Modeling the Pathway from Obesity to Type 2 Diabetes

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Abstract
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1 Introduction

Obesity has become a pressing global health challenge, with alarming increases in both adult and childhood populations. In the United States alone, adult obesity rates have risen dramatically from 30.5% in 1999-2000 to 41.9% by 2020, affecting over 100 million adults. Even more concerning is the doubling of severe obesity rates from 4.7% to 9.2% during the same period. This epidemic extends to the younger generation, with approximately 20% of children and adolescents now classified as obese[1;2].

This widespread metabolic disorder is a significant risk factor for Type II Diabetes (T2D), driven by a complex interplay of insulin resistance, beta-cell dysfunction, and systemic inflammation. These metabolic disturbances result in chronic hyperglycemia, which is associated with severe complications, including cardiovascular disease and neuropathy.

GLP-1 receptor agonists, particularly Semaglutide, have emerged as revolutionary treatments in obesity and T2D management. These medications have demonstrated unprecedented efficacy in clinical trials, enabling significant and sustained weight loss while simultaneously improving glycemic control. The SELECT and STEP trials have validated their effectiveness, with long-term studies showing sustained benefits over two to five years[3;4]. The complete mechanism of action extends beyond the well-understood

effects of appetite suppression and delayed gastric emptying.

1.1 Modeling Objectives

The computational model central to this study was developed prior to the advent of GLP-1 agonists and focuses exclusively on simulating the effects of caloric intake modifications. Our approach involves replicating the observed weight loss patterns from clinical trials by modeling equivalent caloric restrictions. This methodology allows us to examine whether other metabolic parameters—such as glucose and free fatty acid (FFA) levels—align with clinical observations.

This validation process serves two crucial purposes. First, it establishes a baseline understanding of how caloric reduction alone influences the metabolic variables associated with obesity-induced T2D. Second, it provides a framework for evaluating the additional metabolic benefits specific to GLP-1 agonists that cannot be explained by reduced caloric intake alone. By identifying discrepancies between model predictions and clinical outcomes, we can highlight areas requiring refinement, ultimately enhancing the model's clinical relevance for current obesity and T2D therapeutic strategies.

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2 Understanding Obesity and T2D

Historical perspective and modern understanding of obesity and diabetes pathways

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2.1 Historical Perspective

The understanding of obesity and Type 2 Diabetes (T2D) has evolved significantly over the past century. Early theories centered primarily on insulin resistance and beta-cell dysfunction as independent phenomena. Researchers initially viewed obesity as a simple imbalance between caloric intake and energy expenditure, while T2D was considered primarily a disorder of insulin production.

This simplified view, while providing a foundation for early treatments, failed to capture the complex interplay between adipose tissue, systemic inflammation, and metabolic regulation. The discovery of insulin in 1921 by Banting and Best marked a pivotal moment, but the intricate relationship between obesity and diabetes remained poorly understood for decades.

2.2 Modern Understanding

Current research reveals a more nuanced and interconnected pathway between obesity and T2D development. This process typically follows a predictable sequence:

Early-Life Positive Energy Balance: The pathway often begins in youth, where sustained excessive caloric intake relative to energy expenditure leads to increased fat storage. This early pattern establishes metabolic changes that can persist throughout life.

Adipose Tissue Expansion and Metabolic Signals: As fat mass expands, adipose tissue undergoes both quantitative and qualitative changes. The growing fat mass secretes increasing amounts of:

- Pro-inflammatory cytokines
- Free fatty acids
- Adipokines that impair insulin signaling

Insulin Resistance and Compensation: In response to impaired insulin signaling, pancreatic β-cells increase insulin production to maintain normal glucose levels. This compensation leads to:

- Chronic hyperinsulinemia
- Progressive insulin resistance
- Increased metabolic stress on β-cells

β-Cell Stress and Dysfunction: The sustained demand for high insulin production creates significant stress on β-cells, resulting in:

- Reduced insulin secretion efficiency
- Progressive β-cell death
- Declining functional β-cell mass

Progression to Youth-Onset T2D: The combination of declining β-cell function and persistent insulin resistance ultimately leads to:

- Inability to maintain normal glucose levels
- Development of prediabetes
- Eventually, full T2D onset

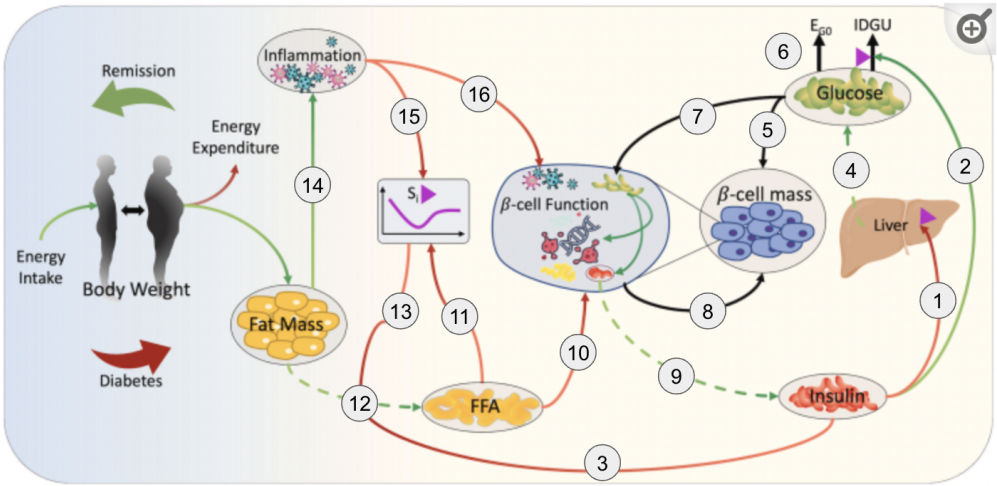

Figure 1: Interconnected pathways in obesity and T2D development. Numbers 1-16 correspond to specific metabolic interactions detailed below.

2.3 Pathway Integration

Understanding these interconnected pathways is crucial for modern treatment approaches. The diagram above (Figure 1) illustrates the complex feedback loops between these systems:

1. **Insulin to Liver:** (Insulin ↑) → (Hepatic Glucose Production ↓)
   High insulin levels increase hepatic insulin sensitivity, reducing the liver's glucose output. In the equation, $HGP = HGP_{\text{bas}} + \frac{\text{hepa\_max}\cdot(a_{\text{hgp}}+k_{\text{gcg}}\cdot gcg)}{(a_{\text{hgp}}+k_{\text{gcg}}\cdot gcg)+\text{hepa\_si}\cdot i}$, larger i (insulin) in the denominator lowers HGP.

2. **Insulin to Glucose:** (Insulin ↑) → (Peripheral Glucose Clearance ↑)
   Insulin enhances glucose uptake in peripheral tissues, increasing clearance. In the glucose balance, $dg = \text{gclamp} + HGP - (eg0 + sci \cdot si \cdot i)g$, a higher i strengthens the removal term $(sci \cdot si \cdot i)g$.

3. **Insulin to FFA:** (Insulin ↑) → (FFA Release ↓)
   Insulin suppresses lipolysis, reducing FFA release. The term $\frac{ksif^{aa}}{ksif^{aa}+(siff\cdot i)^{aa}}$ decreases as i rises, cutting back on FFAs liberated into circulation.

4. **Liver to Glucose:** (Liver → Endogenous Glucose Production)
   The liver contributes to blood glucose through HGP. This endogenous production term, HGP, adds to the glucose pool, influencing overall blood glucose levels.

5. **Glucose to β-cell Mass:** (Glucose homeostasis ↑ or ↓) → (β-cell Mass dynamics)
   β-cell mass adjusts in response to glucose-driven signals for proliferation (p) and apoptosis (a). The metabolic rate m, derived from glucose g, influences p and a, thus determining whether β-cell mass grows or declines.

6. **Glucose to EG0:** (Constant Uptake → Baseline Glucose Clearance)
   Tissues like the brain remove glucose independently of insulin, modeled as $eg0$. This constant term ensures a baseline glucose uptake even in low-insulin states.

7. **Glucose to β-cell Function:** (Glucose ↑) → (β-cell Function ↑, then possibly ↓ with chronic excess)
   Normal glucose enhances β-cell function and insulin secretion. Prolonged hyperglycemia, captured by terms like s_{glucu} and s_{glucd}, eventually impairs function if maintained at excessive levels.

8. **β-cell Function to β-cell Mass:** (Function ↑) → (Mass Maintenance/Growth)
   Higher β-cell function boosts insulin secretion and stimulates proliferation, increasing β-cell mass. Conversely, dysfunctional β-cells fail to support mass, leading to a net decline.

9. **β-cell to Insulin:** (β-cell Activity ↑) → (Insulin Secretion ↑)
   The β-cells produce insulin, with secretion rate isr depending on β-cell function and glucose signals. This links cell health directly to circulating insulin levels.

10. **FFA to β-cell Function:** (FFA ↑) → (β-cell Function ↓)
    Elevated FFAs impair β-cell function (lipotoxicity). The term s_{ffa} increases with FFA, reducing net β-cell functional capacity.

11. **FFA to Insulin Sensitivity (Si):** (FFA ↑) → (Si ↓)
    High FFAs contribute to insulin resistance by lowering Si. The model's $(1 - mffa \cdot \frac{ffa^{nsi\_ffa}}{ffa^{nsi\_ffa} + ksi\_ffa^{nsi\_ffa}})$ term shrinks as FFA grows, diminishing Si.

12. **Fat Mass to FFA:** (Fat Mass ↑) → (FFA Release ↑)
    Larger adipose stores boost lipolysis and FFA release. The $dffa$ equation includes $(cl0 + cl2 \cdot fmass)$, which increases as fat mass grows, raising FFA output.

13. **Insulin Sensitivity (Si) to FFA Release:** (Si ↑) → (FFA Release ↓)
    Improved insulin sensitivity makes insulin more effective at inhibiting FFA release. With higher Si, the term $(ksif^{aa}/(ksif^{aa} + (siff \cdot i)^{aa}))$ declines faster as i rises, reducing FFAs.

14. **Fat Mass to Inflammation:** (Fat Mass ↑) → (Inflammation ↑)
    Excessive adiposity elevates BMI, driving inflammation. The model's $dinfl$ includes a fraction $\frac{bmi^{n\_infl}}{bmi^{n\_infl} + k\_infl^{n\_infl}}$, which rises with BMI, increasing systemic inflammation.

15. **Inflammation to Insulin Sensitivity (Si):** (Inflammation ↑) → (Si ↓)
    Chronic inflammation impairs insulin signaling. In tsi, the factor $(\frac{ksi\_infl}{ksi\_infl + infl})$ diminishes as $infl$ grows, thereby reducing Si.

16. **Inflammation to β-cell Function:** (Inflammation $\uparrow$) $\rightarrow$ (β-cell Function $\downarrow$)
Inflammatory cytokines damage β-cells and hinder insulin production. The term s_{infl} increases with inflammation, reducing net β-cell function (σ).

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3 Setting up the simulation

Processing SELECT trial data and estimating caloric requirements

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3.1 Data from SELECT Trial

To accurately model weight loss across different BMI categories, we analyzed the SELECT trial data[4] using a systematic approach to account for treatment adherence and placebo effects. Our goal was to determine the true treatment effect of semaglutide assuming perfect adherence.

The analysis incorporated three key components from the trial:

- Estimated Treatment Differences (ETD) for each BMI category
- Placebo group weight loss (-1.5% at 4 years)
- Adherence adjustment (+1.5% based on first on-treatment analysis)

The adherence-adjusted weight loss was calculated using:

$$\text{Adjusted Weight Loss} = (\text{ETD} + \text{Placebo Loss}) + 1.5\% \tag{1}$$

BMI Group	**ETD (%)**	**Placebo (%)**	**Initial (%)**	**Adjusted (%)**
BMI <30	-7.52	-1.5	-9.02	-10.52
BMI 30-35	-8.79	-1.5	-10.29	-11.79
BMI 35-40	-9.01	-1.5	-10.51	-12.01
BMI $\geq$40	-9.23	-1.5	-10.73	-12.23

Table 1: Weight loss percentages by BMI category, adjusted for adherence

3.2 Adjusting for our Model

To translate these findings into our simulation framework, we first converted BMI categories to target weights using our model subject's height (1.8m). We then performed a binary search to determine both the pre-treatment caloric intake needed to reach each BMI category and the treatment-phase intake required to achieve the observed weight loss.

This process yielded the following caloric requirements:

When we simulate the model with these caloric requirements, we get the following weight trajectories:

This matched the observed weight loss in the SELECT trial, indicating that our caloric requirements were accurate.

BMI Group	Initial Weight (kg)	Initial Calories	Final Weight (kg)	Final Calories	Weight Change (%)
BMI <30	76.2	2,353	68.2	2,098	-10.5
BMI 30-35	88.5	2,730	78.0	2,401	-11.8
BMI 35-40	102.1	3,152	89.8	2,766	-12.0
BMI ≥40	114.3	3,530	100.4	3,091	-12.2

Table 2: SELECT Trial Analysis Results (Pre-treatment: 7 years, Treatment: 4 years)

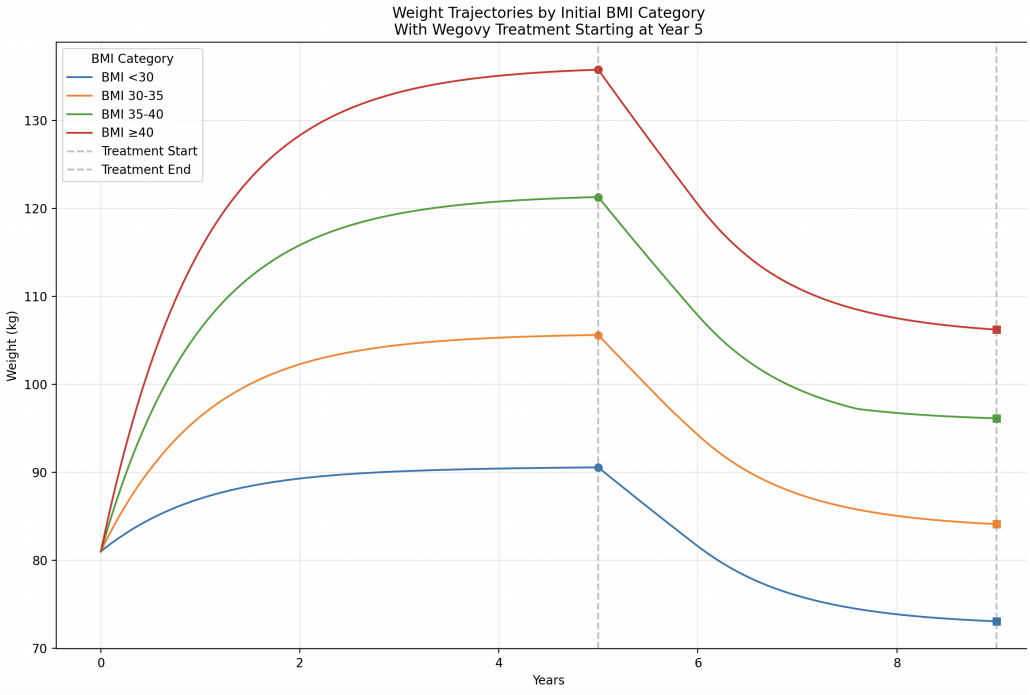

Figure 2: Simulated weight trajectories by BMI category showing pre-treatment weight gain and subsequent Wegovy treatment response

3.3 Creating the Ramp-Up Function

To accurately model the gradual onset of Wegovy's appetite-suppressing effects, we implemented a ramp-up function that simulates the typical clinical titration schedule. The function gradually increases the medication's effect over time, which better reflects real-world patient experiences and helps avoid sudden caloric restrictions.

$$\text{Ramp Factor} = \min\left(\frac{t - t_{\text{start}}}{t_{\text{ramp}}}, 1\right) \tag{2}$$

where:

- $t_{\text{start}} = 1825$ days (5-year pre-treatment period)
- $t_{\text{ramp}} = 60$ days (2-month ramp-up duration)

The caloric adjustment is then applied using:

$$\text{Caloric Reduction} = \text{Target Reduction} \times \text{Ramp Factor} \tag{3}$$

This gradual approach ensures that:

- The treatment effect increases linearly over the first year
- The full effect is achieved only after complete titration
- The simulation better matches clinical observations of weight loss patterns

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4 Section

Small description

4.1 Subsection

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5 Conclusions

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