POST ENDO 2021

Lifestyle, Drugs or the Knife: Treatment of a Growing Problem

Hot Topics: Lessons for Pediatric Endocrinologists

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Lifestyle, Drugs, or the Knife:

Treatment of a Growing Problem — Pediatric Obesity Endo21

Obesity in Youth and Adolescent: Treatment of a Growing Problem

Best Medical Practices in Obesity and Type 2 Diabetes Mellitus in Kids

Seema Kumar, MD

Mayo Clinic, Rochester, MN

Obesity in Youth and Adolescent: Treatment of a Growing Problem

Pharmacotherapy for the Treatment of Adolescent Obesity: Where Are We Now? Where Are We Going?

Ania Jastreboff, MD, PhD

Yale School of Medicine, New Haven, CT

Obesity in Youth and Adolescent: Treatment of a Growing Problem

The Last Resort or a Definitive Treatment: Bariatric Surgery in Adolescents

Thomas Inge, MD, PhD

Children's Hospital Colorado, University of Colorado, Denver, CO

Diagnostic

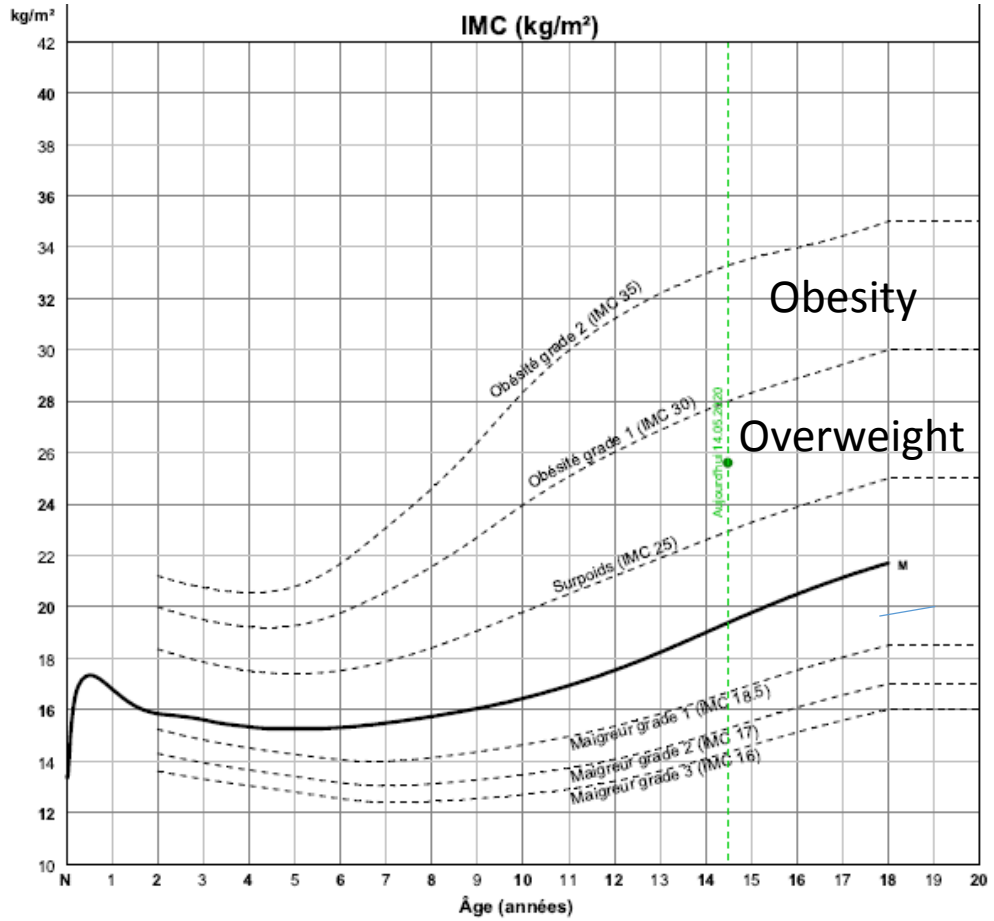
Endocrine Society Clinical Practice Guideline 2017

Child BMI: 85-95th percentile = Overweight (BMI 25 in adulthood)

>95th percentile = Obesity (BMI 30 in adulthood)

> 120% of 95th p. = Extreme obesity (BMI 35 in adulthood)

Child < 2 an BMI > 97.7th P = Obesity (WHO charts)



International Obesity Task Force (IOTF) Cole et al 2000

Definition in Switzerland

Pediatrica 2006 Farpour-Lambert et al

Child:	BMI > 90th percentile = Overweight
	> 97th percentile = Obesity
	> 99.5th percentile = Extreme obesity

DEXA:	Total body fat > 25 % = Obesity in boys
	Total body fat > 30 % = Obesity in girls

Waist circumference: > 2 SD

Recommendation of the European Childhood Obesity Group (ECOG) and IOTF:

Development of local BMI carts

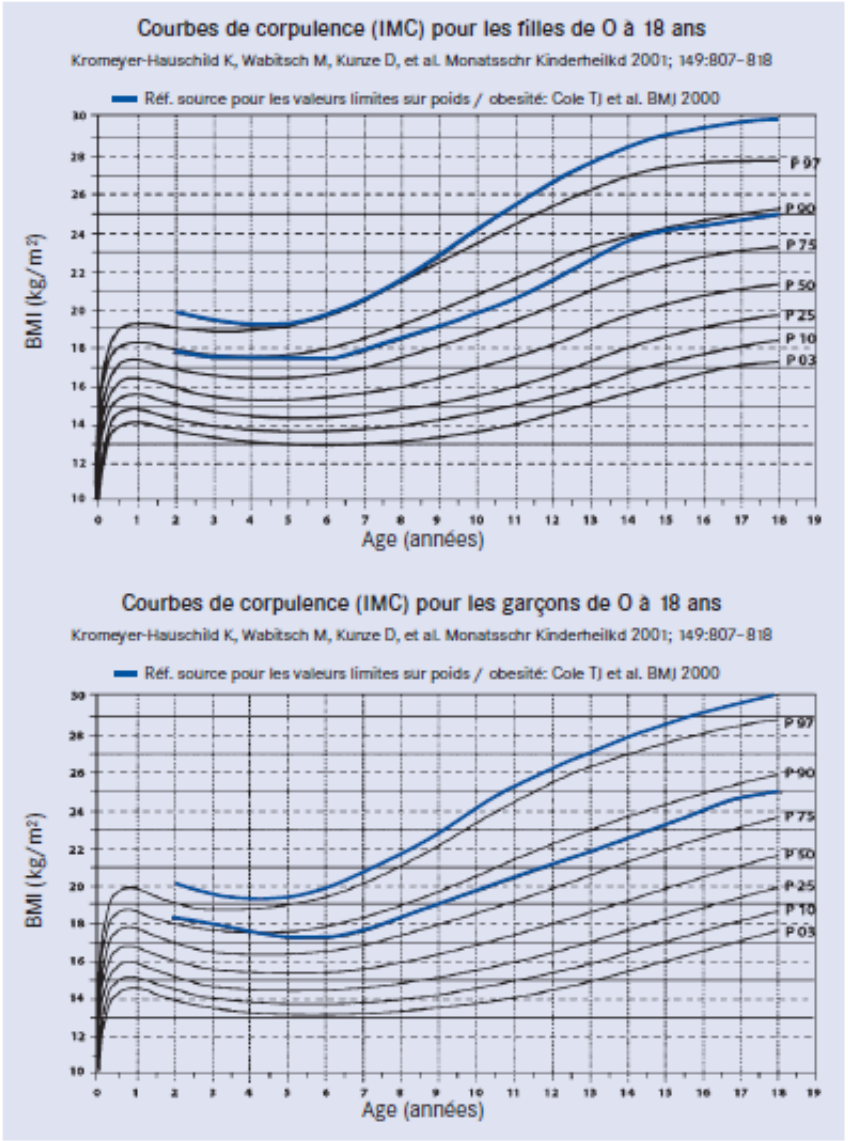


Figure 1: Courbe de corpulence (IMC)[24] pour les filles (en haut) et les garçons (en bas), en comparaison avec la définition internationale du surpoids et de l'obésité (en bleu)[26] (P. Mullis et coll., Inselspital Berne)

Kromeyer/WHO charts

Swiss BMI charts 2019

Prospective study 2017-2019,16540 boys, 13601 girls, min 300 children/year

Median BMI in 18 year old boys:
+ 2kg/m2 in boys and + 1.4 kg/m2 in girls compared to two generations before

Risk dependant on area of origin and minimally influenced by the residential socio-economic situation

2021: Immigration from South European countries accounts for the main part of the Increase in BMI and the prevalence of overweight and obesity in Switzerland

Table 7. Prevalence of overweight and obesity (in percentages) determined by various cut-off definitions (subjects $\geq$ 2 years).

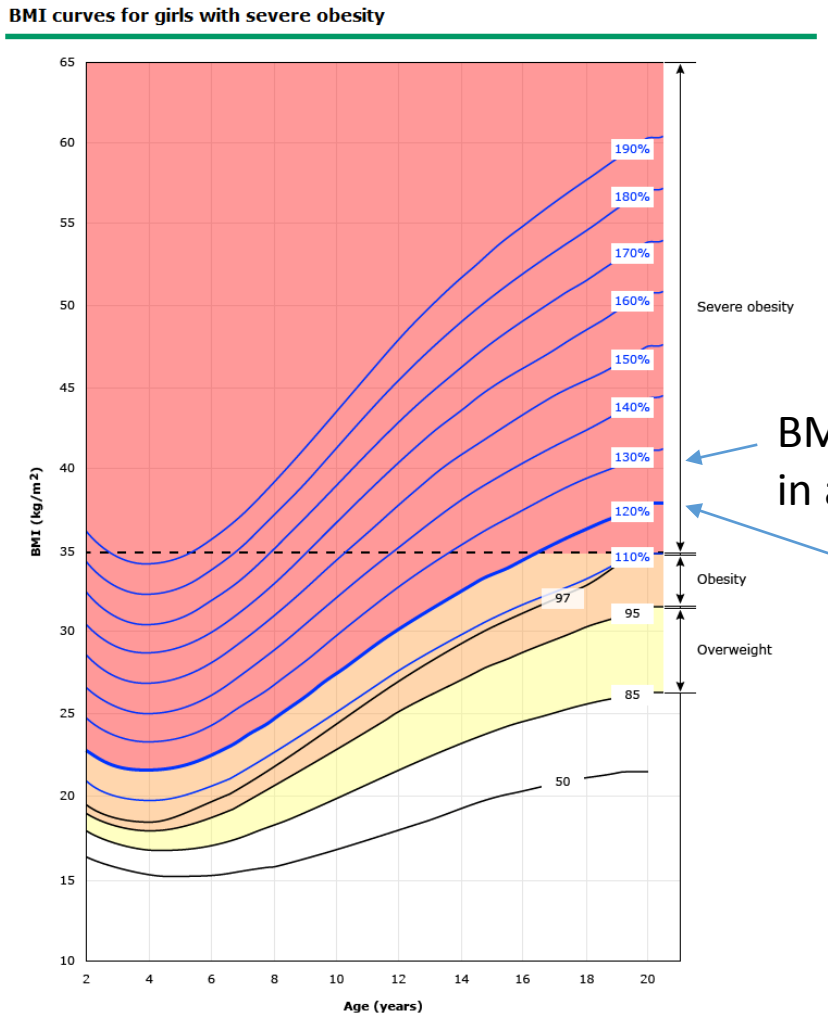
Sex	BMI classification	WHO (90th & 97th percentile)	IOTF cut-offs[a]	Percentiles at BMI = 25 and 30 kg/m^2 with age 18
Boys	Overweight[b]	16.4	16.6	20.4
	Obesity	7.8	4.0	5.0
Girls	Overweight[b]	13.0	14.1	16.9
	Obesity	5.2	3.0	3.6

[a]Cut-offs published by Cole et al. (2000).
[b]Category including obese subjects.
BMI, body mass index; WHO, World Health Organisation; IOTF, International Obesity Task Force.

Eiholzer et al, annals of human biology 2019, BMC Public Health 2021

Classification

Pr Seema Kumar



BMI 40 kg/m2: Indication for weight loss surgery in adults

BMI > 35 kg/m2 = Severe obesity
Or > 120% of the 95th P

Kelly AS et al, Circulation 2013

Recommendations for Assessment

BMI assessment

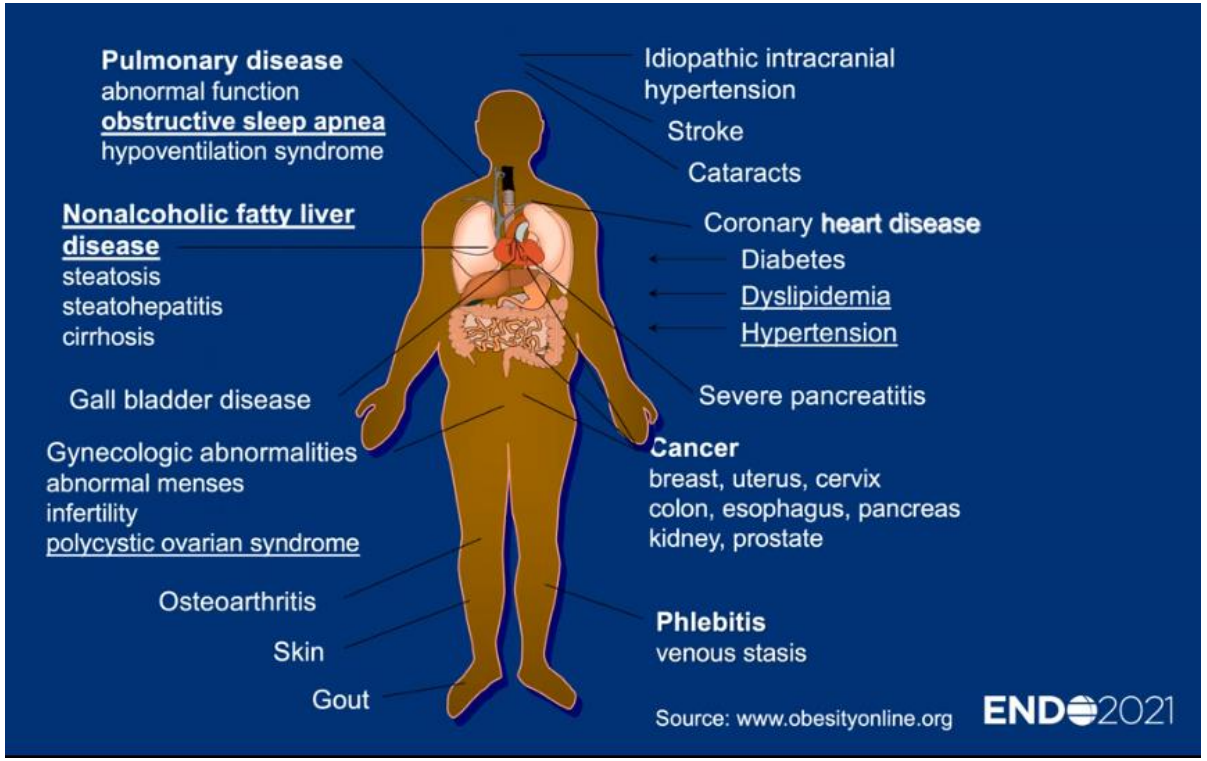
Cause of weight gain

Comorbidities

Nutritional assessment

Eating habits
Family environment
Socioeconomic factors
Cultural factors

Physical activity assessment



Endocrinological investigations → short stature, growth velocity ↓

Genetic Evaluation → if early onset obesity (< 5 years of age)
clinical features of genetic obesity syndromes, extreme hyperphagia, family history of extreme obesity

Lifestyle, Drugs or the Knife ?

Staged Approach

Pr Seema Kumar

Stage 1: - Plus (Life style intervention)
Stage 2: - Structured Weight Management (1x/month)
Stage 3: - Comprehensive Multidisciplinary Intervention (1x/week)
Stage 4: - Tertiary Care Intervention
Highly structures diets, medications, bariatric surgery

Spear BA, Barlow SE, Ervin C et al Pediatrics 2007;120:S254

Lifestyle

Dietary recommendations

5 or more serving of vegetables of fruit daily
Decreased consumption of fast foods, salt intake, sugared beverages
Eat breakfast every day,
Eat most meals at home as a family

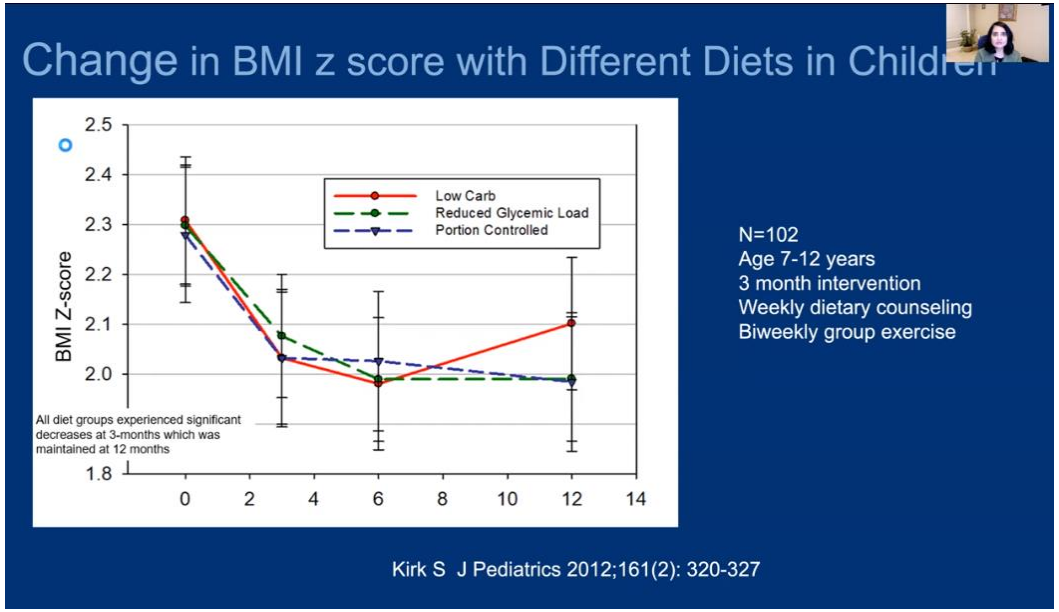
Activity recommendations

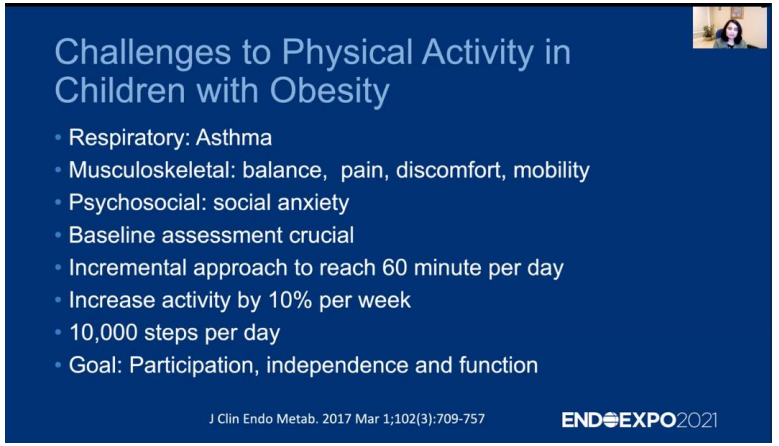
Less than 2 hours of television or other screen time per day
20 min (optimally 60 min) of vigorous physical activity at least 5 days/week)

Psychosocial evaluation

Poor self esteem, eating disorder, low quality of life, depression, substance abuse

Endocrine Society Clinical Practice Guideline 2016





Efficacy of Lifestyle intervention

Cochrane systematic reviews

- Children <6 years (7 trials)
  - Mean difference in BMI z score −0.3 units (95% CI: −0.4 to −0.2) at the end of intervention, -0.4 (95% CI: −0.6 to −0.2) at 12-18 months and 6-8 months and −0.3 units (95% CI: −0.4 to −0.1) at 2 years
- Children< 12 years (37 trials)
  - Change in BMI (at last follow up) −0.53 kg/m^2 (95% CI: −0.82 to −0.24);
  - Mean difference in BMI z score −0.06 units, (95% CI: −0.10 to −0.02)
- Children 12 years and older
  - 28 trials: Change in BMI at last follow up -1.18 kg/m^2 (95% CI: −1.67 to −0.69)
  - 20 trials: Change in BMI z-score was −0.13 units (95% CI: −0.21 to −0.05)

Elis LJ.et al Int J Obes 2018 42, 1823-1833

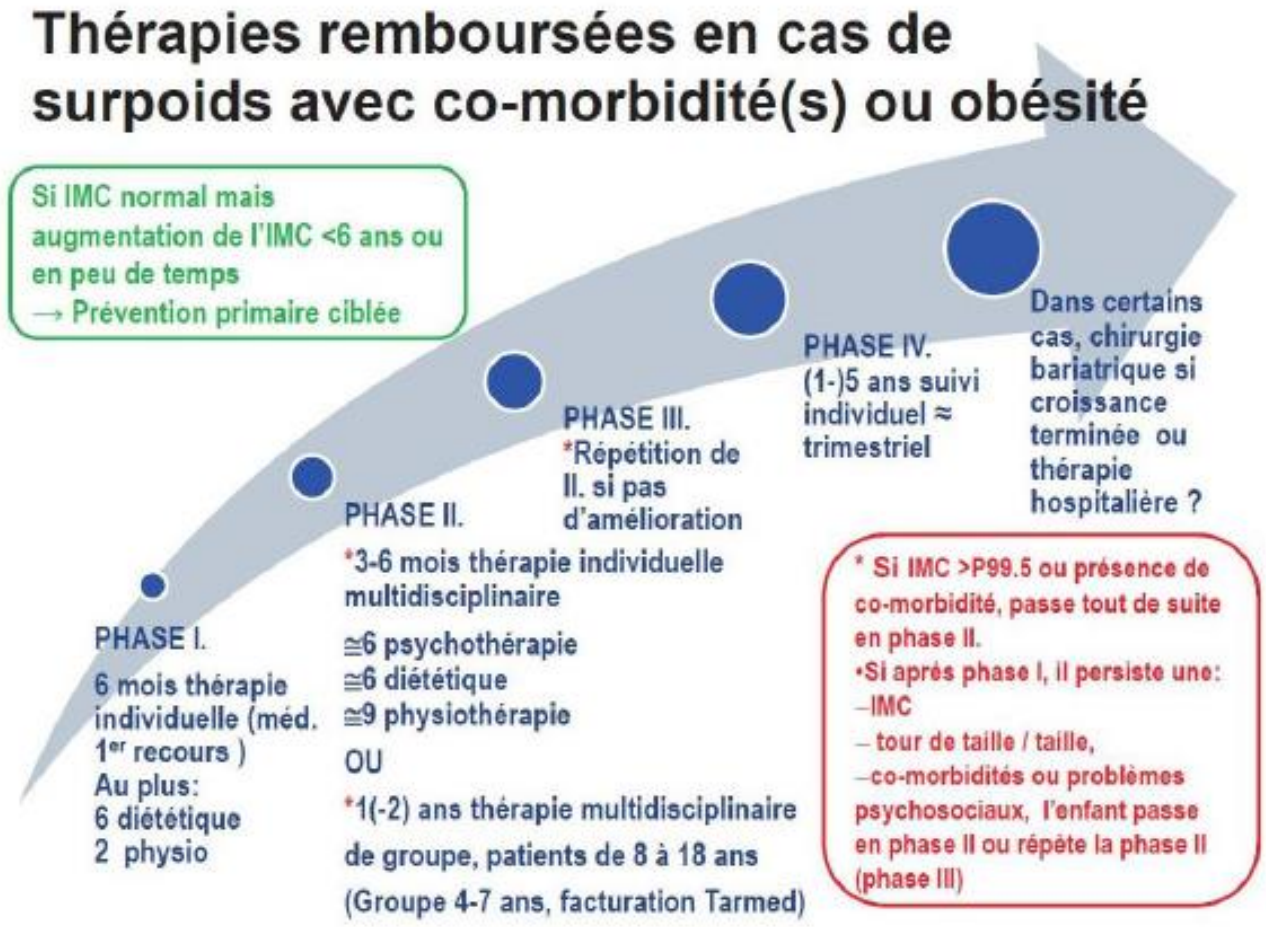
Power experience
(Pediatric Obesity Weight evaluation Registry)

	Change in Percent of 95th percentile for BMI (%BMIp95)		
Age group (y)	4-6 months	7-9 months	10-12 months
2-5	-0.6 (-5 to 4) n=113	-1.7 (-6 to 4) n=69	-1.9 (-8 to 3) n=45
6-11	-1.8 (-6 to 1) n= 1035	-2.0 (-7 to 2) n=635	-2.2 (-7 to 2) n=403
12-14	-2.0 (-6 to 1) n=534	-2.9 (-8 to 1) n=319	-3.7 (-11 to 1) N=207
15-18	-2.1 (-7 to 1) n=451	-3.4 (-9 to 1) n=230	-3.7 (-11 to 2) n=127

Kumar, Kirk et al J Pediatr 2019;208:57-65.e4

Lifestyle changes may be beneficial in achieving small reductions in body weight status in children of all ages, with low adverse event occurrence were reported.
More research needed to identify which specific intervention components are most effective

Formal program of lifestyle intervention in CH



Forum médical suisse 2015; 15(3):58-59

Anti-obesity pharmacotherapy for the treatment of adolescents with obesity: Were are we now ? Were are we going?

Pr Ania Jastreboff

Indication: - obesity and 1 comorbidity or
- extreme obesity and documentation of previous lifestyle therapies

Use only with concomitant lifestyle intervention

Relive weight inducing drugs as psychotropics, glucocorticoids if possible

Drugs for adults used for children > 16 years (physiology similar)

Anti-obesity pharmacotherapy

Weight loss < 5% after 12 weeks - stop treatment

Medication	Approval for adolescent obesity	RCT	Summary of trials
Orlistat	**approved for obesity ≥12 yo**	Yes	• Several RCTs completed. Patients' age range from 10 to 18 years old, and treatment duration up to 54 weeks
Liraglutide	**approved for obesity ≥12 yo** approved for T2DM ≥10 yo	Yes	• Three RCTs completed. Patients' ages range from 7 to 17 years old, and treatment duration up to 56 weeks • One ongoing trial for the effect of liraglutide for weight management in pediatric subjects with Prader-Willi Syndrome
Phentermine	**approved for obesity >16 yo**	No	• Retrospective chart review
Topiramate	approved for seizure ≥2 yo approved for migraine ≥12 yo	Yes	• Two completed RCTs. Patients' ages range from 9 to 17 years old, and treatment duration up to 36 weeks
Phentermine/ Topiramate	*Not approved*	Yes	• Three RCTs in progress. Patients' ages range from 12 to 25 years old, and treatment duration up to 56 weeks
Metformin	approved for T2DM ≥10 yo	Yes	• Multiple RCTs completed. Patients' ages range from 6 to 17 years old, and treatment duration up to 2 years; typically 6–12 months
Bupropion/ Naltrexone	*Not approved*	No	• Currently no RCT for children or adolescents with obesity
Bupropion	*Not approved* used off-label ADHD, mood	No	• Currently no RCT for children or adolescents with obesity
Setmelanotide	**approved for obesity due to POMC, PCSK1, & LEPR def ≥ 6 yo**	No	• Phase 3 trials completed (POMC PCSK1, and LEPR Def) • Phase 3 underway for Bardet-Biedl and Alström syndrome

Slide: Ania M. Jastreboff, MD, PhD: Review of clinicaltrials.gov April 2020.

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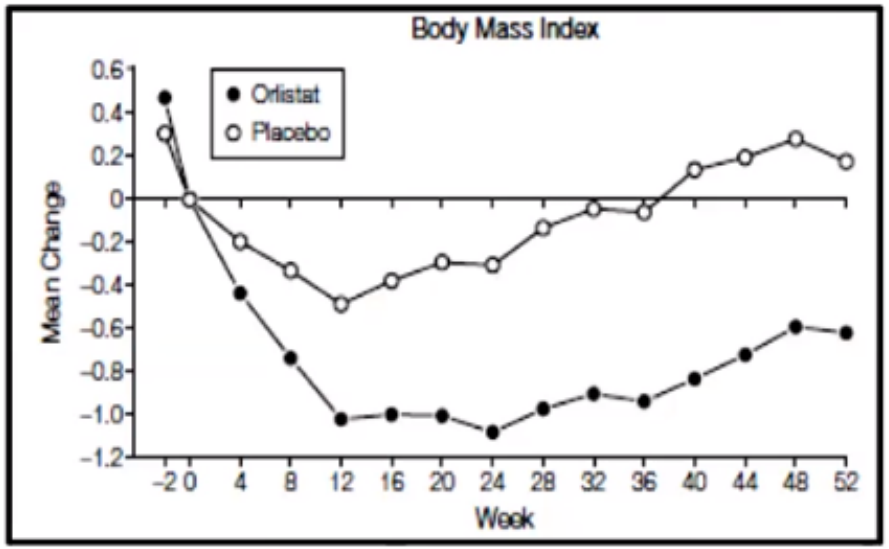
CH	
>12 y	Orlistat mepha, Sandoz Xenical
>12 y + comorbidity > 10 y + diabetes	Saxenda Victosa
	Gabareceptor modulator
>10 y + DT2	

Orlistat

FDA approved for obesity treatment ≥12 years

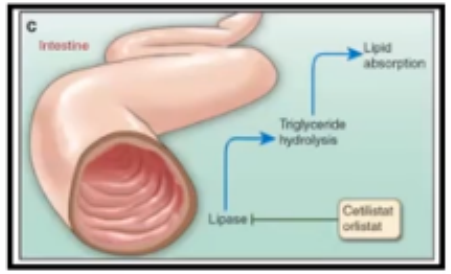


Largest RCT (N=539)

Adolescents with obesity (avg BMI 36 kg/m^2)

Orlistat 120mg TID

2.4% BMI reduction at 1 year (-2.6kg)



- Inhibits gastric and pancreatic lipase
- Causes malabsorption of 30% of ingested fat
- Psyllium reduces side effects of steatorrhea etc.

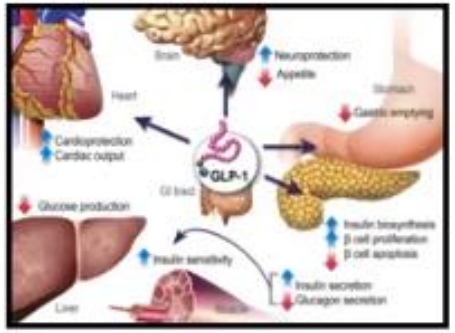
Apovian, *et al.*, Endo Society CPG, *JCEM*, 2015 Chanoine et al. JAMA 2005

Liraglutide

Liraglutide 3.0mg – approved for ≥ 12 yo with obesity

Liraglutide 1.8mg – approved for ≥ 10 yo with T2D

Mechanism	Dose	Side effect	Contraindications
GLP-1 analogue	0.6mg → 1.2mg → 1.8mg → 2.4mg → 3.0mg SC daily	nausea vomiting gall stones pancreatitis risk	medullary thyroid CA, MEN2



In adults:

- FDA-approved for obesity treatment: Liraglutide (Saxenda)
- FDA-approved for T2DM treatment: Exenatide, Exenatide ER, Lixisenatide, Liraglutide (Victoza), Albiglutide, Dulaglutide, Semaglutide

Apovian, *et al.*, Endo Society CPG, *JCEM*, 2015

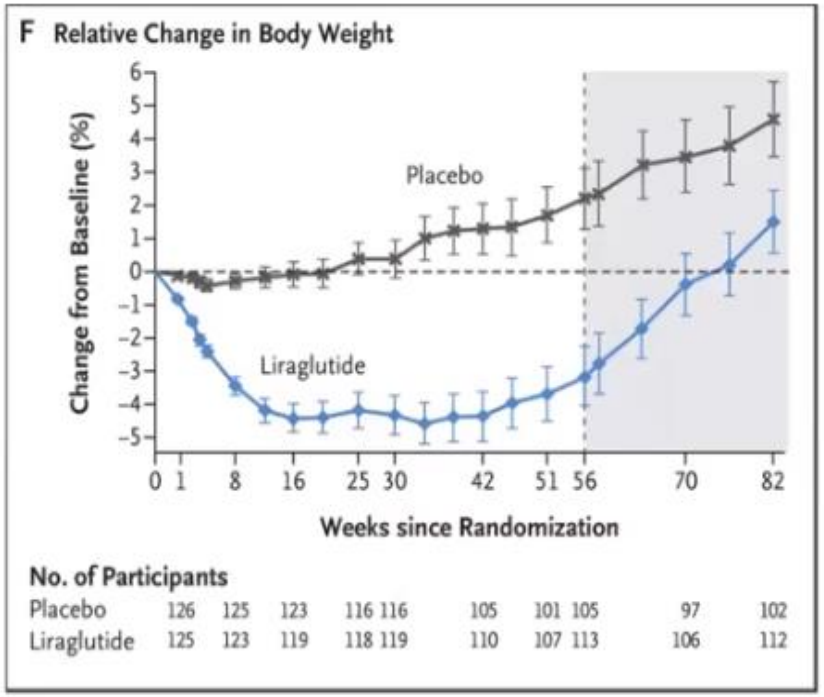
Liraglutide 3.0mg

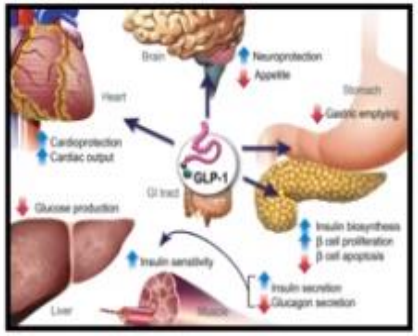
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity

Aaron S. Kelly, Ph.D., Pernille Auerbach, M.D., Ph.D., Margarita Barrientos-Perez, M.D., Inge Gies, M.D., Ph.D., Paula M. Hale, M.D., Claude Marcus, M.D., Ph.D., Lucy D. Mastrandrea, M.D., Ph.D., Nandana Prabhu, M.Sc., and Silva Arslanian, M.D., for the NN8022-4180 Trial Investigators*





RCT
N=251
12-17 yo w/ obesity
avg BMI 35
avg A1c 5.3%
4.5-5% BMI reduction at 1 year

Kelly, *et al., NEJM*, 2020

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Liraglutide (Saxenda) en Suisse pour les adolescents depuis juillet 21

Overweight (IMC 27kg/m2 = > P90 with comorbidity
Or
Obesity > 60 kg or (IMC 30 kg/m2 = > 97 P)

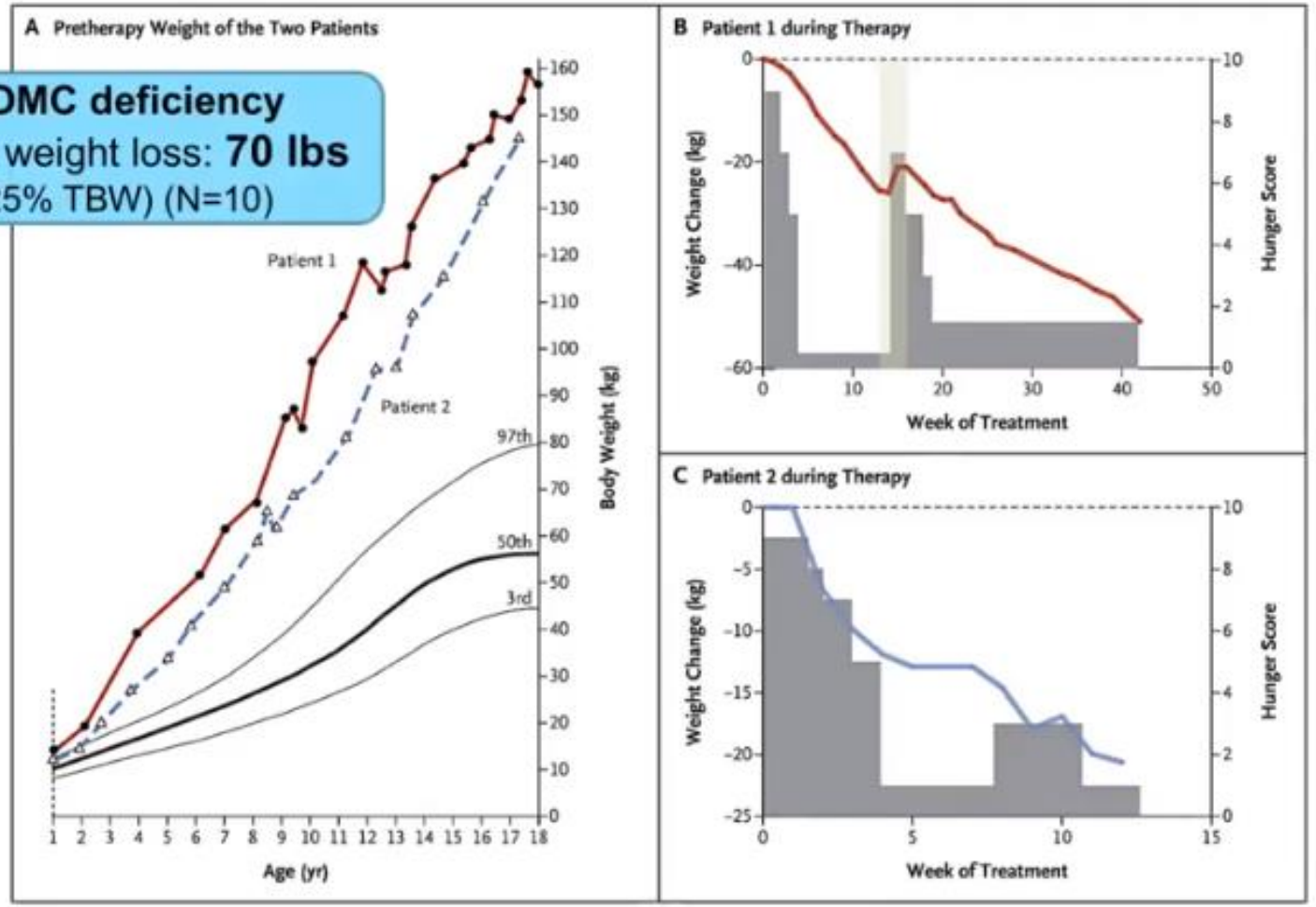
	ans	12	12.5	13	13.5	14	14.5	15	15.5	16	16.5	17	17.5	18
BMI	filles	26.67	27.24	27.76	28.2	28.57	28.87	29.11	29.29	29.43	29.56	29.69	29.84	30
	garçon	26.02	26.43	26.84	27.25	27.63	27.98	28.30	28.60	28.88	29.14	29.41	29.70	30.0

Weight loss < 4% after 12 weeks - stop treatment

Monitoring: pancreatitis, heart rate increase, cholelithiasis
Adverse effects: nausea, vomiting, diarrhoea, hypoglycaemia

Setmelanotide:
MC4R agonist treatment of POMC deficiency

POMC deficiency
Mean weight loss: **70 lbs**
(25% TBW) (N=10)



Kuhnen P *et al.* NEJM 2016

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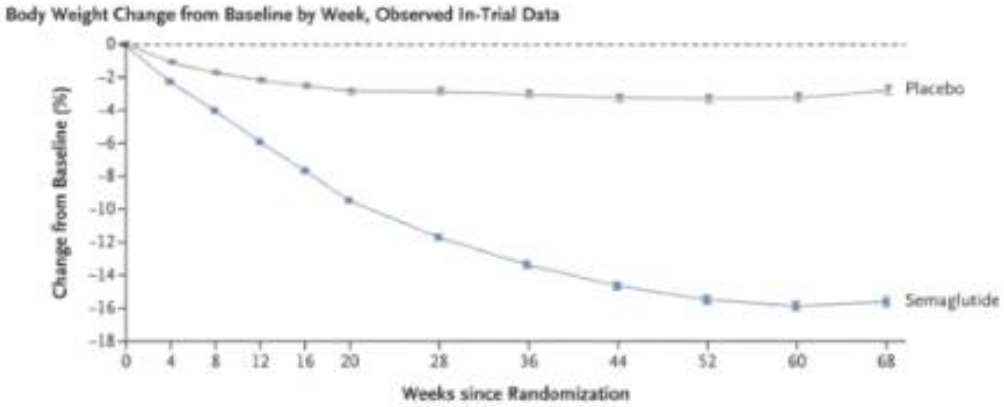
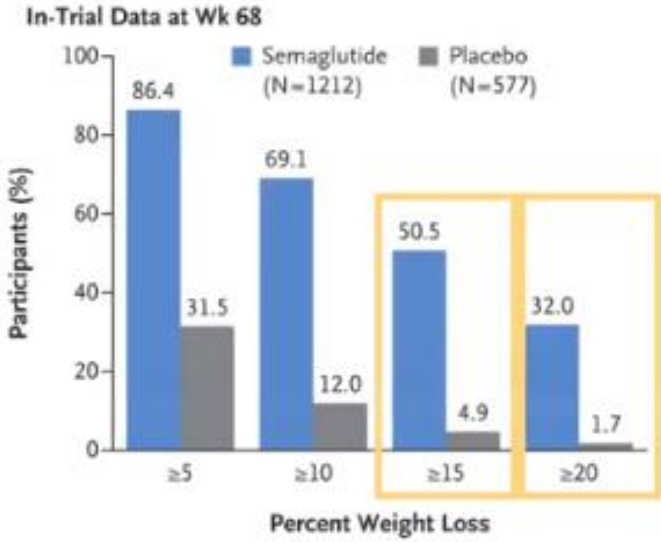
On the horizon… GLP1-a - semaglutide 2.4 mg weekly SC

RCT: n=1,306 (Sema) / n=655 (Placebo)
Avg Age: 46-47 yo, Avg BMI 38, no h/o diabetes





RCT in progress with:

- semaglutide 2.4mg SC weekly, RCT in 12-17 yo, 68 weeks: completion 3/2022
- semaglutide 3mg / 7mg oral daily, RCT 12-21 yo, 12 weeks: completion 7/2024

Bariatric Surgery in adolescents


Pr Thomas Inge

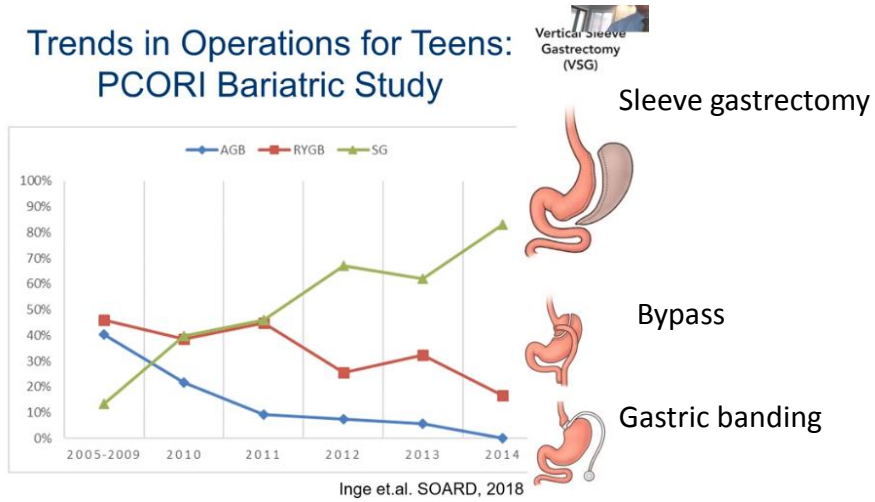
Selection criteria for adolescent bariatric surgery	
BMI	**AND:**
35-40 (Grade 2) 120% of 95P	T2D, obstructive sleep apnea (OAHI >5), advanced NASH, pseudotumor cerebri, Blount's disease, SCFE, GERD, hypertension; No contraindications
>40 (Grade 3) 140% of 95P	Comorbidity not required; No contraindications

Contraindications to surgery

- Medically correctable cause of obesity
- Ongoing substance abuse problem (within the preceding 1 year)
- Medical, psychiatric, psychosocial, or cognitive condition that prevents adherence to postoperative dietary and medication regimens
- Current or planned pregnancy within 12 to 18 months of the procedure.

Primary changes from previous guidelines

- Increased the number of comorbidities qualifying for surgery for those with class II obesity
- Removed requirement for comorbidities for those with class III obesity
- No longer recommend waiting until linear growth is complete
- Added pediatric definitions for severe obesity, using % over the 95th percentile



Inge et.al. SOARD, 2018

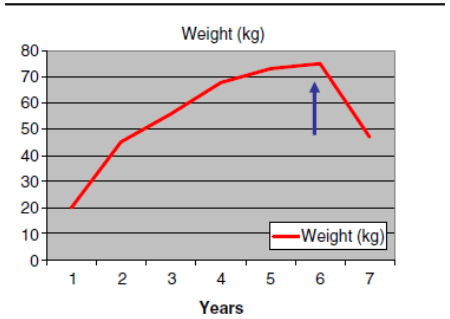
AAP Policy Statement. Pediatrics, 144(6), 2019

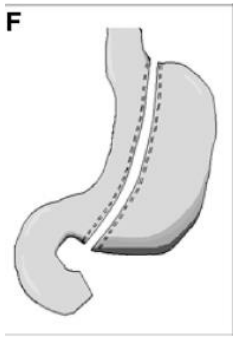
Bariatric Surgery in the Management of Childhood Obesity: Should There be an Age Limit?

Dilip Dan · Dave Harnanan · Shiva Seetahal · Vijay Naraynsingh · Surujpal Teelucksingh

Abstract We report a case of a 6-year-old girl suffer from morbid obesity, Blount`s disease, and signific social and functional impairment who underwent a lapa scopic sleeve gastrectomy. One year later, she has shc remarkable improvement in all aspects of her health emphasizing the success of the procedure. A follow-up laparoscopic Roux-en-Y gastric bypass or biliopancreatic diversion (BPD) are options if she regains weight as she gets older. This case is noteworthy for several reasons. The age of the patient is younger than any currently on record who has had this treatment. Additionally, the utilization of a sleeve gastrectomy as a first-step procedure, to be followed by Roux-en-Y gastric bypass or BPD, remains a novel treatment for morbid obesity in a pediatric population.

Fig. 1 The patient before and after surgery



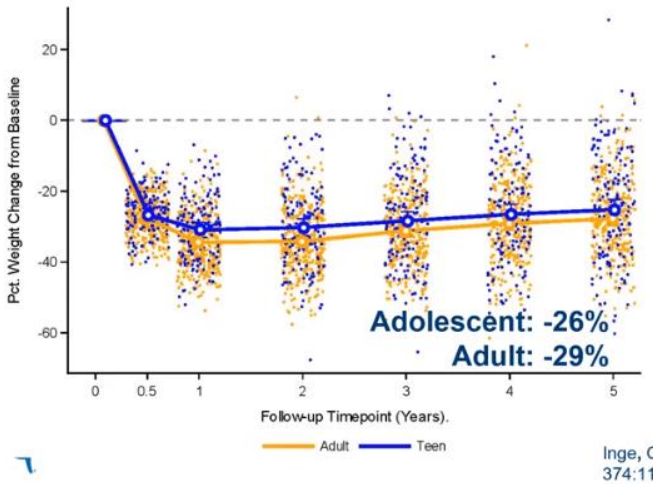


Sleeve gastrectomy

Dilip Dan et al Obesity surgery 20(1), 114-117, 2010

- Teens and adults shed similar weight with the same operation
- Some comorbid conditions (diabetes, HTN) are more responsive to surgical treatment in teens than adults
- The variety of complications are similar between teens and adults but teens may experience more abdominal re-operations than adults

Body weight change after gastric bypass in Adults and Teens



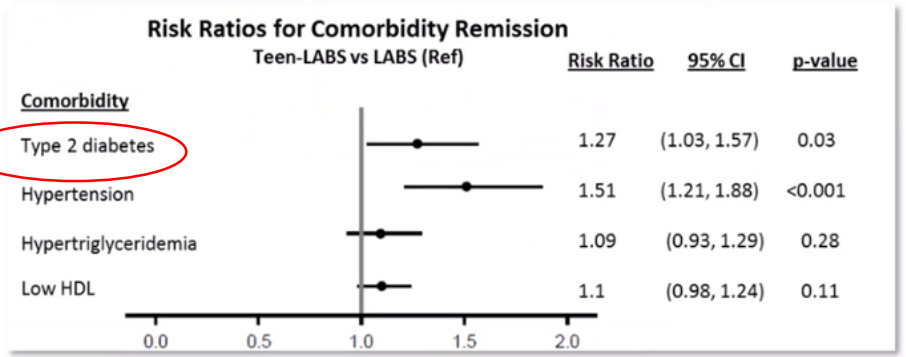
Adolescent:
n=165, age 13-19yrs

Adult:
n=396, ages ≥ 25-60yrs

All gastric bypass

Inge, Courcoulas, Jenkins, Michalsky, et.al. *NEJM* 2019; 374:113-123

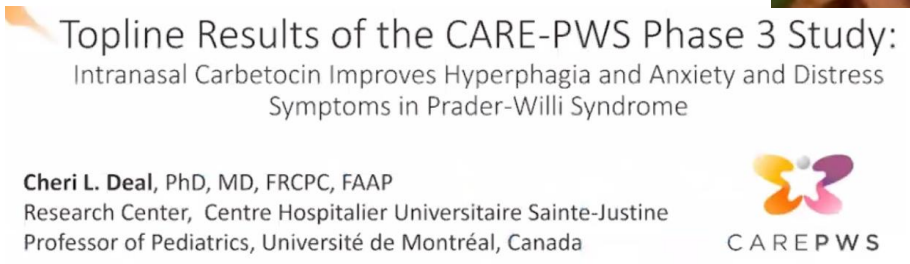
Risk Ratios for Comorbidity Remission

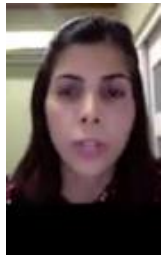


Conclusions and Future Directions

- Metabolic bariatric surgery induces notable weight loss and improvements in wide-ranging complications of obesity, particularly diabetes, likely via improvements in insulin sensitivity, reduction in insulin secretion demand
- Future Directions
  - Important to document mechanisms of metabolic and cardiovascular improvement after surgery in youth with T2DM

ENDO 21: Lessons for Pediatric Endocrinologists
Hot topics





Racial / Ethnic Disparities in the Investigation and Treatment of Pediatric Growth Hormone Deficiency

Colin P. Hawkes[1,2,3], Hareesh Gunturi[2], Andrew Dauber[4,5], Joel Hirschhorn[6,7], Adda Grimberg[1,2]

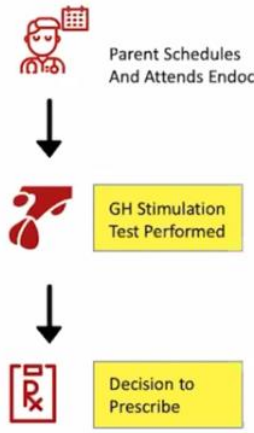
Background: Non-Hispanic White (NHW) children are over-represented in GH treatment Registries
Retrospective study: 2012-2019 Children's hospital Philadelphia

Aim

- To determine if there is racial inequity

  1) in **GH stimulation tests** performed
  2) and/or **GH prescribing**

  amongst children and adolescents referred for endocrine evaluation of short stature.



Results:

NHW children were
- 1.4 (95% CI 1.04 – 1.8) times more likely than NHB children
- 1.7 (95% CI 1.2 - 2.2) times more likely than Hispanic children *to undergo GH stimulation testing*

NHB children treated with GH
- Had **lower peak GH concentration** than treated NHW children
- Had **lower height z-scores** than treated NHW children
- Had a **greater height deficit from midparental height** than treated NHW and Hispanic children

Referred Population

Race	NHW	NHB	Hispanic
n	5,905	800	720
Age, years median (IQR)	11 (7.6, 13.4)	11.2 (7,14)	9.7 (6.6, 13.1)
Male Sex n (%)	3,547 (60%)	515 (64%)	529 (59%)
Commercial Insurance n (%)	4955 (84%)	312 (39%)	528 (58%)
Height Z-score median (IQR)	-2.1 (-2.5, -1.8)	-2.2 (-2.6, -1.8)	-2.2 (-2.7, -1.8)
Height minus MPH Z-score median (IQR)	-1.8 (-2.3, -1.3)	-1.7 (-2.3, -1.2)	-1.4 (-2, -0.8)

Conclusion: lower threshold for GH stimulation testing in NHW children
When peak GH on stimulation testing exceeds 7 ng/ml disparities emerge

- Are we
  - Over-treating & over-investigating (predominantly higher SES) NHW children?
  - Under-treating & under-investigating (predominantly lower SES) NHB children?
- Are these disparities driven by clinicians, parents, or both?

Topline Results of the CARE-PWS Phase 3 Study:

Intranasal Carbetocin Improves Hyperphagia and Anxiety and Distress Symptoms in Prader-Willi Syndrome

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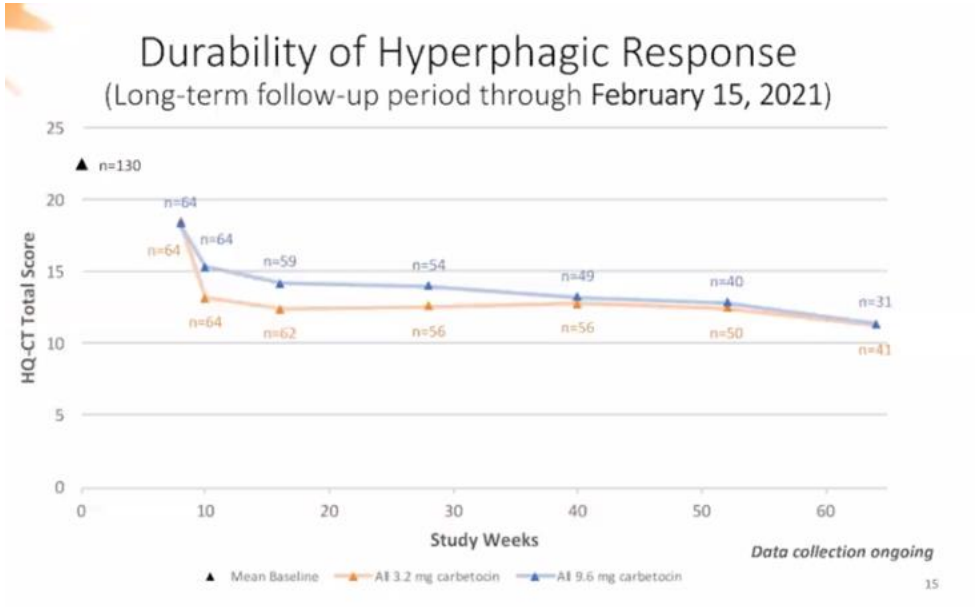
Background:
Oxytocin producing neurons are reduced in PWS
Oxytocin has behavioural effects including anxiety and food ingestion behaviour
Mediator of Leptin

Randomized, placebo-controlled, double –blind, multicentre study (US, Canada, Australia) n= 119 (7-18 yr)

Aim: assess the efficacy of 9.6 and 3.2 mg intranasal carbetocin 3x/day versus placebo on PWS behavioural symptoms, assesse the safety and tolerability of theses doses.



Conclusions

- In the CARE-PWS Phase 3 study, intranasal carbetocin was well tolerated and was associated with reductions in hyperphagia and anxiety/distress behaviors
- Reductions in hyperphagia have persisted in the ongoing long-term follow-up period (mean follow-up duration: over 12 months as of 31 Dec 2020)
- As of 31 Dec 2020, ~95% of patients who completed the study opted to continue in the voluntary extension
- The sponsor and the independent data monitoring committee (DMC) agreed that the aggregate data support continued advancement of the 3.2 mg dose as the lowest effective dose
- The sponsor will be working closely with regulatory authorities to discuss bringing carbetocin to patients as quickly as possible

Pubertal Onset Occurs in Female Mice Lacking Paternally Expressed *Dlk1* Despite Lower Leptin and Kisspeptin Levels

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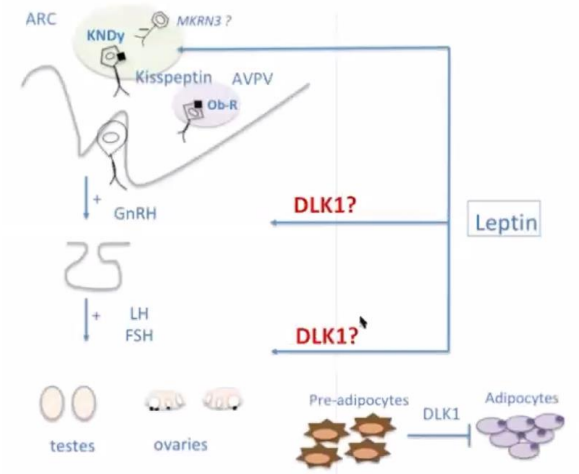
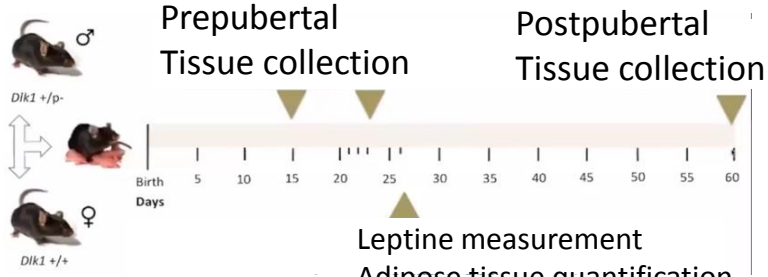
Background: **Paternally Inherited *DLK1* Deletion Associated With Familial Central Precocious Puberty**

DLK1 inhibits adipocytes differentiation and notch signalling that modulates kisspeptin neuronal development. Leptin has a positive role on puberty onset



AIM: Explore the influence of Dlk1 in the regulation of reproductive axis and its link between metabolism and reproduction

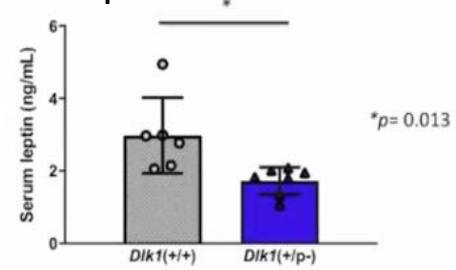
Method: Dlk1 knockout mouse model. Prepubertal, peripubertal and postpubertal tissue collection



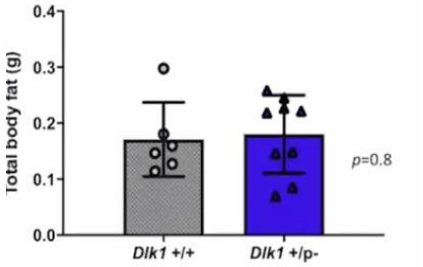
- DLK1 is an important link between body weight and pubertal development.
- The absence of *Dlk1* may attenuate the metabolic effects of low body weight and low leptin levels on puberty onset ('Relative precocious puberty')
- *Dlk1* may be acting downstream or independently of kisspeptin to regulate the reproductive axis.

DLk1 knockout mice at puberty

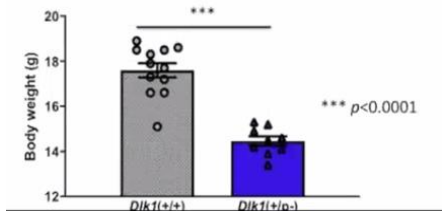
Leptine-Elisa



Body fat



Body weight



Merci pour votre attention