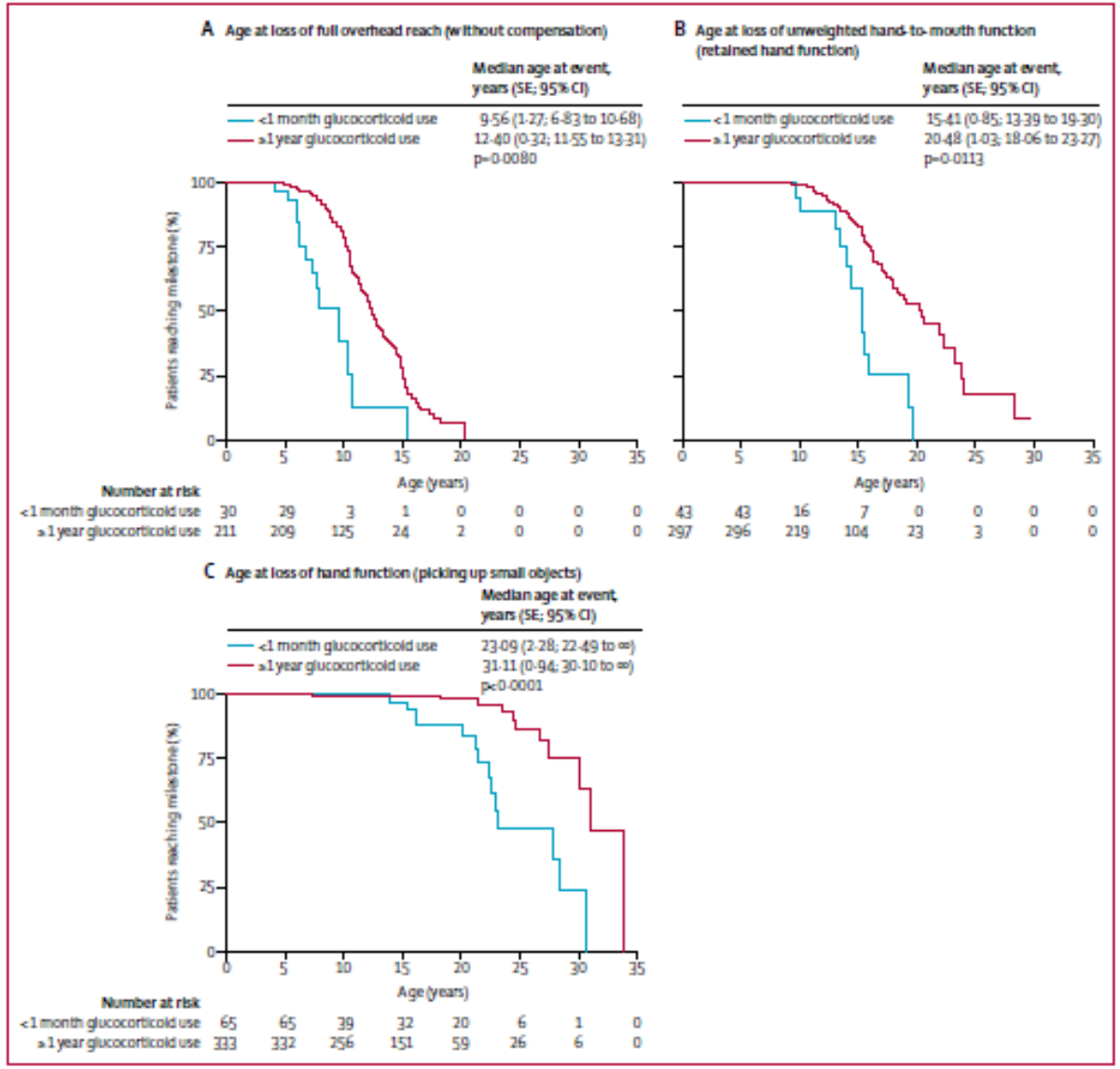

Figure 2: Age at loss of upper limb milestones
Kaplan-Meier analyses comparing cumulative glucocorticoid use (<1 month or never treated vs ≥1 year) for (A) age at loss of full overhead reach function without compensation (reaching Brooke score 3·2); (B) age at loss of unweighted hand-to-mouth function (Brooke score ≥5); and (C) age at loss of distal hand function or ability to pick up small objects (Brooke score 6).

Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study
McDonald CM et al. *Lancet 2018;391:451-61*

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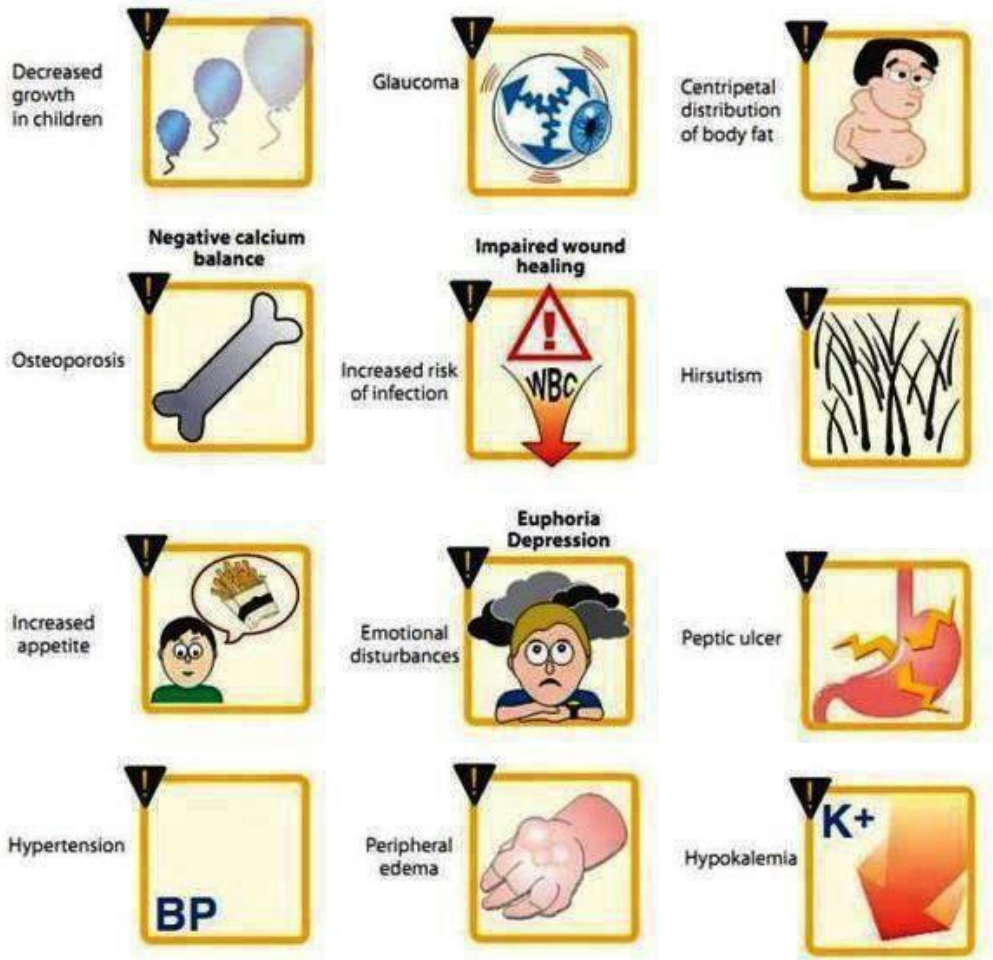
Other Benefits of GC in DMD

- Pulmonary function: Improved pulmonary function (FVC 47% vs 88% for 15 yr olds, Biggar et al, NMD 2006); Moxley et al, J Child Neurol 2010
- Cardiac function: Silverside et al Am J Cardiol 2003; Markham et al Ped Cardiol 2005, NMD 2008; Houde et al, Ped Neurol 2008; Barber et al J Peds 2013
- Spine: 10% spinal curve >20 deg (vs 90% no GC treatment) by age 18 (Biggar et al, NMD 2006); Houde et al, Ped Neurol 2008

CORTICOSTEROIDS
Side Effects



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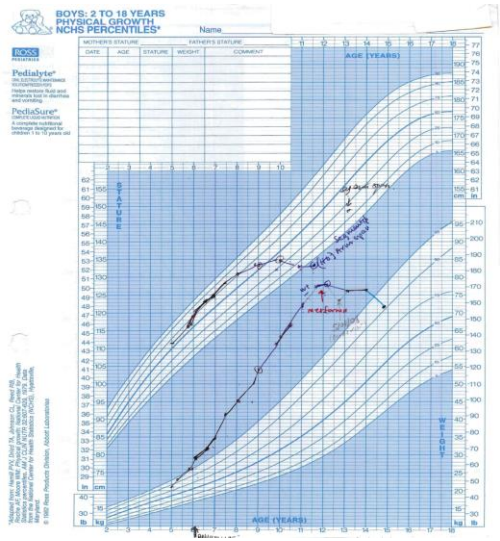
Endocrine: Growth and excessive weight gain, face fullness

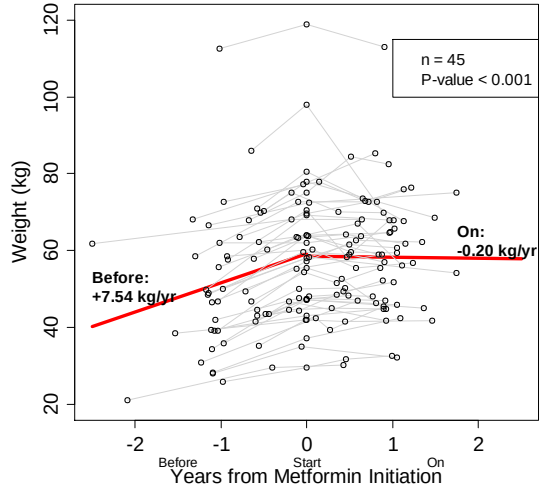


- Patients with height<3rd %tile for age before glucocorticoid therapy 9.4% (9/96)
- Patients with height<3rd %tile for age after long-term glucocorticoid use 72.3% (68/94)
- Patients with same or lower weight %tile at most recent clinic visit 86.3% (82/95)
- Patients with higher weight %tile at most recent clinic visit 13.7% (13/95)

Long-Term Outcome of Interdisciplinary Management of Patients with Duchenne Muscular Dystrophy Receiving Daily Glucocorticoid Treatment. Wong BL et al , J Peds 2017; 182:296-303

Change in Weight Gain: All Subjects

Rate of weight gain decreased from +7.5 kg/yr before to -0.2 kg/yr on metformin



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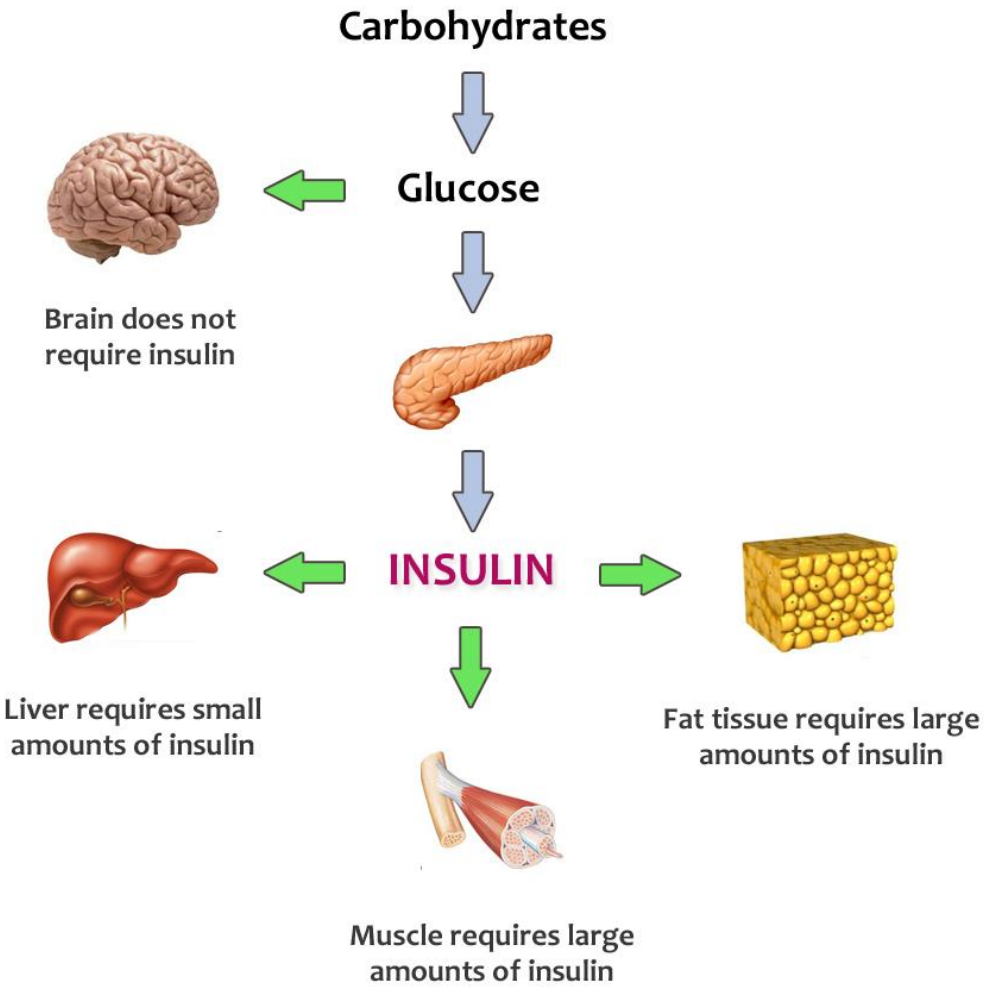
INSULIN RESISTANCE

Insulin resistance in DMD patients

- **Evidence of Insulin Resistance and Other Metabolic Alterations in Boys with Duchenne or Becker Muscular Dystrophy.** ***Rodriguez-Cruz M et al. International Journal of Endocrinology 2015***
  - ***"Obesity, hyperinsulinemia, and IR were observed in DMD/BMD patients and are independent of corticosteroids treatment. "***

What is Insulin?

- Peptide hormone composed of 51 amino acid residues
- Produced in the Islets of Langerhans in the pancreas
- Causes most of the body's cells to take up glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen in the liver and muscle
- Latin *insula* for "island"



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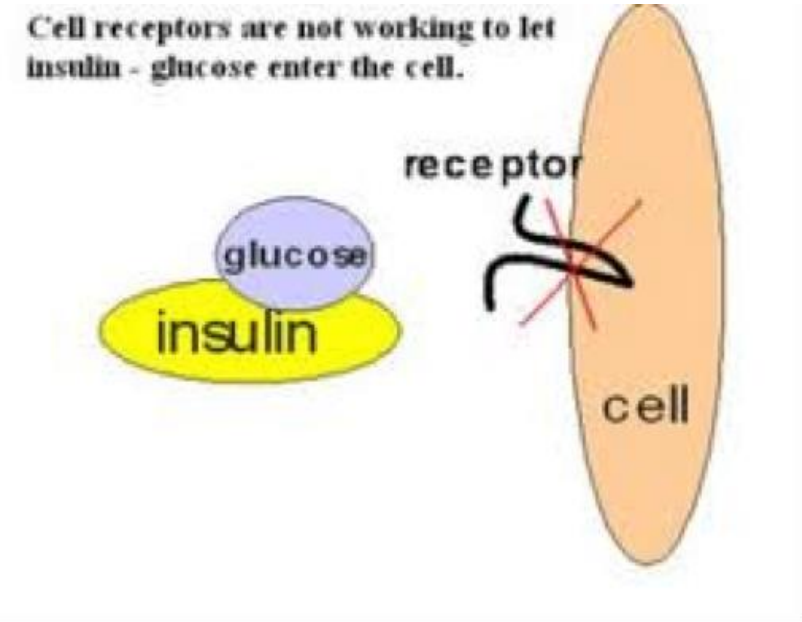

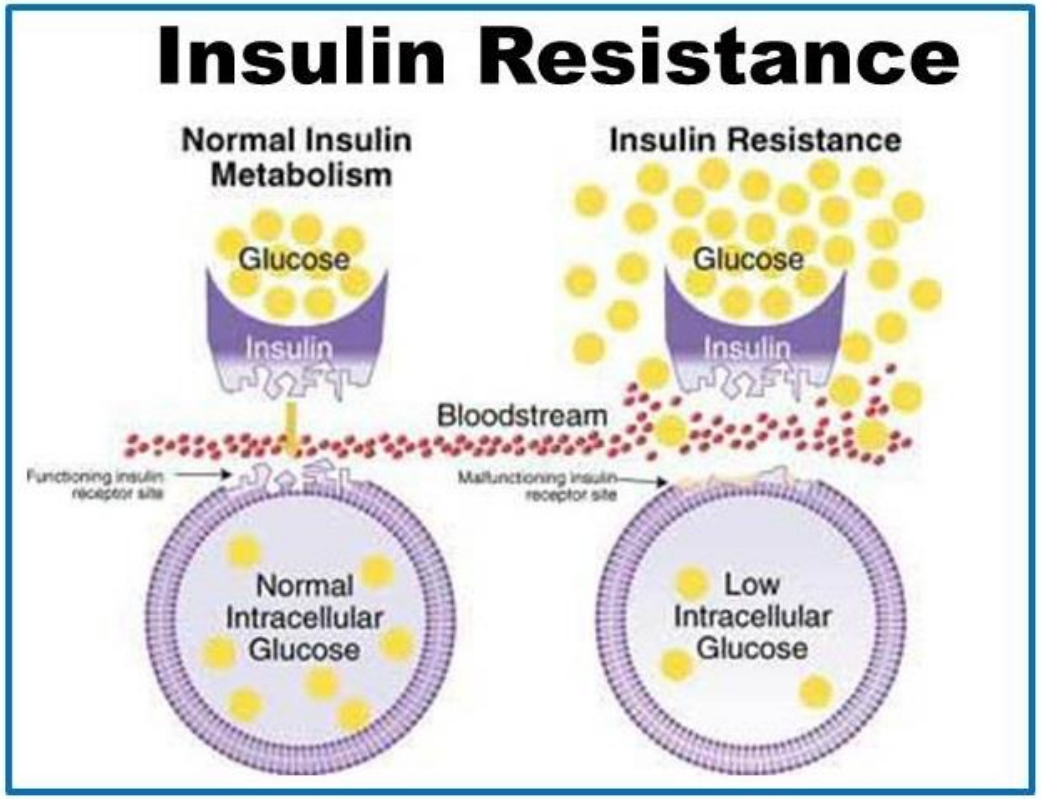

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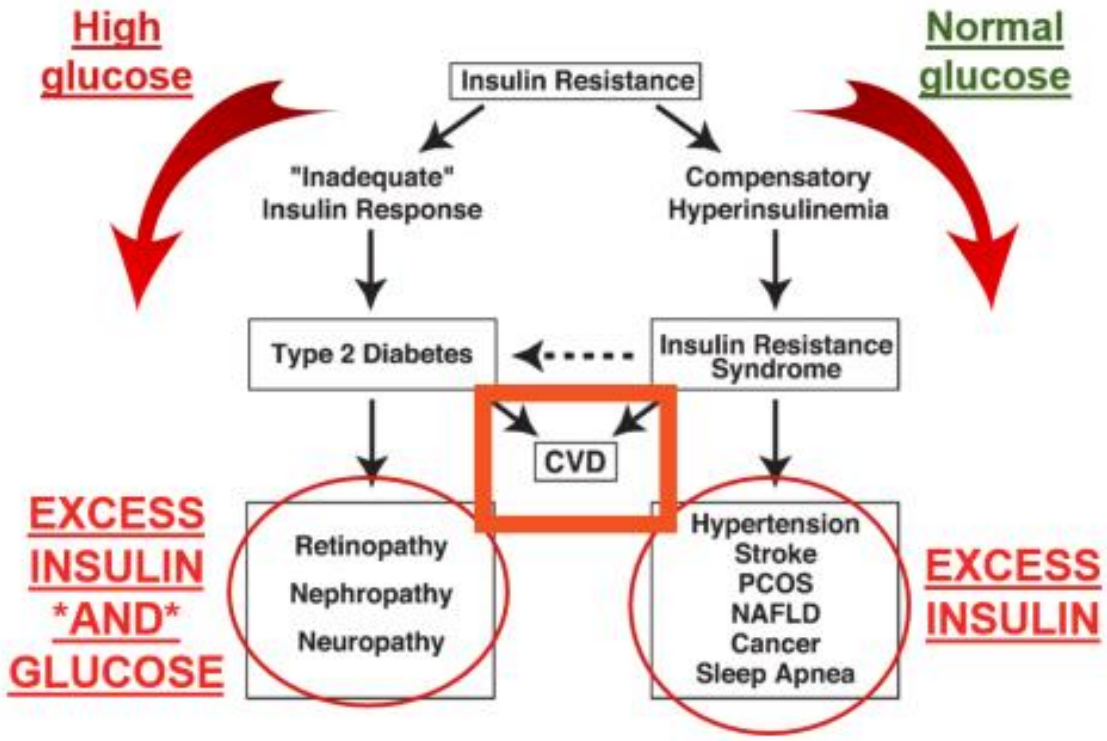

"People who develop type 2 diabetes usually pass through earlier stages of insulin resistance and prediabetes, although those often go undiagnosed. Insulin resistance is a syndrome (a set of signs and symptoms) resulting from reduced insulin activity; it is also part of a larger constellation of symptoms called the metabolic syndrome"

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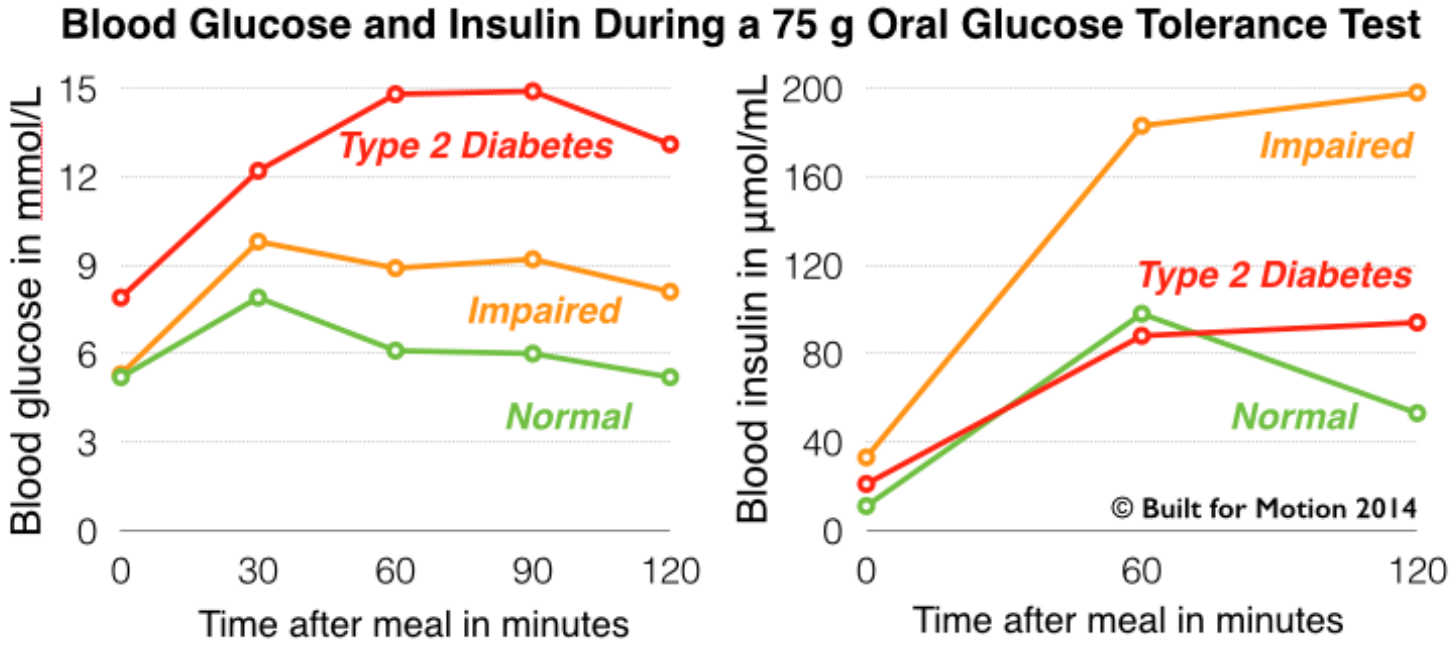
- Fasting insulin, glucose

QUICKI – Quantitative Insulin Sensitivity Check Index
(Insulin sensitivity the inverse of Insulin resistance
1/ log fasting insulin and log fasting glucose in mg/dl
IR <0.339

- *Oral Glucose Tolerance Test: Glucose, Insulin*



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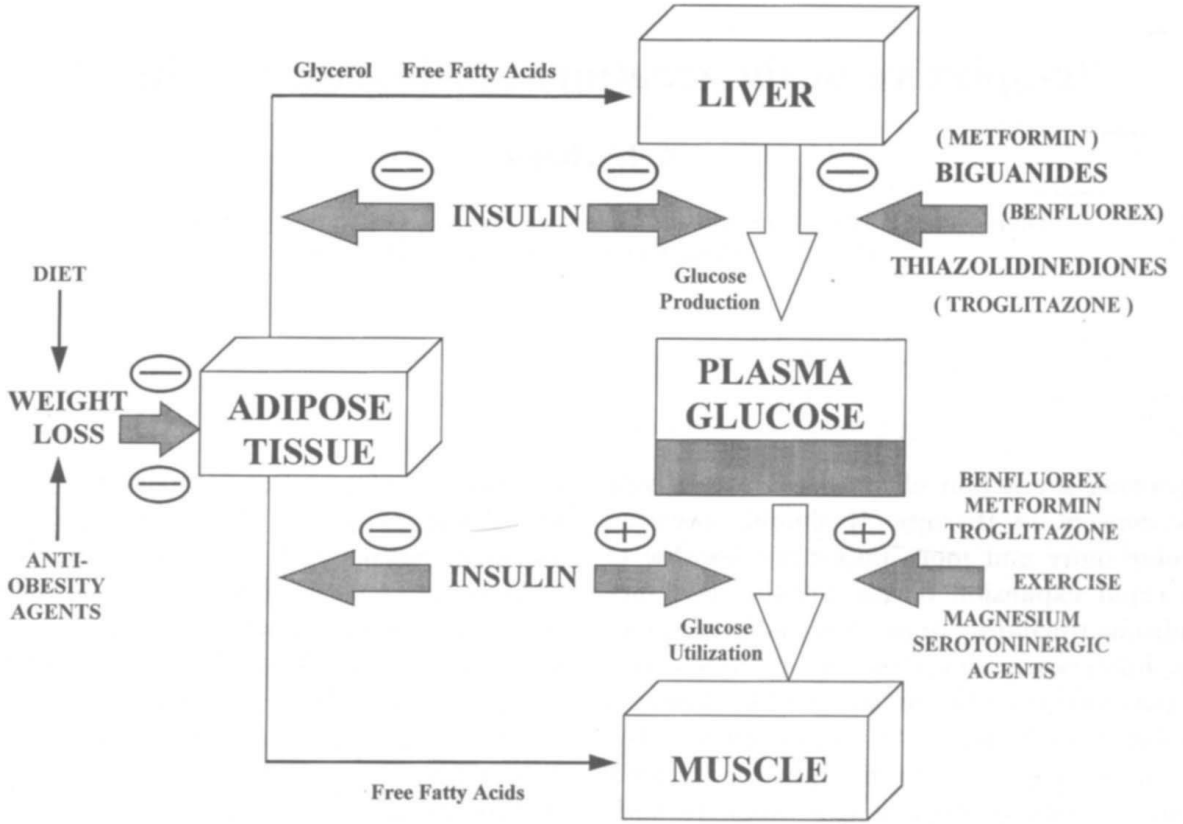
Approaches to treatment of Insulin Resistance:

- reduction of excessive weight in obese patient
- modification of dietary habits
- pharmacological : metformin

Perspective in the treatment of Insulin Resistance.
A.J. Sheen



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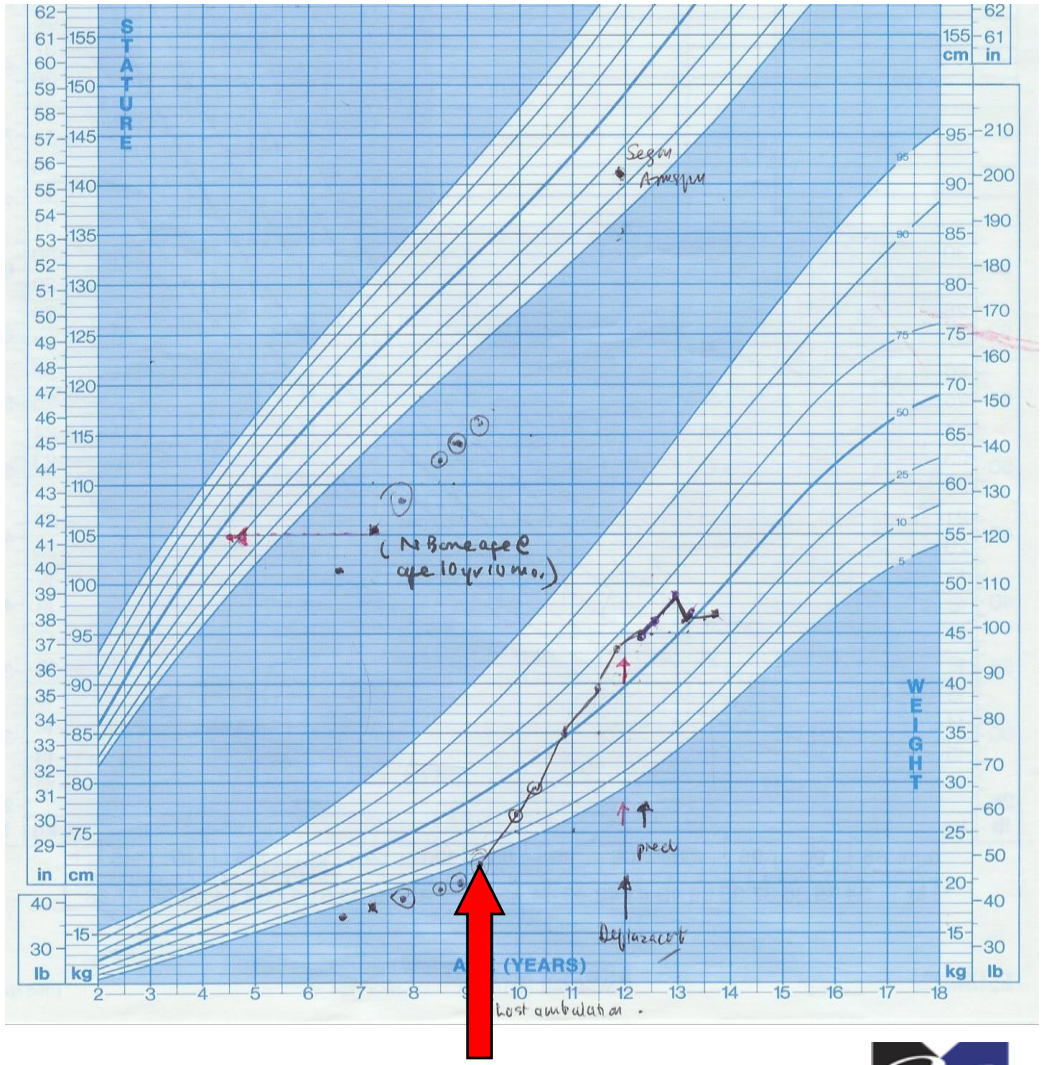
Obesity with loss of ambulation (steroid naïve DMD patient) - dietary need to decrease daily caloric intake



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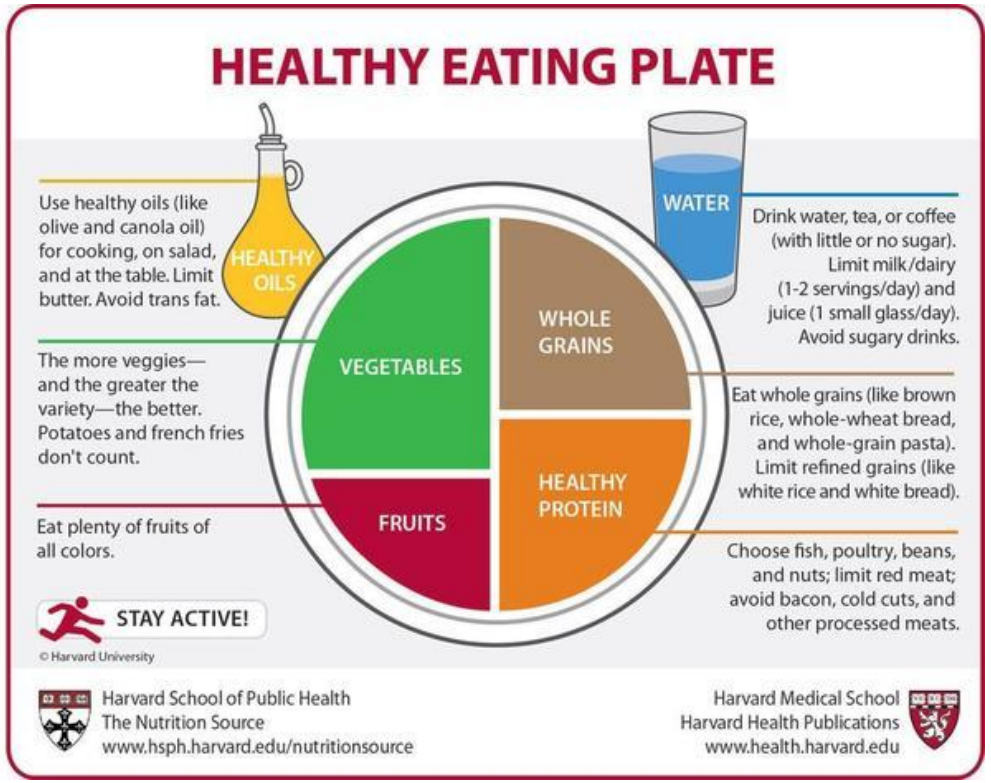
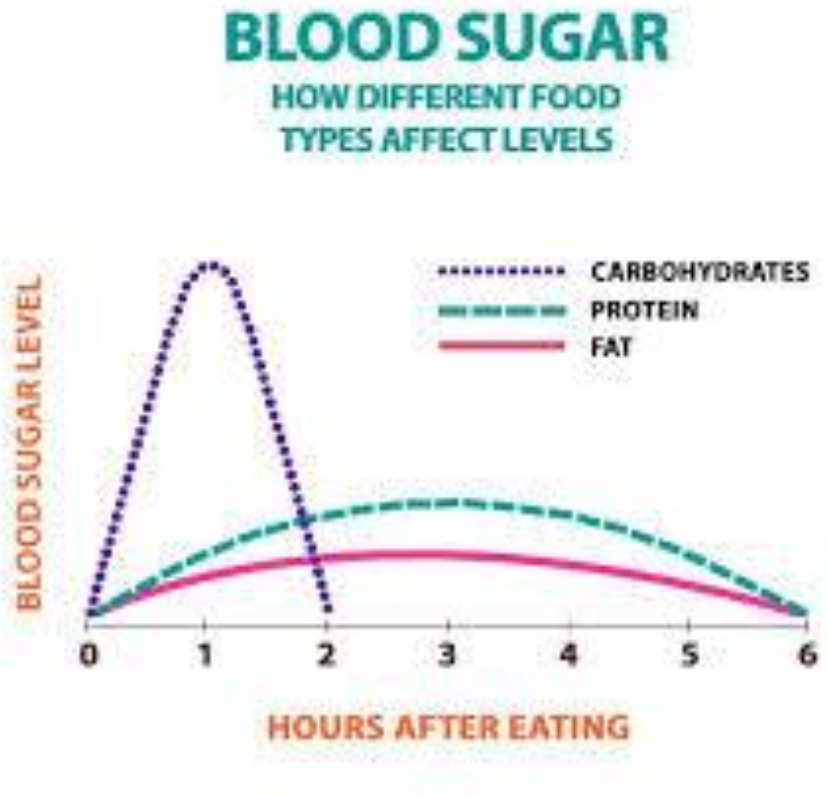
Dietary Health education





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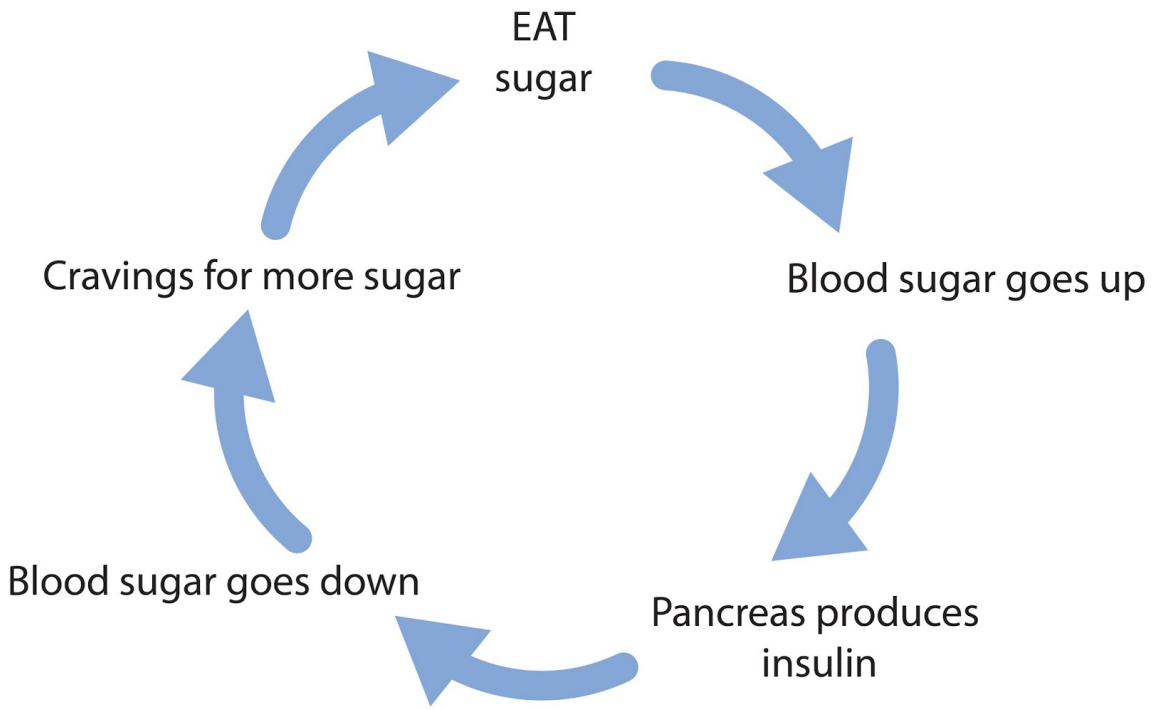

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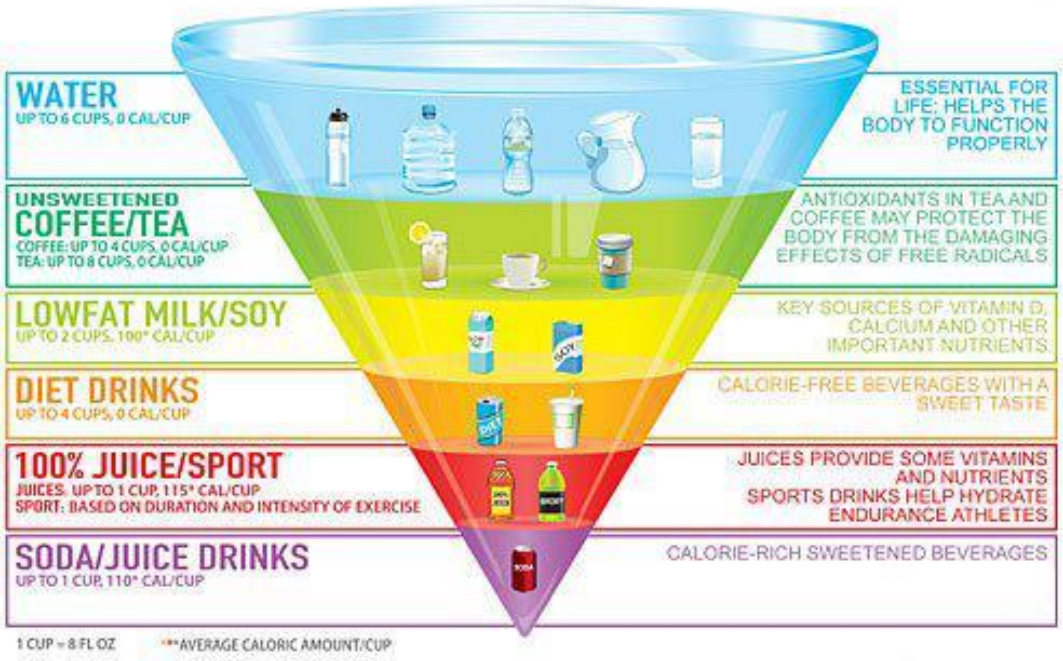

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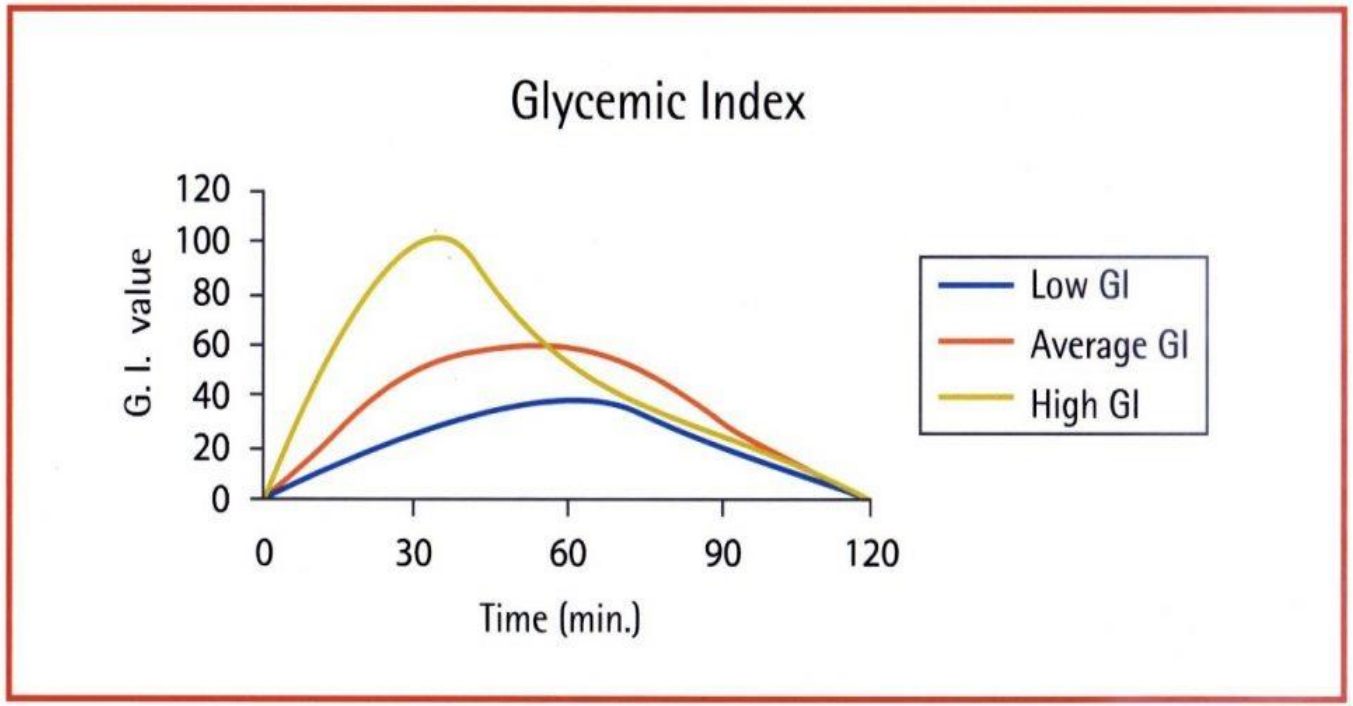
Low glycemic index diet



High Glycemic Foods = 70+ (STOP - Try to Avoid)
Moderate Glycemic Foods = 55-69 (Use with Caution)
Low Glycemic Foods = 0-54 (GO - Ideal to Consume)

METFORMIN

Metformin studies

- Metformin for Weight Loss in Pediatric Patients Taking Psychotropic Drugs. 12 wk open label metformin 500 mg tid, n=19, 15 with significant loss of weight and BMI. *Morrison JA et al. Am J Psychiatry 2002;159: 655-657*
- Metformin for Obesity in Prebubertal and Pubertal Children: A Randomized Controlled Trial. N=140, 1 g metformin/day vs placebo for 6 months. Decreased BMI z score and improved inflammatory and CV related obesity parameters in prepubertal children, not in pubertal children. *Pastor-Villaescusa B et al. Pediatrics, 1 July 2017;140:e20164285*
- Metformin therapy to reduce weight gain and visceral adiposity in children and adolescents with neurogenic or myogenic motor deficit. N=42, 6 mo metformin vs placebo. Significant decrease in wt and BMI. *Casteels K et al. Ped Diabetes 2010;11:61-69.*
- Treatment with oral metformin improves muscle function in *mdx* mice. *RL Terry. DJ Wells. NM Disorders 2012;22:847*
- Improved muscle function in Duchenne muscular dystrophy through L-arginine and metformin: an investigator-initiated, open-label, single-center, proof-of-concept-study. *Hafner P et al. PLoS ONE 2016;11:e0147634.*
- Effect of Combination L-Citrulline and Metformin Treatment on Motor Function in Patients With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. Hafner P, Bonati U, Klein A, et al. *JAMA Netw Open.* 2019;2(10):e1914171. doi:10.1001/jamanetworkopen.2019.14171
- Metformin Reduces Metabolic Complications of Systemic Glucocorticoid Therapy. Korbonits et al. The Lancet Diabetes and Endocrinology, online February 25, 2020.

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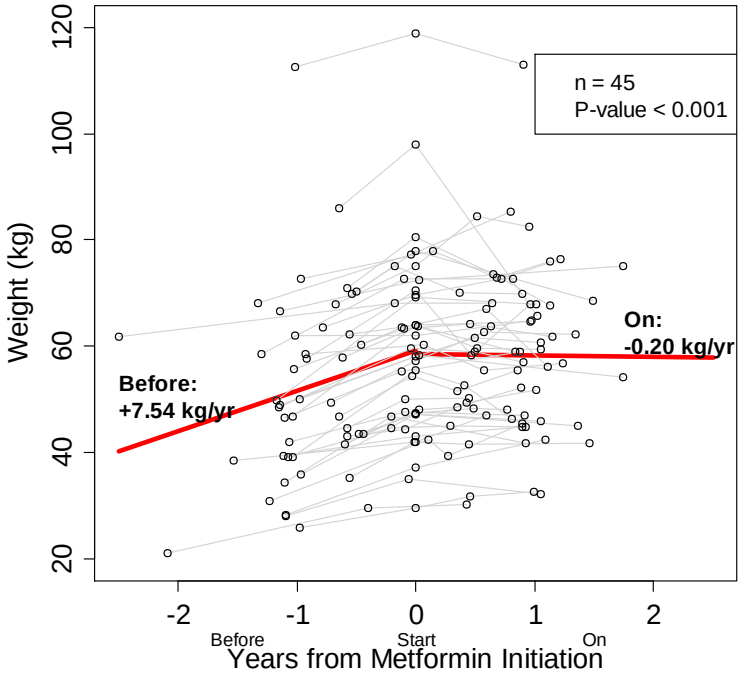
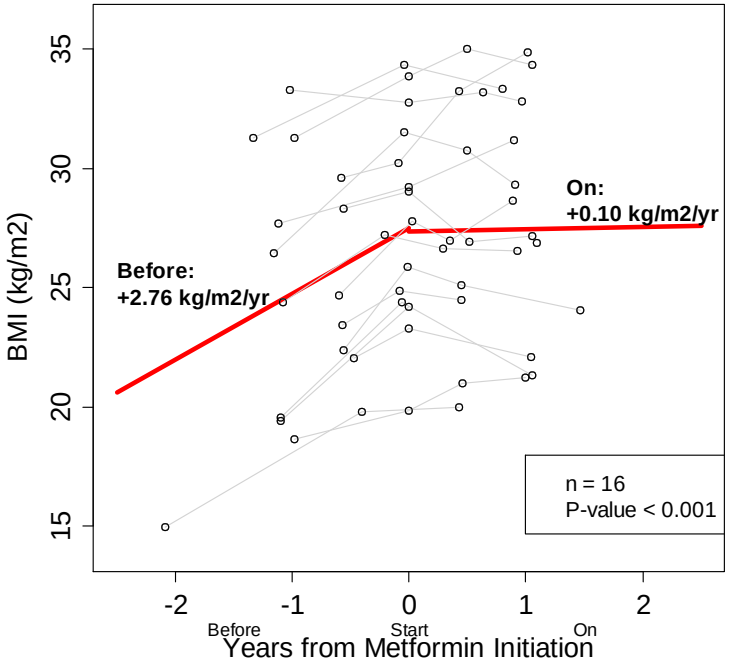
Metformin reduces weight and BMI in DMD boys on long term daily glucocorticoid therapy with excessive weight gain and insulin resistance.

Weatherspoon S, Wong B, Collins J, Rutter M. Neuromusc Disord 2012; 22:866



Change in Weight Gain: All Subjects

Rate of weight gain decreased from +7.5 kg/yr before to -0.2 kg/yr on metformin



Change in BMI Gain: Ambulatory Subjects

Rate of BMI change decreased from +2.8 kg/m^2/yr before to +0.1 kg/m^2/yr on metformin

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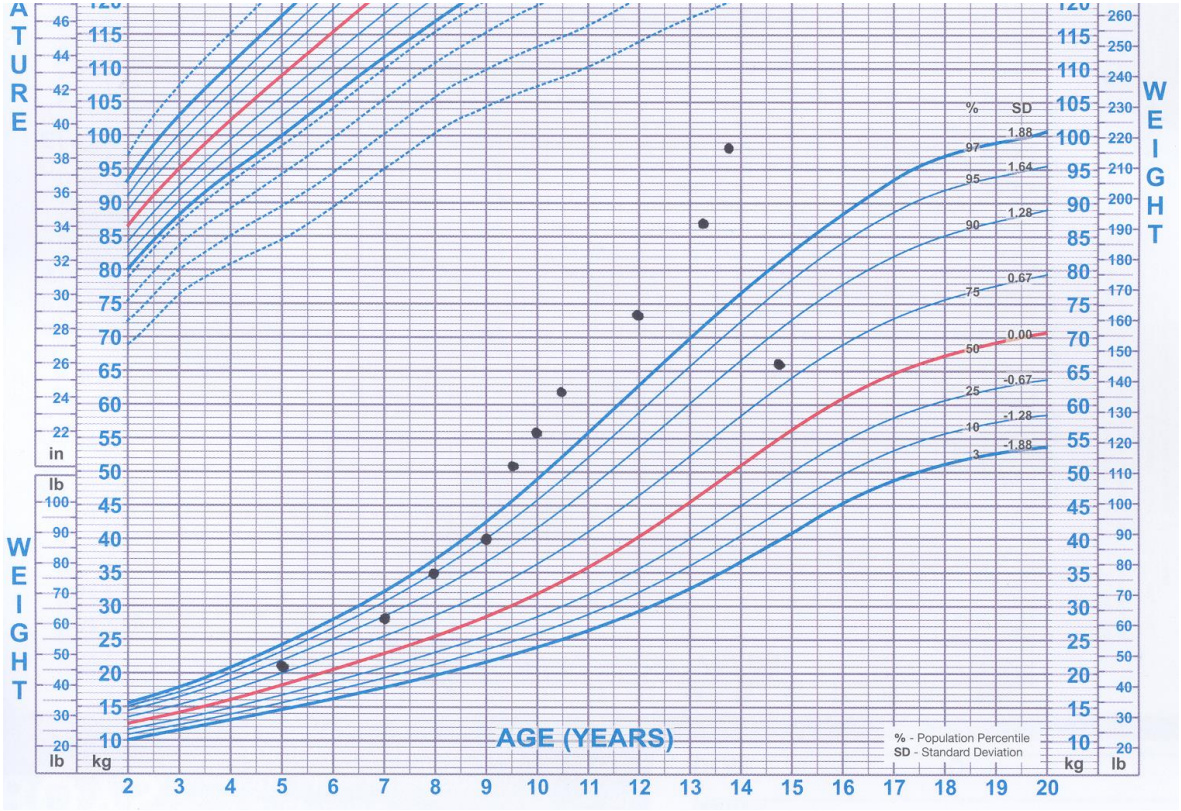
Weight reduction on metformin



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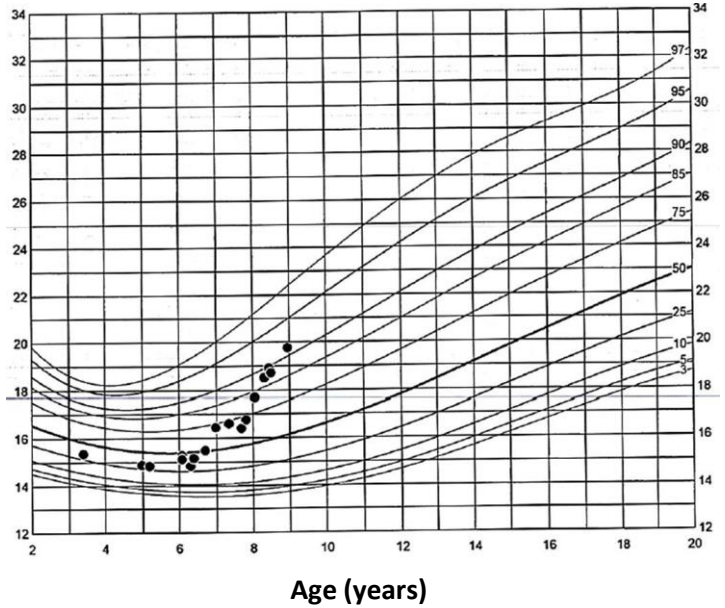
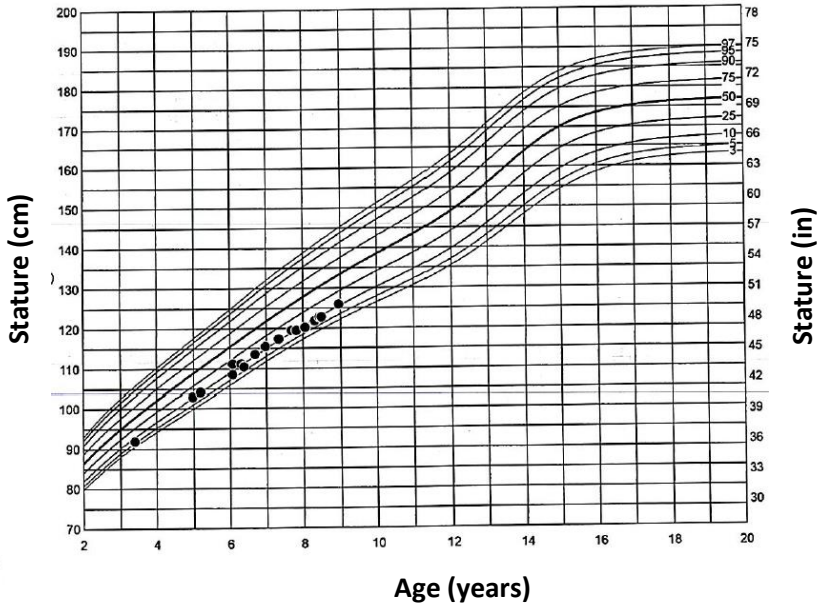
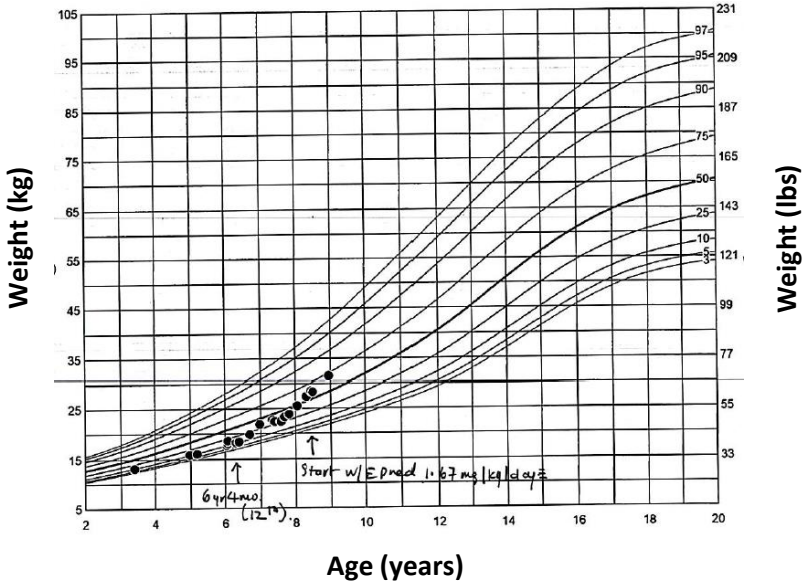
Weekend steroids







Growth Chart: United States SMI-for-age Percentiles (Boys, 2 to 20 years)

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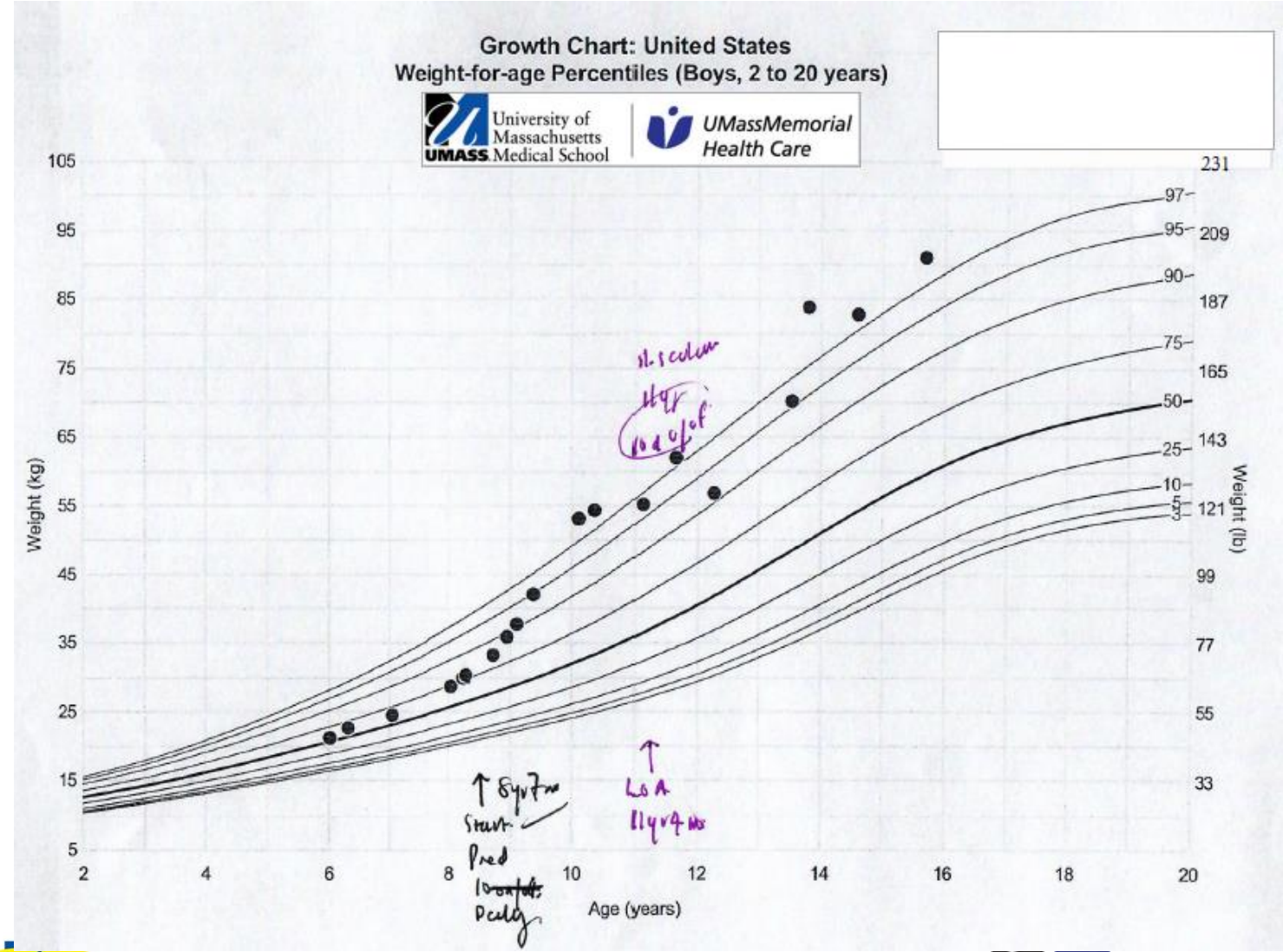
Daily prednisone to 10 days on/off



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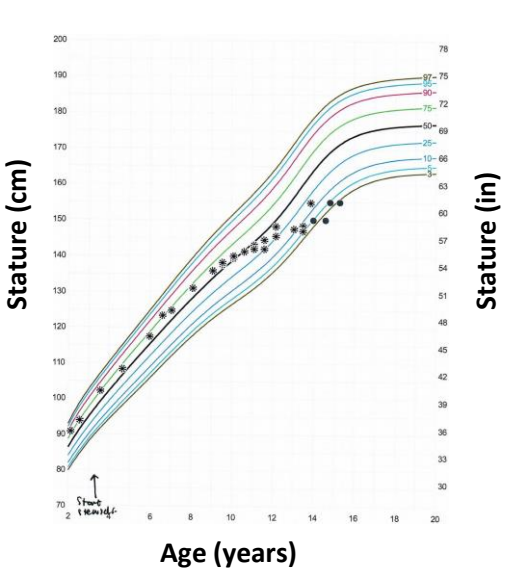
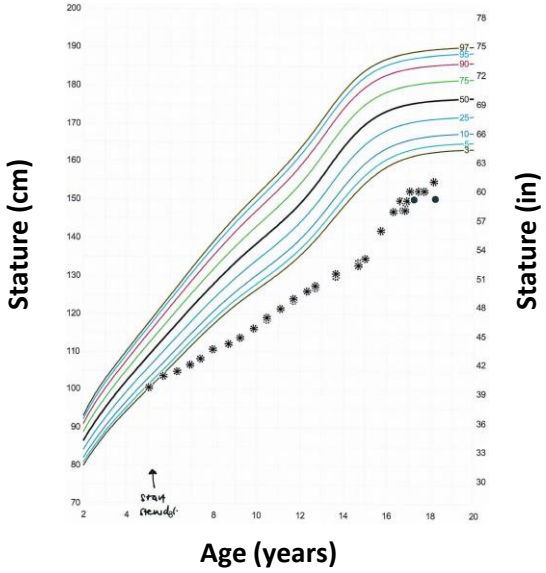
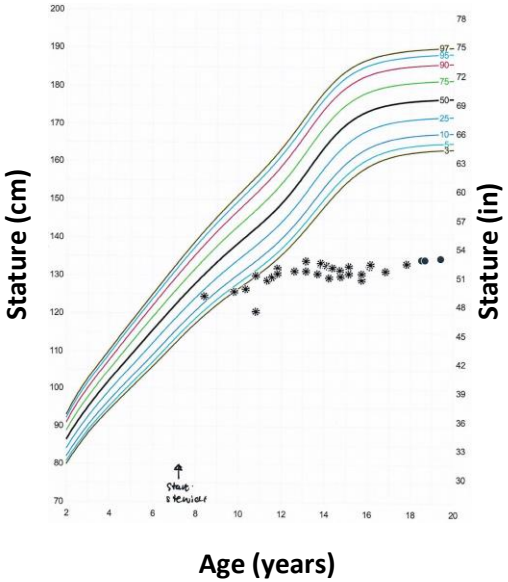
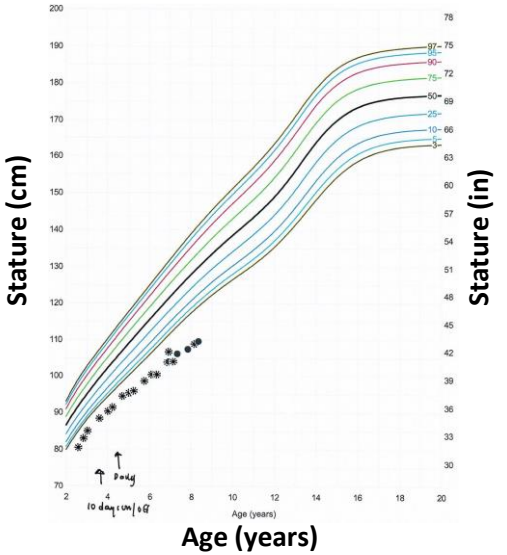
Growth Chart: United States
SMI-for-age Percentiles (Boys, 2 to 20 years)









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Growth Chart: United States
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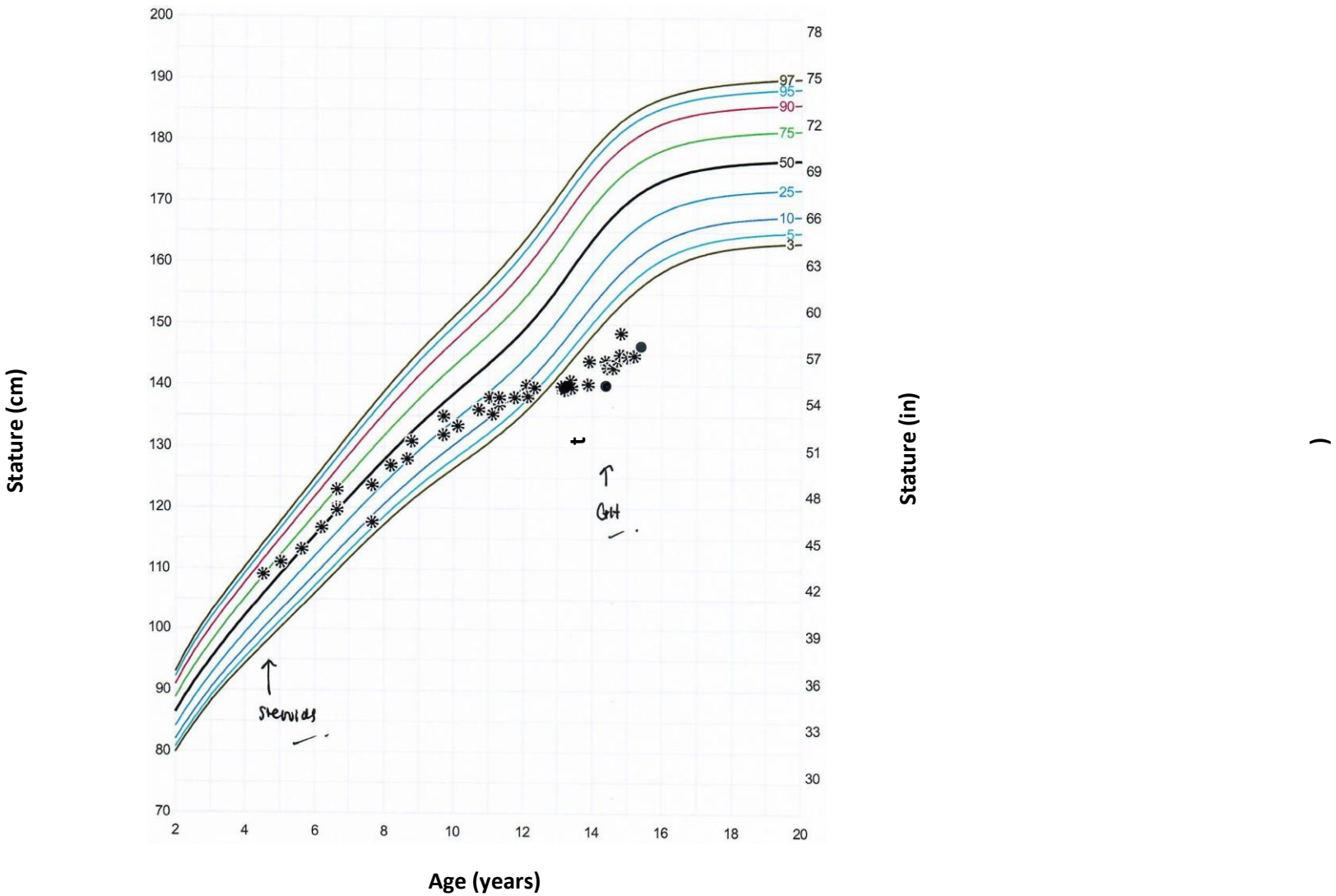

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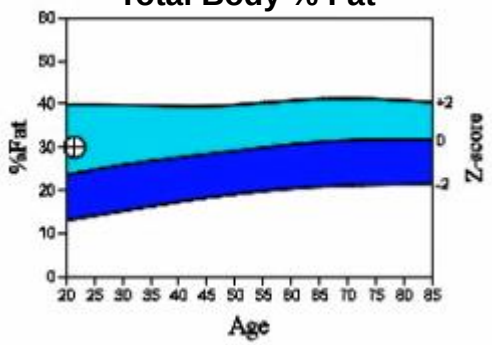
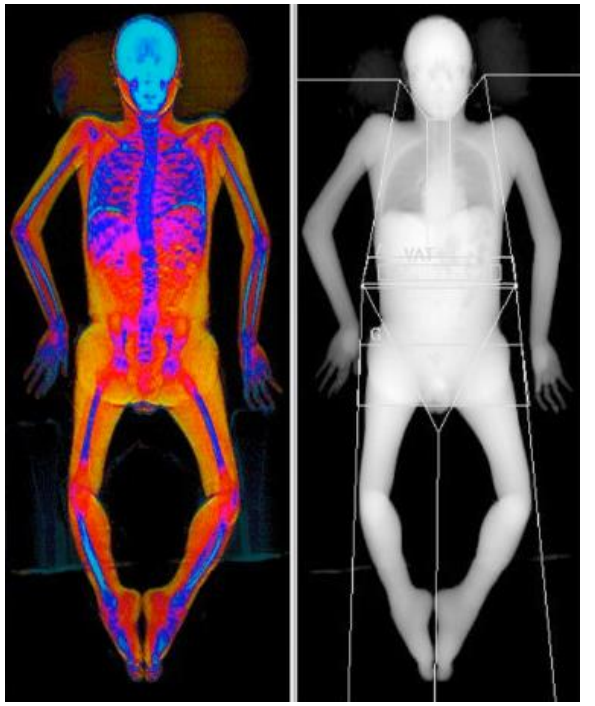
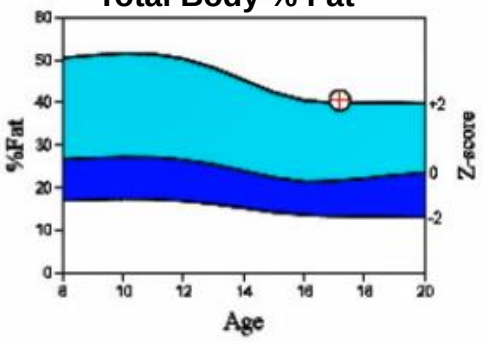
Deletion of 45

Total Body % Fat





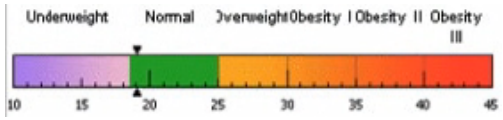
Total Body % Fat



Adipose Indices			
Measure	**Result**	**T-Score**	**Z-score**
Total Body % Fat	30.0	0.8	0.9
Fat Mass/Height² (kg/m²)	5.49	-0.4	-0.2
Android/Gynoid Ratio	0.59		
% Fat Trunk/% Fat Legs	0.61	-2.4	-2.2
Trunk/Limb Fat mass Ratio	0.70	-2.0	-1.8
Est. VAT Mass (g)	309		
Est. VAT Volume (cm³)	334		
Est. VAT Area (cm²)	64.0		
Lean Indices			
Lean/ Height² (kg/m²)	12.2	-3.8	-3.8
Appen. Lean/Height² (kg/m2)	4.61	-4.9	-4.8
Est. VAT = Estimated Visceral Adipose Tissue			

Source: 2008 NHANES White Male

World Health Organization Body Mass Index Classification
BMI – 19.1 WHO Classification Normal



Adipose Indices			
Measure	**Result**	**T-Score**	**Z-score**
Total Body % Fat	40.6		2.0
Fat Mass/Height² (kg/m²)	6.71		0.6
Android/Gynoid Ratio	0.69		
% Fat Trunk/% Fat Legs	0.73		-0.7
Trunk/Limb Fat mass Ratio	0.96		0.8
Est. VAT Mass (g)	503		
Est. VAT Volume (cm³)	543		
Est. VAT Area (cm²)	104		
Lean Indices			
Lean/ Height² (kg/m²)	9.52		-6.4
Appen. Lean/Height² (kg/m2)	3.23		-9.2
Est. VAT = Estimated Visceral Adipose Tissue			

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Pubertal delays

- **Testosterone Therapy in Patients with Duchenne Muscular Dystrophy and Glucocorticoid-induced Pubertal Delay**

Keefe C, Wong B, Rybalsky I, Shellenbarger K, Tian C, Khoury J, Hornung L, Rutter M.

T therapy was associated with induction of puberty in 14 of 33 (45%) GC-treated boys with DMD.

We observed stabilization of body fat accrual, and stabilization of lean mass decline on T therapy, as compared to pre-T.

We observed increased absolute BMC on T therapy, as compared to pre-T.

Although data on longer-term treatment and with higher doses / serum concentrations are needed, T therapy should be considered in the management of GC-treated male patients with DMD and delayed puberty.

Thank you

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