Update on Obesity and Type 2 Diabetes

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Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

NAME OF PRESENTER: Omar Ali

Disclosed no conflict of interest

Outline

• Obesity
• Treatment of Obesity
• Type 2 Diabetes
• Treatment of Type 2 diabetes
• Some parting thoughts...
Obesity

- Ideally, a measure of excess body fatness
- But it is hard to directly measure total body fat
- So we use BMI as a surrogate measure of fatness
- Not perfect, but close..

CDC Guidelines for BMI

**ADULTS**
- BMI 25.0-29.9 = overweight
- BMI>30 = Obese
- BMI>40 sometimes labelled morbid obesity or class III Obesity

**CHILDREN**
- BMI <5th percentile = underweight
- BMI 85-95th percentile = overweight
- BMI >95th = Obese
  - >120% of 95th%ile: Severe Obesity (Roughly 35 for older adolescents)
  - (Reference values are from the NHANES 1971-74 data)

Health Consequences?

- Social stigmatization/self-esteem issues
- Asthma
- Diabetes
- Non-alcoholic fatty liver disease
- Obstructive sleep apnea
- Mobility and Hygiene issues
- Cardiovascular disease risk
- Osteoarthritis
- Cancer
Prevalence

- Globally **2.1 billion people** (nearly one-third of the global population) were overweight or obese in 2013 (Lancet 2013).
- Up from **857 million** in 1980.
- In the US 2/3rd of Adults and 1/3rd of children are overweight or obese (about half of those are obese, rest overweight)
- **17%** (or 12.7 million) of US children aged 2—19 years are obese.

WorldWide Problem

![Worldwide Prevalence of Obesity Map](map.png)

Socioeconomic Status

![Socioeconomic Status Graph](chart.png)
How NOT to Predict Progression of an Epidemic

- The objective was to illustrate potential burden of obesity prevalence and health-care costs of obesity and overweight in the United States that would occur if current trends continue.
- By 2048, all American adults would become overweight or obese, while black women will reach that state by 2034.
- In children, the prevalence of overweight (BMI >/= 95th percentile, 30%) will nearly double by 2030.

Actual Trend

- From 2003 through 2010, the prevalence of obesity in ALL children decreased slightly from 15.21% to 14.94%. Similarly, the prevalence of extreme obesity decreased from 2.22% to 2.07%.
- The prevalence of obesity among children aged 2 to 5 years decreased significantly from 13.9% in 2003-2004 to 8.4% in 2011-2012 (small numbers)
- There was no significant change in obesity prevalence among adults between 2003-2004 and 2011-2012
Not Just in the US

- Data from many countries show a decline or stabilization of obesity levels, especially in children.
- In Germany a study of children aged 4 to 16 years found a **significant decline** in overweight or obesity between 2004 and 2008 among the youngest children (aged 4-7 years) and a stabilization in other ages.
- In England BMI still increasing, but rate of increase has **decreased**.

Why This Success?

- We don’t know
- Awareness
- Change in environment?
  - Planned/Conscious (less fast food, more veggies, more exercise, better communities)
  - Unplanned (what set off the epidemic?)
  - Hitting genetic limits? (not likely in children)
- Medical Treatment? (Not)
- Statistical blip?

Body Mass Index for Age at or Above the 97th Percentile by Race/Ethnicity in 1999-2006

- Non-Hispanic white
- Non-Hispanic black
- Mexican American


Body Mass Index for Age at or Above the 97th Percentile by Race/Ethnicity in 1999-2006

- Non-Hispanic white
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Take Home Message #1

- Obesity IS a major public health problem
- But the epidemic may be peaking OR may have already peaked in the US
- Let’s not celebrate quite yet, but the endless repetition of “rapidly increasing obesity in American children” is factually incorrect
What Causes Obesity?

- After all, the body DOES regulate weight
- That regulation can clearly fail
- Why?
- Probably related to an imbalance of:
  - Evolution
  - Physiology
  - Civilization

Human Evolution and Calorie Availability

- Pre- and early hominids:
  - Foragers
  - Meat scavengers
  - Then increase in hunting component (ice ages, increased intelligence)
  - For >2M years, hominids evolved with variable and limited food supplies.

Evolution and Obesity

- Human evolution therefore
  - Favors energy intake and storage
  - Protects against weight loss (malnutrition), not against wt. gain
  - Innate human taste preferences for high caloric density “storage” foods
    - Fat
    - Sugars
  - Preference for conservation of body energy (resting state)
- Evolution of Civilization
  - Increased food availability
  - Increased caloric density
  - Minimized physical effort
Summary: The Cause of Obesity

The successful but excessive evolution of civilization to serve our evolved physiologic needs.

Calories per person per day

From a low of 2100 calories per day to a high of 3600 calories per day

But There May be More to it than Calories and Lack of Exercise

- Stress (almost certainly a factor)
- Toxins? (e.g. BPA in urine of obese ppl)
- Viruses (e.g. induction of obesity in chickens exposed to an adenovirus)
- Change in Macronutrient ratio (e.g. we eat more carbs, at least in US. Also, also less dairy)
- Change in micronutrient composition (e.g. lower vitamin D in the obese; chicken or egg?)
- Screen time (may lower REE BELOW resting level)
- Sleep deprivation
- Anti-psychotic meds
- Central Heating (decreased REE, decreased brown fat?)
- Assortative mating?
Summary

• Obesity is widespread
• Obesity is increasing worldwide. But may have plateaued in the US (at the forefront of the epidemic)
• And may even be DECLINING in American children
• Due to increased availability of calories and decreased activity (and other things?)

What to do about it?

Universal BMI Measurement

• Parents frequently do NOT know their child’s weight and what is normal
• Parents underestimate fatness (“puppy fat”, “solidly built” etc)
• Early intervention is better
• BUT
  – Stigmatization (studies show children’s CONSCIOUSNESS of being fat is more closely tied to being stigmatized and bullied than is actual BMI)
Stigmatization?

• At least one study showing that parent’s attempts to make pre-teens watch their diet were associated with WORSE BMI in teenage years
• Some parents will not maintain an “ideal” balance between parental love and acceptance on the one hand and the need to discipline the child on the other.
• Some families are then likely to end up with intra-family conflict, depression...worsening obesity

Fat-bashing.....

Moral Panics

• Moral panic is the intensity of feeling expressed in a population about an issue that appears to threaten the social order. Moral panics are characterized by:
  - Concern: Perception that the behaviour of the group or category in question is likely to have a negative impact on society.
  - Hostility: Hostility towards the group in question increases, and they become “folk devils”. A clear division forms between “them” and “us”.
  - Consensus: Widespread acceptance that the group in question poses a very real threat to society.
  - Disproportionality: The action taken is disproportionate to the actual threat posed by the accused group.
  - Volatility: Moral panics are highly volatile and may disappear as quickly as they appeared
Screened. Found to be Obese..then?

- Identifying a problem without being able to offer a reliable solution
- May be counterproductive
- We do not have infinite resources. Priorities?
  - Fitness versus Fatness
  - Unhealthy Environment, Poor School Performance, Socialization, Criminality, Drug Use
- It may still be worthwhile to target BMI universally...but the issue is not straightforward

Treating Obesity- Is it even possible?

- In terms of converting someone from obese to normal weight- NO
- ALL diets fail in >90% of the people by the second year
- Diets that WORK do NOT lead to normal weight in almost anyone
- People remain overweight, just LESS overweight
- Which is OK. Health risks change dramatically with 5-10% weight loss

Dr Campos (Professor of Law)

- Every discussion of this subject should start with an acknowledgment that we don't know how to turn fat people into thin people.
- Nothing better demonstrates the depth of our cultural neurosis on these issues than the fact that we're talking about how to best employ scarce public health resources to achieve something that no one knows how to achieve.
- I don't want to be telling people with a BMI of 25 or higher (146 pounds and 177 pounds for average-height women and men respectively) that they have something wrong with them that needs to be "cured."
Take Home Message #2

- Universal screening is recommended
- But may (at least in some cases) be counter-productive
- One size does not fit all. In many children with mild obesity, targeting obesity may be a lower priority and should not be allowed to overwhelm common sense

Interventions...

Diet

- What dietary factors are driving this epidemic?
- What is/are the best diets to lose weight?
Is it the Fat?

• We are getting fat
• We eat fat
• Fat is the most calorie dense nutrient
• Hence, eating fat is causing us to become fat
• Is this true?

Probably Not True!

• In aggregate, it is certainly NOT the fat

As weight has gone up:

• The proportion of fat in the American diet has declined from 40 to 32%
• Almost all processed foods are available in low-fat versions.
• People are very conscious of fat intake and are constantly trying to limit it.
• Yet, obesity is increasing!
• Annual grain consumption per capita in the US has increased by 60 pounds per person since the 70's
• Total caloric intake has increased by 500 calories per head per day.
• Percentage of fat has decreased from 40 to 32%
• Protein intake is practically unchanged.
• The increased caloric intake is mostly carbs!
• Of course, it may still be a different story on an individual basis...

Fat intake and prevalence of overweight among US adults

American Nutrient intake 1971 to 2000
Between 1965 and 2002, U.S. beverage consumption increased from 11.8 to 21.0% of all calories consumed

- 222 more kilocalories per person per day
- With sugar-sweetened beverages accounting for 60% of the increase

**NEJM 2011-Nurses Health Study**

- Weight change was most strongly **positively** associated with (per serving)
  - potato chips (1.69 lb)
  - potatoes (1.28 lb)
  - sugar-sweetened beverages (1.00 lb)

- Inversely associated with
  - intake of vegetables (−0.22 lb)
  - whole grains (−0.37 lb)
  - fruits (−0.49 lb)
  - nuts (−0.57 lb)
  - yogurt (−0.82 lb)
Not enough vegetables?

Take Home Message #4

- Increased intake of carbs in general and refined sugar in particular (mostly in the form of sugar-sweetened beverages) is the biggest driver of the obesity epidemic

So which diet works best?
Metabolic parameters

• TG dropped more in the low-carb group (-28% vs... +1.4% at 1 year)
• No significant difference in total cholesterol or LDL
• HDL rose 18.2% in the low-carb group vs... 3.1% in the low-fat group
• Insulin sensitivity improved significantly in both groups by 6 months but not at 12 months.
Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet.


- 2-year trial, 322 obese subjects: low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non-restricted-calorie.
  - The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group.
  - Ratio of total cholesterol to HDL cholesterol decreased 20% in the low-carb group and 12% in the low-fat group.
  - Changes in FBG and insulin levels were more favorable in the Mediterranean diet than among those assigned to the low-fat diet.

2 years out...

![Graph showing weight changes between diet groups after 2 years.]

Same Groups at 6 years out...

![Graphs showing changes in weight, HDL, LDL, FBG, and insulin levels between diet groups after 6 years.]
Low Carb diets best for Wt loss and CV risk factors


Take Home Message #5

- Low-carb diets work better than low-fat diets in most studies and lead to bigger improvements in metabolic parameters
- Nothing works to make obese people THIN
- Most dieters regain weight in 2-3 years
Some things that do seem helpful

Fiber

- Yes, its good for you
- Decreases glycemic index
- Decreases cholesterol absorption
- Increases satiety
- The quest for fiber makes you eat natural food instead of preserved processed food......
- But it doesn’t make you lose weight much better than any other diet

Monounsaturated fat rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. Paniagua J, et al.

- Eleven volunteers, offspring of obese type 2 diabetic patients.
- On high carb diet, fat mass was redistributed toward the abdominal depot compared with isocaloric MUFA-rich and high-SAT diets.
- Carb rich diet was also associated with decreased postprandial mRNA adiponectin levels in peripheral adipose tissue
- and lower insulin sensitivity index values from a frequently sampled IVGTT in patients (ANOVA P < 0.05).
Am J Clin Nutrition May 2014: Dairy and Yogurt to prevent cardiometabolic diseases. Review

• Replacing SFAs with carbohydrates with a high glycemic index is associated with a higher risk of CAD.
• Paradoxically, observational studies indicate that the consumption of milk or dairy products is inversely related to incidence of CVD.
• Calcium and other bioactive components may modify the effects on LDL cholesterol and triglycerides. Yogurt may also exert beneficial probiotic effects.
• The consumption of yogurt, and other dairy products, in observational studies is associated with a reduced risk of weight gain and obesity as well as of CVD, and these findings are, in part, supported by randomized trials.

Glycemic Index

• The glycemic index (GI) indicates a food’s effect on a person’s blood glucose and typically ranges between 50 and 100, where 100 represents the standard, an equivalent amount of pure glucose. i.e. how fast blood glucose rises in response to a standard amount of any given food
• White bread has a high glycemic index, but so does watermelon
• But watermelon has far fewer carbs per serving
• To solve this problem, the concept of glycemic load was introduced (GI x grams of carbs per typical serving of the food)
• Some studies indicate that lower glycemic index is better especially in diabetes, but the evidence of benefit in obesity and prediabetes is not as convincing as originally postulated.
• Higher carb load load matters more than glycemic index
• Stress on GI may cause people to avoid healthy foods (fresh fruits and vegetables)
• Fails to account for effect of other elements of “real-life” meals (e.g. fat, protein, bubbles in bread)

Cooler Temps May Boost Calorie-Burning 'Brown Fat,' Mouse Study Suggests
Time of Day?

- Some suggestion that all meals are not created equal
- Better to eat during the day?
- Evidence is not yet conclusive

Many Meals or Few?

- No one knows for sure...

Probiotics, Prebiotics and Synbiotics

- Probiotics are live cultures that increase the content of beneficial bacteria in the gut (e.g. yogurt with live cultures)
- Prebiotics are complex molecules that pass undigested into the lower gut and serve as substrate for the growth of healthy bacteria
- Synbiotics are combinations of probiotics and prebiotics that increase the number of good bacteria in the lower gut
- All of them seem to be good for you
Sleep Deprivation

- Alterations in energy expenditure and energy intake have been observed after experimental sleep disruption.
- Most studies indicate that the weight gain associated with sleep restriction is likely due to increased energy intake.
- Less than 6 hours of sleep per night in adults is associated with increased weight gain and metabolic abnormalities.

Fructose?

- Excessive intake of fructose is associated with worsening metabolic parameters (just because it means more sugar? Or specific fructose effects on liver metabolism?)
- Sucrose is 50% fructose.
- High Fructose Corn Syrup = 55% Fructose.
- HFCS is bad not because it has far more fructose than sugar, but because its CHEAPER than sugar.

Other good things...

- Breastfeeding
- Eat Breakfast
- Eat nuts (in moderation)
- Eat avocados
- Eat lentis/pulses
- Eat fresh fruits and vegetables (fewer toxins, more antioxidants)...but evidence of benefit is not dramatic
- Get enough calcium and vitamin D
Exercise

Is BMI more important than being fit?

No
• Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC)1,2,3,4,5,6
• 334,161 European men and women. The mean follow-up time was 12.4 y
• Avoiding all inactivity would theoretically reduce all-cause mortality by 7.35% (95% CI: 5.88%, 8.83%). Corresponding estimates for avoiding obesity (BMI >30) were 3.66% (95% CI: 2.30%, 5.01%). The estimates for avoiding high WC were similar to those for physical inactivity.

## Take Home Message #6

• Fitness trumps Fatness

### Fitness trumps fatness

<table>
<thead>
<tr>
<th>Adiposity Measure</th>
<th>No. of Deaths</th>
<th>Ratea</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>WC</td>
<td>115</td>
<td>0.8</td>
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<tr>
<td>BMI ≥30</td>
<td>51</td>
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<td>1.2 (1.0, 1.4)</td>
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<td>Waist circumference</td>
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<td>1.2 (1.0, 1.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>66</td>
<td>1.2</td>
<td>1.2 (1.0, 1.4)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- Estimates for BMI ≥30 were similar to those for avoiding obesity (BMI >30). The estimates for avoiding high WC were similar to those for physical inactivity.
Increasing Energy Output

• Exercise:
  – How much would it take to become thin?
  – A lot more than an average adult or child will voluntarily do.
• But you CAN become fitter even if you don’t slim down

Alterning Normal Physiology

Heavy exercise = 8-10 kcal/min for a 70 kg person
Rule of thumb: 500 Cal per hour
1-2 hours per day to offset a 500-1000 calorie dietary excess.
A typical burger, fries and coke = 700-1000 calories.

Recommend Exercise

• Activities that can be incorporated into everyday life, such as brisk walking, gardening or cycling
• Supervised exercise programs
• Other activities, such as swimming, aiming to walk a certain number of steps each day, or stair climbing.
• Take into account the person’s current physical fitness and ability for all activities.
• Encourage people to also reduce the amount of time they spend inactive, such as watching television, using a computer or playing video games.
DRUGS

• May add an additional few kg of weight loss (individual patients may benefit much more)
• There is no miracle pill because:
  – Redundancy
  – Multiple functions
  – For example, Rimonabant

Orlistat

• Gastrointestinal lipase inhibitor: Orlistat is the only drug available for children for long-term treatment of obesity.
• It blocks the digestion and absorption of ingested dietary fat. (reversible inhibitor of pancreatic, gastric, and carboxyl ester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract)
• Side effects include flatulence, fecal incontinence, cramps, and oily spotting. There can also be impairment of absorption of vitamin A, E, and beta-carotene.

Lorcaserin

• Serotonin agonists: Lorcaserin is a selective serotonin agonist that acts centrally to reduce appetite, aiding weight loss.
• Adverse effects include headache, upper respiratory infections, dizziness, and nausea.
• While there is little evidence of serotonin-associated cardiac valvular disease (as seen with nonselective serotonergic agonists fenfluramine and dexfenfluramine), long-term data is currently limited.
• Not approved for children
Sympathomimetics
- Sympathomimetic medications: Phentermine and diethylpropion currently approved for short-term treatment of obesity.
- Stimulate early satiety.
- Side effects include increased blood pressure and increased pulse.
- They are Schedule IV drugs with a potential for abuse. Other sympathomimetic drugs that have been removed from the market due to concerns about cardiovascular safety are sibutramine, phenylpropanolamine, and ephedrine.
- Not approved in children

Bupropion and Fluoxetine
- Antidepressants: While not FDA-approved for treatment of obesity alone, bupropion and fluoxetine are antidepressants that have been associated with modest weight loss.

Zonisamide and Topiramate
- Antiepileptic drugs: Zonisamide and topiramate (also used in migraine therapy) have been associated with weight loss in clinical trials but are not currently FDA-approved for treatment of obesity alone.
Combinations

- Phentermine and Topiramate (Qsymia)
- Bupropion and Naltrexone (Contrave)
- Not approved for children

Pramlintide and GLP-1 agonists

- Pramlintide (synthetic human amylin), and glucagon-like polypeptide-1 agonists (exenatide, liraglutide) have been associated with weight loss in the treatment of individuals with diabetes.
- The FDA has approved liraglutide for weight-loss in adults as the drug Saxenda

Meta-analysis: **Metformin Treatment** in Persons at Risk for Diabetes Mellitus

*The American Journal of Medicine, Volume 121, Issue 2 (February 2008)*

<table>
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<th>Study Year (Reference)</th>
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<tr>
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<tr>
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<td>Huang 2006 (6)</td>
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<td>Li 1999 (8)</td>
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<td>Minja 2000 (9)</td>
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<td>Mukherjee 2006 (10)</td>
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</table>

Total 100.0

Test for heterogeneity: Chi² = 17.96 (P < 0.05), I² = 49%
Test for overall effect: Z = 2.88 (P = 0.004)
Take Home Messages

• Metformin may help obese adolescents lose weight
• It may prevent weight gain
• It definitely delays onset of diabetes
• Side effects are minor and usually tolerable
• Cost is low

Take Home Message #7

• Metformin may be the first line drug to use in patients not responding to lifestyle advice
• Orlistat may help too but side effects limit its use

Bariatric Surgery
Bariatric Surgery DOES Work

Pediatric patients
Guidelines were issued in 2004 by the pediatric surgery association and they recommend surgery for:
• Adolescents who have failed 6 months of organized attempts at weight management, as determined by their primary care provider
• Have attained or nearly attained physiologic maturity
• Severely obese (BMI > 40) with serious obesity-related comorbidities or have a BMI of > 30 with less severe comorbidities
• Demonstrate commitment to comprehensive medical and psychologic evaluations both before and after surgery
• Agree to avoid pregnancy for at least 1 year postoperatively
• Be capable of and willing to adhere to nutritional guidelines postoperatively
• Provide informed assent to surgical treatment.
• Have a supportive family environment

Laparoscopic Sleeve Gastrectomy
(Gastric Sleeve)
Weight loss after malabsorptive bariatric surgery reaches a nadir ~12–18 months postoperatively.

There is usually about 10% regain of weight during the next decade.

Weight loss is more gradual for the restrictive LAGB procedure but may continue for several years.

In purely restrictive procedures, failure to experience optimal weight loss has been associated with consumption of calorically dense liquids that can pass through the stoma without producing satiety.
Public Health

- Legislative and other community-wide efforts to tackle obesity
- 12 million obese children
- 30,000 pediatricians
- We need public health efforts rather than a one-on-one medical model of disease treatment

Availability of healthy food

As part of its report, Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation, the IOM identified the goal “to create food and beverage environments that ensure that healthy food and beverage options are the routine, easy choice.”

Problem: we don’t really know enough about what is healthy or unhealthy

Healthy Food is not necessarily more expensive

- The USDA recently issued a report comparing the prices of healthy and less healthy food
- The results of this analysis show that the actual cost of healthier food is not necessarily higher than unhealthy food.
- Availability and preparation habits may matter more
• A “food swamp” is defined as “a geographic area where the overabundance of high energy food (for example, caloric snacks sold at convenience stores) inundate[s] healthy food options.”
• Food Swamps are typically areas with multiple fast food options, but limited or no fresh food options
• Food Swamps and Food Deserts can overlap

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Public Policy

• Food labels
• Menu Calories
• School lunches
• School Soda machines/Snacks
• PE at school
• Taxes on unhealthy food. Soda and chips are the low hanging fruit

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Public Policy.

• More parks, recreation areas, bike paths
• Public transport
• Exercise opportunities at work
• Safer streets
• Communal activities
• Big city living? (farms>Big Cities>>suburbs)
• Homework?
What Works in Public Policy

- point-of-decision prompts such as signage encouraging the use of stairs;
- school-based interventions for children and youth (e.g., increased frequency/duration of physical education classes, additional training for teachers);
- comprehensive worksite programs that include counselling, education, incentives and access to supportive facilities such as locker rooms, showers and gyms;
- point-of-purchase strategies, such as menu and shelf labelling, to increase the purchase and consumption of healthier foods;
- workplace, school and municipal policies and environmental supports that increase access to healthier foods and beverages (e.g., in vending machines restaurants and cafeterias);
- systematic nutrition reminders and training for health care providers.

The Talk

- “Easy-gainers” and “the naturally thin”
- Hard to lose weight. Your body will fight wt loss
- Persevere
- You DON’T have to become thin, just fitter
- Focus on health and function rather than appearance.
- Avoid scare tactics as they don’t really influence behavior

Encourage:

- Physical activity. Small changes add up. Walk to health.
- Mono-unsaturated fats (Olive oil, avocados, nuts, canola, sunflower, corn, peanut, butter)
- Polyunsaturated fats (canola, other vegetable oils, fish, nuts, avocados, cheese) in moderation
- Saturated fat may be more or less neutral
- Increase fiber
- More fruits and vegetables...probably
- Involving the whole family
- Public Health Measures
Discourage:

- Trans fats (margarine, shortenings, deep-fry oil, but new versions have less or no Trans fat)
- Soda-pop AND juice (EAT fruit, don’t drink it)
- Processed foods and fast food
- Packaged snacks
- Screen time
- Yo-yo dieting
- “Fatism” and bullying of overweight people

We know less than we imagine, but more than we use...

Recommendations should be based on real data, not fashionable opinion
What seems like common sense may still be false

Fig 4. Weight change and mortality among overweight diabetes patients with an ‘intention to lose weight’.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0146889
Type 2 Diabetes in youth

- The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both.

- **Type 2 Diabetes**: Diabetes due to a progressive insulin secretory defect on the background of insulin resistance

- Typically characterized by a combination of insulin resistance and beta-cell dysfunction associated with obesity. In some cases, antibodies are present and the patient may have features of both type 1 and type 2 diabetes.

- The term *diabetes* (Greek: διαβήτης) was coined by Aretaeus of Cappadocia.

- In 1675 Thomas Willis added the word *mellitus* to the disease, a word from Latin meaning "honey", a reference to the sweet taste of the urine. This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, and Indians.
History, continued

- 1922: Sir Frederick Grant Banting and Charles Herbert Best showed that they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs.
- Banting, Best, and colleagues (including Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto.
- The first patient was treated in 1922. For this, Banting and laboratory director MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip.
- Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision.
- The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936.

Banting and Best

Some more history

- 1942: Identification of the first of the sulfonylureas
- 1955: The determination of the amino acid sequence of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize)
- 1960s: Radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)
- 1990s: Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects
- Analog Insulins
  - Lispro (Humalog) 1996 (lysine–proline switch)
  - Aspart (Novolog) 2000 (proline replaced by aspartate)
  - Glargine (Lantus) 2000 (crystals)
Pathophysiology

Genetic Risk for Obesity/T2DM

<table>
<thead>
<tr>
<th>Calories, sedentary lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Insulin resistance/hyperinsulinemia/EARLY beta cell dysfunction</td>
</tr>
<tr>
<td>PCOS, Metabolic Syndromes</td>
</tr>
<tr>
<td>Acanthosis Nigricans</td>
</tr>
<tr>
<td>T2DM</td>
</tr>
<tr>
<td>Islet cell destruction</td>
</tr>
<tr>
<td>Insulin-deficient T2DM</td>
</tr>
</tbody>
</table>

Progression from pre-diabetes

- Risk of progression: IFG+IGT>IGT>IFG
- Abnormal A1c and OGTT may be discordant, but since both are associated with future complications and diabetes, so treat whichever is abnormal

Diabetes risk is also not the same in everyone who is obese

- Everyone who is obese does not have diabetes
- Diabetes rates are higher in those with a family history of diabetes
- They are also much higher in some ethnic groups
- Especially Native Americans, Pacific Islanders, Arabs and South Asians
T2DM in Children

- T2DM: disease in the child who typically
  - BMI ≥85th for age and gender
  - has a strong family history of T2DM
  - has substantial residual insulin secretory capacity at diagnosis (reflected by normal or elevated insulin and C-peptide concentrations)
  - has insidious onset of disease
  - demonstrates insulin resistance (including clinical evidence of polycystic ovarian syndrome or acanthosis nigricans)
  - and lacks evidence of diabetic autoimmunity.

Defining T2D in Children

- Dysglycemia is a continuous spectrum
- Cut-off in adults was designed to capture risk of developing complications
- Since kids with T2D have more rapid deterioration and earlier complications: should cut-off be different?
- For now, same as adults
Presentation

- Asymptomatic – Approximately 40 percent
- Symptomatic (eg, polydipsia and polyuria) without ketonuria or acidosis – 57 to 70 percent
- Diabetic ketoacidosis (DKA) – 5 to 13 percent (more in AA)
- Hyperglycemic hyperosmolar state (HHS) – Uncommon but serious (more in AA)
- In adolescent girls, vaginal discharge or vulvovaginitis due to candidiasis can be the initial chief complaint

| Characteristics of type 1 and type 2 diabetes mellitus in children and adolescents |
|-----------------------------------------------|-----------------|-----------------|
| **Type 1 diabetes** | **Type 2 diabetes** |
| Prevalence | Common | Increasing |
| Age at presentation | Throughout childhood | Puberty |
| Onset | Acute severe | Insidious to severe |
| Affected relatives | Common | About one-third |
| Insulin resistance | 3 to 10 percent | 73 to 90 percent |
| Inheritance | Polygenic | Polygenic |
| HLA-DR1/3/4 | Strong association | No association |
| Ethnicity | Most common in non-Hispanic white | All |
| Insulin secretion | Decreased/absent | Variable |
| Insulin sensitivity | Normal when controlled | Decreased |
| Insulin dependence | Permanent | Episodic |
| Obesity or overweight | 20 to 25 percent overweight | >60 percent obese |
| Acetohexicotic state | 12 percent | 30 to 50 percent |
| Pancreatic antibodies | Yes | No |

Clinical features distinguishing type 1 diabetes, type 2 diabetes, and maturity onset diabetes of the young

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis (years)</td>
<td>Majority &lt;25 but may occur at any age</td>
<td>Typically &lt;25 but incidence increasing in adolescents, paralleling increasing rates of obesity in children and adolescents</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Weight</td>
<td>Usually thin, but with obesity developing by adolescence, becoming more common</td>
<td>&gt;60 percent at least overweight</td>
<td>Similar to general population</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Normal when controlled</td>
<td>Decreased</td>
<td>Normal (may be decreased in cases)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>Infrequent (5 to 10 percent)</td>
<td>Frequent (75 to 90 percent)</td>
<td>Multigenerational, n. &gt;2 generations</td>
</tr>
<tr>
<td>Risk of diabetic ketoacidosis</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Management of type 2 diabetes in children and adolescents

Prevalence of type 1 and type 2 diabetes in children and adolescents in the United States, 2001 and 2009

Incidence of diabetes mellitus by age group
• Half to three quarters of children and adolescents with T2DM have at least one affected parent
• TODAY Study (Treatment Options for Type 2 Diabetes in Adolescents and Youth), 60 percent of study participants had a positive family history of diabetes in a first degree relative while 89 percent had a positive family history of diabetes with the addition of grandparents
• The offspring of a parent with T2DM has an estimated 20 percent risk of developing T2DM by late adulthood
• The risk rises to 30 percent if both parents are affected (about six times the risk of an individual without parental T2DM).
• In monozygotic twins with one affected twin, the other twin has a 90 percent chance of developing diabetes

Treatment
• Initial treatment of blood pressure consistently at, or above, the 95th percentile on at least 3 occasions should consist of efforts at weight loss reduction, limitation of dietary salt, and increased activity.
• If, after 6 months, blood pressure is still above the 95th percentile for age, gender, and height, initiation of an angiotensin-converting enzyme inhibitor (ACEI) should be considered to achieve blood pressure values that are less than the 90th percentile.
• If ACE inhibitors are not tolerated because of adverse effects (most commonly cough), an angiotensin receptor blocker could be used.
• If adequate control of hypertension is not achieved, referral to a physician specialist trained in the treatment of hypertension in youth is recommended.

• Oral agent plus a single injection of a long-acting insulin: Twice a day BG monitoring (fasting plus a second BG concentration – ideally 2-hour post prandial)
• Multiple Daily Insulin Injections: Pre-meal and Bedtime Testing
• Although normoglycemia may be difficult to achieve in adolescents with T2DM, a fasting BG concentration of 80-130 mg/dL is a reasonable target for most.
A New Approach: Monthly GA Testing

- Glycated hemoglobin (HbA1c) marker for patients with anemia (hemolytic, iron deficiency, iron treatment)
- Accurate glycation marker during pregnancy
- Accurate glycation marker for patients with diabetic nephropathy on hemodialysis
- Accurate glycation marker for patients with hemoglobinopathies (Sickle Cell)
- Stable, accurate, and timely marker during pregnancy
- Glycated albumin marker for patients with chronic renal failure (diabetic nephropathy)
- Shows change in short-term glycemic control status
- Serum GA may better reflect postprandial hyperglycemia
- Accurate glycation marker for patients with anemia (hemolytic, iron deficiency, iron treatment)

Co-morbidities

- Hypertension
- Dyslipidemia
- Retinopathy
- Microalbuminuria
- NAFLD (more in Hispanics)
- Depression
- Orthopedic (SCFE, Blount disease)

Complications: type 1 vs type 2

- Hypertension more common in type 2 diabetes compared to type 1 (36 and 28%).
- Youth with type 2 diabetes have significantly higher rates of microalbuminurina and hypertension than their peers with type 1 diabetes, despite shorter diabetes duration and lower A1C.
- The results of this study support recommendations for early complications screening and aggressive targeting of glycemic control in patients with type 2 diabetes.

Hypertension

- Hypertension is a significant comorbidity associated with endothelial dysfunction, vessel stiffness, and increased risk of future CVD and chronic kidney disease for the child with diabetes.
- It is present in 36% of youth with T2DM within 1.3 years of diagnosis and was present in 65% of youth with T2DM enrolled in the SEARCH for Diabetes in Youth Study (SEARCH study).

Higher risk for CVD

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>27.24</td>
<td>65.63</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>18.11</td>
<td>65.63</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>10.05</td>
<td>61.46</td>
</tr>
<tr>
<td>High waist circumference</td>
<td>21.28</td>
<td>95.89</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>21.4</td>
<td>92.7</td>
</tr>
</tbody>
</table>


Dyslipidemia

- Long-term complications of T2DM in children and adolescents are not as well documented as those found in adults.
- The SEARCH study found that 65% of 2,096 youths with T2DM had hypertriglyceridemia, and 60% had a low HDL level.

**Retinopathy**

- Retinopathy is well documented in adults but descriptions of its frequency and associations with other comorbidities in youth are limited.
- Some observational and case control studies show that retinopathy in adolescents with T2DM is present earlier than in adults, whereas others indicate that it appears much later.

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**Screening**

- Patients with T2DM should have an initial dilated and comprehensive eye examination performed by an ophthalmologist or optometrist shortly after diabetes diagnosis.
- Subsequent examinations by an ophthalmologist should be repeated annually.
- Less frequent examinations may be considered (eg, every 2–3 years) after 1 or more normal eye examinations.
- More frequent examinations are required if retinopathy is progressing.

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**Microalbuminuria**

- It may be present at diagnosis in youth with T2DM.
- Higher rates of microalbuminuria have been reported among youth with T2DM than T1DM.
- Diabetic nephropathy may also be more frequent and severe among youth with T2DM.
Microalbuminuria

- An abnormal value should be repeated as exercise, smoking, and menstruation can affect results and albumin excretion can vary from day to day.
- The diagnosis of persistent abnormal microalbumin excretion requires documentation of 2 of 3 consecutive abnormal values obtained on different days.
- Orthostatic proteinuria is not uncommon in adolescents and usually is considered benign.
- For that reason, all patients with documented microalbuminuria should have a first morning void immediately on arising to determine if this is the case.

Screening

- Screening for microalbuminuria should begin at the time of T2DM diagnosis and be repeated annually.
- microalbumin-to-creatinine ratio is recommended.

Treatment

- Treatment with an ACE inhibitor should be initiated in nonpregnant individuals with confirmed persistent microalbuminuria, even if blood pressure is not elevated.
- If possible, treatment with an ACE inhibitor should be titrated to normalization of microalbumin excretion.
Finger-stick BG monitoring

- **Newly Diagnosed T2DM**: Fasting, Premeal, and Bedtime Testing regardless of prescribed treatment plan until reasonable metabolic control is achieved.
  - Once BG concentrations are at target levels, the frequency of monitoring can be modified depending on the medication used, the regimen’s intensity, and the patient’s metabolic control.
- **Single bedtime long-acting insulin**: committee suggests daily fasting BG measurements.
- **Oral agents**: an infrequent or intermittent monitoring schedule may be adequate

Depression

- Depression is a significant comorbidity that can complicate the medical management of diabetes and is associated with poor adherence.
- Lawrence et al also found higher levels of depressed mood to be associated with poor glycemic control and number of emergency department visits among participants with both T1DM and T2DM, compared with youth with T1DM and T2DM who had minimal levels of depressed mood.

NAFLD

- Serum alanine aminotransferase (ALT) is elevated more than twice normal in about 20 percent of youth with T2DM, and in most cases this is attributable to NAFLD
- Abnormalities include hepatic steatosis (increased liver fat without inflammation) and nonalcoholic steatohepatitis (NASH, increased liver fat with inflammation).
- NASH may lead to fibrosis, cirrhosis, and liver failure if untreated.
- However, for patients with simple steatosis or mild steatohepatitis, the likelihood and risk factors for progression to more severe liver disease are unknown.
Nonalcoholic fatty liver disease

- Baseline aspartate aminotransferase and alanine aminotransferase concentrations should be obtained, especially if treatment with lipid lowering drugs is instituted.
- Referral to a pediatric or internal medicine gastroenterologist may be indicated.

Obstructive sleep apnea

- The diagnosis of obstructive sleep apnea can only be made reliably by using a sleep study.
- If the diagnosis is made, an electrocardiogram and possibly an echocardiogram should be obtained to rule out right ventricular hypertrophy.
- Referral to a pediatric cardiologist, internal medicine cardiologist, or sleep specialist may be indicated.

Orthopedic problems

- These comorbidities (especially slipped capital femoral epiphysis and Blount disease) require immediate referral to a specialist in orthopedics and will limit the physical activity that can be prescribed to the individual.
• Obesity, specially CENTRAL obesity (android)
• Positive family history
• Specific racial and ethnic groups (Native American>African American>Hispanic>Pacific Islander>Asian>White)
• Female gender
• Conditions associated with insulin resistance (PCOS, Metabolic Syndrome)
• Substantial residual insulin secretion (may be low at dx due to glucotoxicity)

To compare the prevalence of diabetes complications and their risk factors in youth with type 1 versus type 2 diabetes

• Hypertension were more common in type 2 diabetes compares to type 1 (36 and 28%).
• Youth with type 2 diabetes have significantly higher rates of microalbuminuria and hypertension than their peers with type 1 diabetes, despite shorter diabetes duration and lower A1C.
• These results support recommendations for early complications screening and aggressive targeting of glycemic control in patients with type 2 diabetes.

Second line oral agents

• SU are most frequently used second-line therapy because of their well-established efficacy and low cost but with known side effects of hypoglycemia and weight gain
• DPP IV inhibitors and GLP-1 agonists not yet approved for children.
• SGLT-2 inhibitors are class of drug recently being used in treatment of T2DM. Both Canagliflozin and Dapagliflozin have received US FDA approval. Not yet approved in children. Increased risk of UTI.
Statins and Diabetes

- Statins increase the risk of type 2 diabetes
- Sattar et al: 13 statin trials with 91,140 participants. Statin therapy associated with 9% increased odds for incident diabetes (odds ratio, 1.09; 95% CI 1.02–1.17)
- In those at risk for CV disease, risks are outweighed by CV benefits: 5 to 10 major adverse cardiovascular events prevented for each excess case of T2DM with 4 years of statins
- But the younger you start, the less favorable the risk-benefit ratio?
- Mechanism uncertain
- Little or no effect of statins on known diabetics

Crucial Diabetes Trials

- DCCT: 1983/93 TYPE 1 DM. Showed value of good control in preventing complications
- United Kingdom Prospective Diabetes Study (UKPDS), 1977-97, released in 1999, found similar results for people with type 2 diabetes
- ACCORD: Older Adults with TYPE 2 DM:
  - Intensive treatment was worse than standard care
  - Fibrates did NOT help reduce CVD
- ADVANCE: T2DM, No increase in mortality, but no benefit in those ≥65%
- T2DM trial: adolescents with T2DM, either metformin alone, metformin and a lifestyle intervention, or metformin plus rosiglitazone. The addition of rosiglitazone but not the lifestyle intervention was superior to metformin alone. The metformin treatment failure rate was higher than is seen in older adults with T2DM and suggests that younger adults with T2DM are likely to require more aggressive polypharmacy early in the course of their disease. This trial also suggests that the benefits of lifestyle interventions in adolescents with T2DM may be limited

Primary Glucose Lowering Effect of Metformin May be in the Gut

- Delayed release metformin (Met DR) is formulated to deliver drug to the lower bowel to leverage the gut-based mechanism of metformin action with lower plasma exposure. Met DR was assessed in two studies. Study 1 compared the bioavailability of single daily doses of Met DR to currently available immediate-release metformin (Met OD) and baseline values from study 2. Met OD was administered twice daily (Met OD bid).
- RESEARCH DESIGN AND METHODS Study 1 was a Phase 1, multicenter, randomized, double-blind crossover study in 20 subjects. Study 2 was a 2-week, Phase 2, multicenter, placebo-controlled, double-dose, double-blind study in 248 subjects with T2DM and DM. The study used Met OD once daily (Met OD qd) or 1,500 mg extended-release once daily (extended-release Met OD qd).
- RESULTS The bioavailability of 250 mg Met OD bid was ~60% that of Met OD and Met OD (Study 1). In Study 2, Met OD and 1,500 mg Met OD qd produced statistically significant, clinically relevant, and sustained reductions in fasting plasma glucose. The level was maintained throughout the day. Subjects had a higher cholesterol/lipid profile, with LDL cholesterol values being lower than those in the Met OD qd group. The level of total cholesterol and triglycerides in the Met OD qd group was lower than in the Met OD qd group. All adverse events were consistent with Met OD and Met OD qd, without any change in HbA1c. All treatments were generally well tolerated, and adverse events were consistent with Met OD and Met OD qd, providing further evidence for a gut-based lower bowel mediated mechanism of metformin action.

CONCLUSIONS Dissemination of the glucose effect from plasma exposure with gut-restricted Met DR provides strong evidence for a primarily lower bowel-mediated mechanism of metformin action.
Known and Unknown Unknowns...

• How bad is obesity?
• What diets are best?
• Are most guidelines bunk?
• Could weight loss be bad for some people with type 2 diabetes?
• Is weight loss bad for victims of heart disease?

Thank you