Obesity in 2022:
A New Era in Obesity Care

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Obesity Treatment 2022: Innovations in Obesity Care
Disclosures

I am currently or have recently been a paid consultant to the following companies and organizations:

Amgen
Boehringer Ingelheim
Gelesis
Gilead Sciences
Eli Lilly & Company
Novo Nordisk

Optum Health
Pfizer
Rhythm Pharmaceuticals
U.S. National Institutes of Health
The Obesity and Nutrition Institute
Xeno Biosciences
Something to consider ...

In 1984, the first papers from the CDC documented that obesity had become epidemic in the U.S.

In 1984, HIV infection was a death sentence ...

... today, HIV infection barely affects life expectancy in the U.S.

Why haven’t we made the same progress in obesity?
What is Healthy People?

**Healthy People 2030** is the U.S. government’s current prevention agenda for building a healthier nation.

It is a statement of national **health** objectives designed to identify the most significant preventable threats to **health** and to establish national goals to reduce these threats.

It was begun in 1979 and is renewed every 10 years.
Healthy People 2020 study

We characterized 3 types of goals:

**Outcome goals:** Objective, **clinical outcomes**

**Process goals:** Changes in **provider behaviors**, clinical access and procedures

**Nutrition/activity goals:** Changes in **patient behaviors** related to **eating** or **physical activity** (presumed to be determinant of body weight regulation)
Measurement of success toward Healthy People goals

<table>
<thead>
<tr>
<th>Progress toward target</th>
<th>Movement away from target</th>
</tr>
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<tbody>
<tr>
<td>100%</td>
<td>-50%</td>
</tr>
<tr>
<td>50%</td>
<td></td>
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</table>
Obesity outcome goals

NWS-8: **Increase** the proportion of **adults who are at a healthy weight**

NWS-9: **Reduce** the proportion of **adults who are obese**

NWS-10.4: **Reduce** the proportion of **children and adolescents** aged 2 to 19 years **who are considered obese**

HDS-9.1: **Increase** the proportion of **adults with pre-hypertension** who meet the recommended **guidelines for body mass index (BMI)**

HDS-10.2 **Increase** the proportion of **adults with hypertension** who meet the recommended **guidelines for body mass index (BMI)**
Healthy People 2020 outcome goals

Diabetes, Heart Disease and Cancer

Diabetes Outcome Goals

Heart Disease Outcome Goals

Cancer Outcome Goals

Kadambi N, Kaplan LM, 2021
Obesity-related Healthy People 2020 goals

Progress toward 2020 goals

Obesity Outcome Goals

Kadambi N, Kaplan LM, 2021
Obesity process (system behavior) goals

NWS-6.1: Increase the proportion of **physician office visits** made by patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia **that include counseling or education related to diet or nutrition**

NWS-6.2: Increase the proportion of **physician office visits** made by **adult patients who are obese** that include counseling or education related to weight reduction, nutrition or physical activity

NWS-6.3: Increase the proportion of **physician visits** made by **all child or adult patients** that include counseling about nutrition or diet
Obesity-related nutrition goals

NWS-17.1: Reduce the consumption of calories from solid fats
NWS-17.2: Reduce the consumption of calories from added sugars
NWS-17.3: Reduce consumption of calories from solid fats and added sugars
NWS-19: Reduce consumption of saturated fat in the population aged 2 years and older
Obesity-related Healthy People 2020 goals

Progress toward 2020 goals

**Obesity Outcome Goals**

**Obesity Process Goals**

**Obesity-related Nutrition Goals**

Kadambi N, Kaplan LM, 2021
Healthy People – U.S. obesity prevalence goals 2000-2030

Obesity Prevalence (U.S. Adults)
Healthy People – U.S. obesity prevalence goals 2000-2030

Obesity Prevalence (U.S. Adults)

<table>
<thead>
<tr>
<th>Year</th>
<th>Baseline</th>
<th>Target vs. Actual</th>
<th>Target vs. Actual</th>
<th>Target vs. Actual</th>
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<tbody>
<tr>
<td>HP 2000</td>
<td>0%</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>HP 2010</td>
<td>+34%</td>
<td>-23%</td>
<td>-33%</td>
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<tr>
<td>HP 2020</td>
<td>+51%</td>
<td>+25%</td>
<td>-10%</td>
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<tr>
<td>HP 2030</td>
<td>+34%*</td>
<td>+25%*</td>
<td>-7%</td>
<td></td>
</tr>
</tbody>
</table>

Kadambi N, Kaplan LM, 2021
One more thing to consider ...

This is not a uniquely – or even primarily – a U.S. problem

In the past 40 years, **not a single country** in the world has experienced a reduction in the prevalence of obesity

The data show that **we** have failed miserably.
Why have we failed to control obesity?

- The rapid worldwide growth of obesity continues despite increasing knowledge about the health benefits of exercise and healthy diets
  - The growth is worldwide
  - Rich countries and poor
  - All continents, races and cultures
- What are we missing?
  - Is obesity really a primarily volitional problem?
  - Is lifestyle-based therapy adequate to solve it?
Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations.

We enjoy the comfort of opinion without the discomfort of thought.

John F. Kennedy
The world as we know it is built on a story. To be a change agent is, first, to disrupt the existing story of the world, and second, to tell a new story of the world so that people have somewhere to go.

Charles Eisenstein, Author

What is the current story of obesity?

How does it need to change?
In thinking about obesity, our focus has been on biological tools and tactics rather than strategy

- Appetite and other drives to eat
- Food consumption
- Energy expenditure
- Energy balance

But obesity is not the act or process of eating or even gaining weight, it is the state of having too much body fat.
For most tissues, the body seeks a target mass

Red blood cells  Liver

... including fat

Physical **tissue destruction or removal** leads to **rapid regrowth**
Physical removal of body fat leads to rapid regrowth

Defense of a biologically determined body fat mass

Woods SC et al., 1989
Many people don’t realize ...

Whatever the external causes or contributors...

... the final common pathway of all obesity is internal to the body and reflects disrupted physiology
Body fat mass is a physiologically-regulated phenotype

- At multiple stages during development
  - Loss of baby fat
  - Fat changes with puberty
  - Fat changes with aging
  - Fat changes with menopause
- During and after pregnancy

This regulation occurs \textbf{without} our conscious or purposeful input

\textbf{Obesity} results from \textit{inappropriate regulation} of body fat mass
Why obesity is a disease

It results from abnormal physiology
It directly causes pathology
By itself, it diminishes health

Obesity also causes abnormal physiology and disease
It is also a risk factor for other diseases
But it needs to be recognized, respected, treated, and prevented as a disease in its own right
Central controller and effector organs

Heating, Ventilating and Air Conditioning (HVAC)

- Boiler
- Chiller
- Thermostat
- Sensor
- Radiator
- Hot Water
- Fresh Air In
- Stale Air Out
What you might do if your house is too cold

• Buy and install a bigger furnace
• Disconnect your air conditioning system
• Turn up the thermostat
• Determine why its too cold and correct the underlying problem
  • are the windows open
  • is the furnace pilot lit
  • is the oil tank empty
  • is the thermostat set correctly
Feedback regulation of energy metabolism

- GI Tract
- Sensory Organs
- Environmental sensing
- Muscle
- Liver
- Bone
- Irisin
- Metabolic activity and needs
- Leptin
- Energy stores
- Adipose tissue
- Food intake
  - Nutrient handling
  - Energy expenditure
Genes underlying obesity are expressed selectively in the nervous system

>80% of obesity-associated genes are expressed in the nervous system selectively

Locke AE et al. Nature 2015
There must be CNS-driven physiological programs ...

- To **establish** the current **target fat mass** (current fat mass “set point”)
- To **defend** the target fat mass
  - To **store fat** if the body is **below the target**
  - To **mobilize fat** if the body is **above the target**

**Obesity develops because of disruption of the first of these programs.**

In all common forms of obesity, the second program (defense of the target fat mass) appears unaffected.
Why defend the fat mass?

- The body **needs** to defend its appropriate fat mass
  - To shed the excess calories consumed daily
  - To recover appropriately from acute illness or injury
- The body **defends** its fat mass
  - Even if it is abnormally high (i.e., obesity)
What this means ...

Obesity results from \textit{genetic and environmentally driven dysfunction} of the normal fat mass regulatory mechanisms ...

... leading to an \textit{inappropriately elevated} defended body fat mass
The modern environment causes obesity by driving up the target (defended) fat mass

Years of Exposure
Defense of fat mass and body weight

Defended fat mass

Intentional weight gain

Intentional weight loss

Counter regulation

Jonathan Purnell, personal communication
The body uses food intake and energy expenditure to reach and defend its intended fat mass.

There must be physiological programs to drive and coordinate these effects.
During most of adult life, the body defends a fat mass “set point,” a process mediated by metabolic adaptation.
Most body functions are regulated to a set point

- Body temperature
- Water balance
- Immunological activity
- Blood clotting
- Electrolyte balance
- Red blood cell mass

Each of these characteristics is tightly regulated and can be adjusted in response to biological need.
Metabolic compensatory mechanisms - respiratory

- **Baseline**
- **Hypercapnea**
- **Restoration phase**

**Blood CO₂**

**Breathing rate**

- **Restricted breathing**
- **Restoration of normal breathing**

**Physiological compensation**

**Increased respiratory drive**

**Time (minutes)**

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Metabolic compensatory mechanisms – fluid volume

**Thirst**

**Hydration status**

- **Baseline**
- **Hypovolemia**
- **Restoration phase**

**Time (hours)**

- **Euvolemia**
- **Dehydration**
- **Physiological compensation**
- **Increased thirst**
- **Renal fluid conservation**

- **Increased thirst**
- **Renal fluid conservation**
Metabolic compensatory mechanisms – calorie reduction

Appetite / food intake
Fat mass / body weight

Restrictive eating
Increased appetitive drive
Energy conservation
Physiological compensation

Baseline
Hypoadiposity
Restoration phase

Increased
Decreased
Defended fat mass

Time (months)
Together, what this implies is that ...

Overeating does not cause obesity ...

... obesity causes overeating
And ...

Undereating does not fix obesity ...

... fixing obesity leads to undereating

These conclusions have critical implications for the long-term control of obesity
Obesity and its care: a battle of forces that influence the target (defended) fat mass

Bariatric Surgery

Defended body fat mass

Abnormal dietary constituents → Unhealthy muscle → Sleep deprivation → Stress → Disrupted circadian rhythms → Weight gain inducing medications
Defense of set point

Above set point

Gravity

At set point

Gravity

Buoyancy

Below set point

Buoyancy

How could you stably change the vertical position of the ring?
Physiological vs. non-physiological weight loss

Non-physiological weight loss
(e.g., fat excision, caloric restriction, intensive exercise)

Defended Fat Mass

Isolated calorie restriction

Physiological compensation

Increased appetitive drive
Decreased thermogenesis

Restoration of fat mass

Pre-treatment
Short-term weight loss leading to hypoadiposity
“Maintenance” phase (restoration phase)
The major problem is that nearly all obesity treatment in common usage is not physiologically driven.

*Note that eating healthier and moving at least some ARE physiological treatments; but their overall efficacy is limited.

(These subtleties are why understanding obesity is so hard!)
Diabetes Prevention Program (DPP) long-term outcome study

Weight loss abates over time

DPP Research Group, *Lancet* 2009
Any **durably effective** therapy will change the set point

This is the basis of its long-term effectiveness
Physiological vs. non-physiological weight loss

Physiological weight loss
(e.g., physiologically-directed lifestyle change, effective medications, bariatric surgery)

Defended fat mass

Fat mass

Treatment initiation

Decreased appetitive drive
Increased thermogenesis

Pre-treatment
Initial weight loss
Long-term weight loss (not a separate phase)
Physiological vs. non-physiological weight loss

Physiological weight loss
(e.g., physiologically-directed lifestyle change, effective medications, bariatric surgery)

Defended fat mass

Fat mass

Pre-treatment

Initial weight loss

Long-term weight loss (not a separate phase)

Treatment initiation

Decreased appetitive drive

Increased thermogenesis
Removal of effective therapy returns the set point to baseline

Body Fat (and Weight)

Defended fat mass

Begin treatment

Immediate physiological effect

Decreased appetite drive

Increased thermogenesis

Stop treatment

Immediate physiological effect

Increased appetite drive

Decreased thermogenesis
We are entering a new era in obesity treatment: powerful, long-acting peptidomimetics
Glucagon-like peptide 1 (GLP-1)

• GLP-1(7-37) is a 31-amino acid peptide
• Secreted predominantly from L-cells in the gut
• Also secreted by CNS neurons (hindbrain nucleus tractus solitarius)
• Signals through widely distributed G-protein-coupled receptor

![GLP-1 peptide sequence diagram](image-url)
Pleiotropic effects of GLP-1

Adverse effects
- ↑ nausea and vomiting
- ↑ heart rate
- Pancreatitis risk

Efficacy effects
- ↑ insulin biosynthesis
- ↑ beta cell proliferation
- ↓ beta cell apoptosis
- ↑ neuroprotection
- ↓ appetite
- ↑ gastric emptying
- ↓ insulin sensitivity
- ↓ glucose production
GLP-1 and anti-obesity GLP-1 receptor agonists

**Native human GLP-1**
- Enzymatic degradation by DPP-4
- **t½ = 1.5–2 minutes**

**Liraglutide**
- C-16 fatty acid (palmitoyl)
- Albumin-bound
- Slow absorption from subcutis
- Resistant to DPP-4
- **t½ = 13 hours**

**Semaglutide**
- C-18 fatty di-acid
- Albumin-bound
- Slow absorption from subcutis
- Resistant to DPP-4
- **t½ = 7 days**

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; bis-ADA, bis-aminodiethoxyacetyl; t½, half-life


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GLP-1 receptor agonists have widely varying effects on obesity

Adapted from O’Neil PM et al., Lancet 2018; phase 2 study
Maintenance of semaglutide-induced weight loss at two years

STEP 5 Trial
Subjects without Diabetes

Body weight change (%) vs. Time since randomization (weeks)

Placebo
Semaglutide 2.4 mg
Limited effect of IBT on semaglutide-induced weight loss

**STEP 1 Trial**
Subjects without Diabetes

**STEP 3 Trial**
Subjects without Diabetes
Intensive Behavioral Therapy
Long-term benefit of AOMs requires continued treatment

STEP 1 Trial
Subjects without Diabetes

Wilding JPH et al., NEJM 2021
Dual agonists

- Designer molecules that activate two receptors
- Effective when there is a benefit to activating both receptors in the same cell
- Several of the common targets for treatment of metabolic disorders:
  - GLP-1
  - Glucagon
  - GIP
  - PYY
- Because of the success of GLP-1 agonists for the treatment of diabetes, obesity and NASH, GLP-1 agonism is the most common component of dual agonists
Design of dual agonists

**Peptide fusion**

Ligand 1  Ligand 2

Receptor 1  Receptor 2

**Peptide chimera**

Ligand 1  Ligand 2

Receptor 1  Receptor 2
Tirzepatide – a dual GLP-1 + GIP agonist

- **GLP-1 and GIP are the two known incretins** - peptides secreted from enteroendocrine cells in the gut mucosa in response to food ingestion

- **Incretins stimulate insulin and amylin secretion from pancreatic β-cells** under conditions of normal or elevated blood glucose

- **GLP-1 in the brain** decreases appetitive drive and induces fat metabolism and weight loss

- **The role of GIP** on appetite, fat metabolism and energy balance is less clear

- **Tirzepatide** is a single synthetic peptide that **stimulates both GLP-1 and GIP receptors**
Tirzepatide – a peptide chimera dual GLP-1 + GIP agonist

**Human GLP-1**

- **DPP-4**
- **Tyr**
- **Ala**
- **Glu**
- **Gly**
- **Thr**
- **Phe**
- **Thr**
- **Ser**
- **Asp**
- **Val**
- **Ser**
- **Lys**
- **Ala**
- **Gln**
- **Gly**
- **Leu**
- **Tyr**
- **Ser**
- **Val**
- **Glu**
- **Thr**
- **Ala**
- **Trp**
- **Leu**
- **Val**
- **Lys**
- **Gly**
- **Arg**
- **Gly**

**Human GIP**

- **DPP-4**
- **Tyr**
- **Ala**
- **Glu**
- **Gly**
- **Thr**
- **Phe**
- **Ile**
- **Ser**
- **Asp**
- **Tyr**
- **Ser**
- **Asp**
- **Gln**
- **Gln**
- **His**
- **Ile**
- **Lys**
- **Asp**
- **Met**
- **Ala**
- **Ile**
- **Glu**
- **Phe**
- **Val**
- **Asn**
- **Trp**
- **Leu**
- **Leu**
- **Ala**
- **Gln**
- **Lys**
- **Gly**
- **Lys**

**Tirzepatide**

- **C-20 fatty di-acid**
- **Glu**
- **(AEAA)**
- **Tyr**
- **Aib**
- **Glu**
- **Gly**
- **Thr**
- **Phe**
- **Thr**
- **Ser**
- **Asp**
- **Tyr**
- **Ser**
- **Gln**
- **Ala**
- **Gln**
- **Ile**
- **Lys**
- **Asp**
- **Leu**
- **Aib**
- **Ile**
- **Asp**
- **Ala**
- **Gly**
- **Gly**
- **Thr**
- **Phe**
- **Phe**
- **Ser**
- **Ile**
- **Ser**
- **Tyr**
- **Ile**
- **Ile**
- **Leu**
- **Aib**
- **Leu**
- **Val**
- **Trp**
- **Lys**
- **Ala**

**GIP = glucose-dependent insulinotropic peptide**
Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*
Weight reduction on tirzepatide – subjects without diabetes

Subjects on treatment
(Efficacy Estimand)

Weight change from baseline (%)

<table>
<thead>
<tr>
<th>Time from randomization (weeks)</th>
<th>Placebo</th>
<th>TZP 5 mg</th>
<th>TZP 10 mg</th>
<th>TZP 15 mg</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.4%</td>
<td>-16.0%</td>
<td>-21.4%</td>
<td>-22.5%</td>
</tr>
</tbody>
</table>

Baseline wt. = 231 lbs.

Average weight reduction 35-52 lbs.

Jastreboff AM et al., NEJM 2022
So now there are three highly effective obesity therapies ...

**Bariatric surgery**

**Semaglutide**

- C-18 fatty di-acid
- Aib = aminoisobutyric acid

**Tirzepatide**

- C-20 fatty di-acid
- \( \text{AEAA}_3 \)
Lessons of bariatric surgery

- Magnitude matters
- Physiology matters
Malabsorption is associated with hyperphagia

Extensive small bowel resection

Cosnes et al., Gastroenterology 1990
Food intake after intestinal bypass

Intestinal bypass is a truly malabsorptive procedure ... but different from short bowel syndrome, spontaneous food intake *decreases* after this operation.

Bray et al., *Intl J Obes* 1976
Effects of surgery are opposite to those of restrictive dieting

<table>
<thead>
<tr>
<th></th>
<th>Calorie restriction</th>
<th>Metabolic surgery</th>
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<tbody>
<tr>
<td>Energy expenditure</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Appetite</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hunger</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Satiety</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Reward-based eating</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Stress response</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Gut peptides</td>
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<td></td>
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<tr>
<td>Ghrelin</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>GLP-1, PYY, CCK, amylin</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
Lessons of semaglutide

- GLP-1 agonism may not be necessary to prevent obesity, but it is **sufficient to overcome** the pathophysiological lesions of many types of obesity.

- Despite the complexity of body fat regulation, there is at least one mechanism (GLP-1 signaling) that can substantially **re-regulate the whole system**.
Lessons of tirzepatide

- Semaglutide is not a fluke
- It can even be improved upon
- It matters why tirzepatide causes more weight loss than semaglutide

C-18 fatty di-acid

Aib = aminoisobutyric acid

- Cys
- Glu
- BisADA
- His
- Aib
- Glu
- Gly
- Thr
- Phe
- Thr
- Ser
- Asp
- Val
- Ser
- Phe
- Ser
- Ser
- Val
- Tyr
- Ser
- Leu
- Gln
- Lys
- Ile
- Ala
- Trp
- Leu
- Arg
- Arg
- Gly

26
34

Aib = aminoisobutyric acid

Fatty acid
Is GLP-1 a unicorn?

- Are there mechanisms other than GLP-1 that can exert *widespread, beneficial influence* on fat mass regulation?

- Identifying other mechanisms *sufficient to normalize body fat regulation* will determine future opportunities in managing and preventing obesity.
**Amylin receptor agonists – novel candidate AOMs**

**Human Amylin**
- Co-secreted from β-cells with insulin
- Specific agonist of amylin receptors
- No activity on related calcitonin receptors
- Short half-life (1–2 hours)
- Modest weight loss effect in rodents, humans

**Pramlintide**
- Selective agonist of amylin over related calcitonin receptors
- Optimized for treatment of diabetes
- Short half-life
- Modest weight loss effect in rodents, humans

**Cagrilintide**
- Non-selective agonist of amylin and calcitonin receptors
- Long half-life
- Strong weight loss effect in rodents, humans
- Phase 2 study: **10.8% weight loss at 26 wk**

Adapted from Fletcher MM et al., *J Pharmacol Exp Ther* 2021
Combination therapy with semaglutide and cagrilintide

Phase 1B trial – 20 weeks (4 weeks at target dose)
Semaglutide target dose 2.4 mg/week in all groups
NO lifestyle intervention in any group

Body weight change from baseline (%)

Cagrilintide target dose/week (mg)

Semaglutide alone
Obesity therapy since the 1950s

1960-2025

Maximum Average % Weight Loss

Year


0% 5% 10% 15% 20% 25% 30% 35%

Bariatric surgery

Laparoscopy

Standards and accreditation

Intensive lifestyle therapy

Kaplan LM et al., 2022
Little progress in anti-obesity pharmacotherapy

![Graph showing maximum average weight loss and key milestones from 1960 to 2025. The key milestones include the identification of leptin, intensive lifestyle therapy, and bariatric surgery.](image_url)

Kaplan LM et al., 2022
Incremental improvements in anti-obesity medications

![Bar graph showing maximum average weight loss from 1960 to 2025. The graph indicates the following improvements:

- **Gen 2**: Bariatric surgery
- **Intensive lifestyle therapy**: Includes methods such as bupropion-naltrexone, phentermine-topiramate, liraglutide 3.0 mg.]

Kaplan LM et al., 2022
The emergence of truly effective anti-obesity medications

![Graph showing the average weight loss percentage from 1960 to 2025.](image)

- **1960-2025**
- **Max Average % Weight Loss**
  - 0%
  - 5%
  - 10%
  - 15%
  - 20%
  - 25%
  - 30%
  - 35%

- **Year**
  - 1960
  - 1965
  - 1970
  - 1975
  - 1980
  - 1985
  - 1990
  - 1995
  - 2000
  - 2005
  - 2010
  - 2015
  - 2020
  - 2021 (est.)
  - 2025

- **Gen 3**
- Bariatric surgery
- Intensive lifestyle therapy

- **Gen 3 medications**
  - Liraglutide 3.0 mg
  - Semaglutide 2.4 mg
  - Bupropion-Naltrexone
  - Phentermine-Topiramate

Kaplan LM et al., 2022
The emergence of truly effective anti-obesity medications

... mimic the action of native GI and CNS peptides

1960-2025

- Maximum Average % Weight Loss

- Year

- Gen 3

- Bariatric surgery

- Tirzepatide 10-15 mg

- Semaglutide 2.4 mg

- Intensive lifestyle therapy

Kaplan LM et al., 2022
We have entered the 3rd generation of anti-obesity medications

![Graph showing maximum average % weight loss from 1960 to 2030.](image)

Gen 1
- Semaglutide 2.4 mg
- Semaglutide+Cagrilintide
- Danuglipron
- AMG-133

Gen 2
- Tirzepatide 10-15 mg

Gen 3
- Semaglutide 2.4 mg

Kaplan LM et al., 2022
The treatment gap is now closing rapidly

- Invasiveness
- Effectiveness
- Lifestyle Therapies
- Medications
- Semaglutide (17% WL)
- Tirzepatide (22% WL)
- VBLOC
- Gastric Balloon
- Aspire Assist
- Sleeve gastrectomy
- Gastric banding
- Gastric bypass
- Treatment Gap
Combination therapy can enhance effectiveness **without** significantly increasing risk.
The magnitude of weight loss is important

<table>
<thead>
<tr>
<th>Obesity complication</th>
<th>Weight loss for substantial improvement (%)</th>
<th>Benefits increase with increasing weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>5-15</td>
<td>✓</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>✓</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10-15</td>
<td>✓</td>
</tr>
<tr>
<td>Fatty liver disease (NAFLD)</td>
<td>10</td>
<td>✓</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>10</td>
<td>✓</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-15</td>
<td>✓</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>5-10</td>
<td>✓</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>10-15</td>
<td>✓</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>10-15</td>
<td>✓</td>
</tr>
</tbody>
</table>

Adapted from Cefalu WT et al., *Diab Care* 2015
Where will we be next year?

Later in 2022

- Results of trial looking at effect of bariatric surgery on CKD
- Cagrilintide/semaglutide combination begins phase 3 testing
- SELECT semaglutide CV outcomes trial interim analysis
SELECT Trial

- Subjects with BMI $\geq 27$ and established CVD (h/o MI, h/o stroke or symptomatic peripheral artery disease)
- No history of type 2 diabetes
- N=17,600 randomized to semaglutide 2.4 mg/week or placebo
- Primary outcome: 3-factor MACE: CV death, non-fatal MI, non-fatal stroke
- Secondary outcomes: time to CV death, all-cause death, heart failure
- Trial duration based on total major adverse cardiovascular events (MACE)
- Based on total MACE to date, planned interim analysis anticipated in Fall 2022
The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases.

Sir William Osler, 1849-1919
Where will we be next year?

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2023
- Liraglutide goes off patent in 2023
  - Multiple generic pharmaceutical companies will begin to market it beginning next year for treating diabetes
  - And obesity? ... maybe this is a pathway to more equitable access to care
- Potential conclusion and final analysis of SELECT semaglutide CV outcomes trial
Serious barriers to effective obesity care remain
Major challenges to effective obesity care

**PERCEPTION THAT OBESITY IS NOT A DISEASE**
- Misunderstanding of its causes and complications
- Inference that it is the primary responsibility of the patient
- Perception that prevention is far more important than treatment
- Reduced tolerance for any risks of effective treatments

**OBESITY-RELATED PREJUDICE AND STIGMA**
- Discouragement of patients’ seeking medical care for obesity
- Stigma against providers using proven medical and surgical therapies
- Limited availability and reimbursement of proven therapies
- Barriers to development of novel, more effective therapies

*We need to break this vicious cycle*
Major challenges to effective obesity care

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Understanding the science

OBESITY-RELATED PREJUDICE AND STIGMA
- Discouragement of patients’ seeking medical care for obesity
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- Limited availability and reimbursement of proven therapies
- Barriers to development of novel, more effective therapies
Challenges to recognizing obesity as a disease

- Consideration of obesity only as a **risk factor for other diseases**, rather than as a disease on its own

- **Perception that managing obesity is within the ability** of those who have it and, therefore, that its management is their sole responsibility

- Widespread **weight-related stigma** that ascribes blame to the people with the problem and **induces self-blame** in people with obesity

- **Outward manifestation of obesity** that reinforces bias, stigma and discrimination

- Failure to appreciate the normal biology of **body fat mass regulation** that is **disrupted in obesity**
What patients hear

Orson Welles once said “Gluttony is not a secret vice.” Unlike other diseases, most people who suffer from obesity can’t hide it.

It is the very first thing people see when they meet you. And unlike most other diseases, there is a sense of morality to obesity.

“If you only tried harder and exercised some willpower, you could succeed!”

If someone suffers from myopia, they aren’t admonished to just “try harder” to see; “Come on, squint! Wearing glasses or contacts, getting Lasik surgery, that’s taking the easy way out.”
Obesity is grossly undertreated

- 46% of U.S. adults meet recommendations for anti-obesity pharmacotherapy
- < 0.5% are currently treated with anti-obesity medications

How can we change this without going bankrupt?

Adapted from Thomas CE et al., Obesity 2016
Potential therapeutic prioritization strategies

- Degree of obesity (amount of excess body fat) – current criterion
- Overall clinical severity of obesity
  - Presence of specific comorbidities
  - Risk of developing specific comorbidities
  - Overall burden of comorbidities and comorbidity risk
- Overall cost of care and anticipated cost savings with effective therapy
- Patients in whom we’ve already invested in treating obesity (e.g., bariatric surgery)
- Patients highly responsive to obesity pharmacotherapy (by prediction or performance)
- Specific types of obesity (e.g., those of known cause such as genetic, syndromic, hypothalamic or drug-induced)
- Obesity that interferes with effective care of another disease (whether or not a complication of the obesity)
Potential value criteria

• Hard clinical outcome targets
  • Durably maintained weight (not %weight loss) – similar to other diseases
  • Improvement in comorbidities or burden of associated disease
    • Generally requires greater long-term weight loss than has been possible with non-surgical therapy
  • Improvement in clinical risk (e.g., CV outcomes)
  • Decreased cost of care

• Other benefits
  • Improvement in productivity
  • Improvement in patient-reported outcomes
To get all this done ...

We need to ...

- **re-evaluate** what we think we know about obesity
- **recognize** that obesity is a disease *because* it reflects abnormal physiology
- **open our minds** to new ideas and new clinical approaches
- **make obesity a more dominant focus** of all of our attention
... and embrace a “toolbox” of complementary solutions

**Prevention**
- Healthier foods
- Sleep
- Stress reduction
- Circadian
- Physical activity
- Avoid weight gain-promoting drugs
- NEAT

**Lifestyle-based**

**Medications**

**Behavioral**

**Surgery**

**Medical devices**

**Diets**

**Treatment**
We need to integrate different perspectives ...

- Neurophysiology
- Addiction
- Behavior
- Stress
- Foods
- Drugs
- NEAT
- Surgery
- Environment
- Genetics
- Health Risk
- Cost
- Stigma

Exercise

Disease
If we want to treat obesity more effectively ... 

• We have to **fully understand** why it is a disease and how that disease differs from the cultural desire for thinness

• We have to understand what being a disease means for the effective care of obesity (this is the one thing that we can learn from other diseases)

• We have to **fully understand** the barriers to effective obesity care and the forces working against such care

• And most of all, we have to keep **the needs and goals of all people living with obesity** foremost in our minds, even if many have been previously misled by the bias, stigma, blame and discrimination that surrounds them
The 3 most reassuring messages to patients before weight loss

1. **Convey the medical and biological basis** for obesity (removes the blame *without* necessarily saying “it’s not your fault”)

2. **Emphasize the use of limited (achievable) lifestyle changes**

3. **Assure patients that you will not abandon them** (“we now have lots of treatments to choose from”)

Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has.

Margaret Mead, 1901-1978
Cultural Anthropologist

It’s now time to join that “small group” committed to reversing the epidemic of obesity and its many adverse medical, social and economic effects.
Obesity in 2022: A New Era in Obesity Care

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