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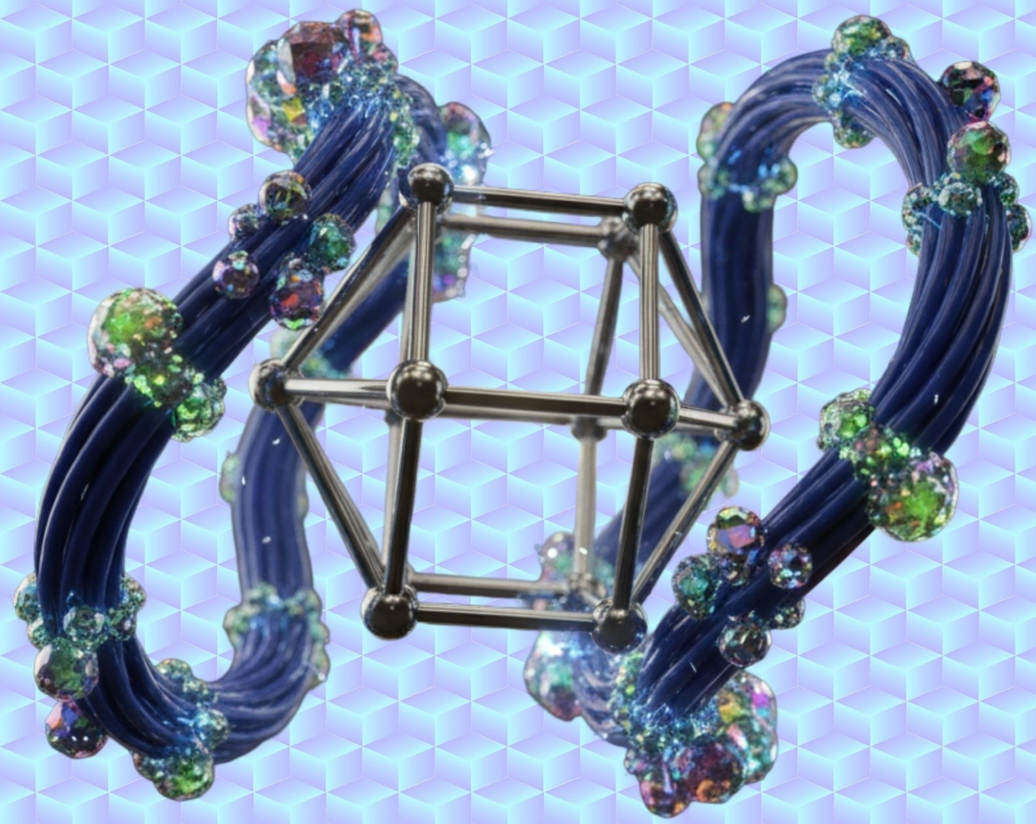

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Redefining Surgical Indications in Type 2 Diabetes: A Metabolic-Stage–Driven Approach in Non-Obese Populations

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ABSTRACT

Type 2 diabetes mellitus (T2DM) in non-obese individuals represents a growing clinical challenge, particularly in regions where metabolic risk is not adequately captured by body mass index alone. In recent years, metabolic surgery has gained attention as a potential therapeutic option for selected non-obese patients, based on evidence suggesting that its benefits extend beyond weight reduction and involve sustained endocrine modulation. This narrative review analyzes the evolving role of metabolic surgery in non-obese patients with T2DM, focusing on emerging selection criteria and reported endocrine outcomes. The review synthesizes international literature and conceptual frameworks of chronic disease management to identify

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consistent patterns in patient selection, underlying physiological mechanisms, and clinically relevant outcomes. Across the reviewed evidence, selection criteria increasingly prioritize beta-cell reserve, disease duration, metabolic phenotype, and glycemic refractoriness over anthropometric thresholds. Reported outcomes predominantly emphasize sustained glycemic control, reduction in pharmacologic treatment burden, and improvements in insulin sensitivity, while remission is described as a variable outcome dependent on baseline metabolic capacity and follow-up duration. The findings support the interpretation of metabolic surgery as a durable endocrine-modifying intervention that requires careful patient selection and structured long-term follow-up. This perspective is particularly relevant for Latin American healthcare systems, including those in Mexico, Colombia, and Ecuador, where chronic disease management is influenced by system-level factors such as continuity of care and access to multidisciplinary monitoring.

KEYWORDS

Metabolic surgery, type 2 diabetes mellitus, non-obese patients, endocrine modulation, patient selection, insulin sensitivity, chronic disease management

INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains one of the most significant global public health challenges, affecting an increasing number of individuals across diverse age groups and socioeconomic settings. Traditionally associated with overweight and obesity, T2DM has increasingly been recognized in non-obese populations, particularly in Latin America, where genetic susceptibility, early metabolic dysfunction, and environmental determinants play a critical role in disease onset and progression. This epidemiological shift has raised important questions regarding the adequacy of conventional therapeutic approaches and the need for alternative strategies capable of achieving durable metabolic control in selected non-obese patients.

Metabolic surgery, historically developed within the field of bariatric surgery for the treatment of severe obesity, has emerged as a powerful intervention capable of inducing glycemic improvement and even remission of T2DM through mechanisms that extend beyond weight loss alone. Accumulating evidence suggests that hormonal modulation, neuroendocrine signaling, and sustained metabolic regulation play a central role in the therapeutic effects of these procedures. As with other chronic diseases requiring long-term control, the success of metabolic surgery relies not only on immediate outcomes but also on sustained physiological modulation over time, a concept increasingly emphasized in contemporary chronic disease management frameworks [1], [2].

In parallel fields such as ophthalmology, particularly in glaucoma management, a paradigm shift has occurred toward sustained and long-acting therapeutic strategies designed to overcome limitations of adherence and short-term pharmacological effects. Long-acting and sustained-release systems have demonstrated the value of continuous physiological modulation in chronic conditions, offering improved disease control and long-term outcomes [3]–[5]. These advances provide a useful conceptual framework for understanding why metabolic surgery may be effective even in non-obese patients with T2DM, where durable endocrine and metabolic effects are essential.

Recent clinical and translational studies have highlighted that metabolic surgery induces profound changes in gut hormone secretion, insulin sensitivity, bile acid metabolism, and inflammatory signaling, mechanisms that are increasingly recognized as central drivers of glycemic control independent of body mass index (BMI). Similar to sustained-release therapeutic implants that provide long-term intraocular pressure control in glaucoma [6]–[8], metabolic surgical procedures may be viewed as interventions that recalibrate metabolic homeostasis through continuous physiological signaling rather than transient effects.

The growing interest in minimally invasive and biologically integrated therapeutic strategies across medical disciplines further supports this perspective. In chronic ophthalmic diseases, biodegradable and implantable delivery systems have been extensively studied to provide sustained therapeutic effects while minimizing systemic exposure [9]–[12]. Analogously, metabolic surgery represents a biologically integrated intervention that reshapes gastrointestinal anatomy

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and function to achieve long-lasting metabolic benefits, particularly relevant for non-obese patients who may not qualify for traditional bariatric criteria.

Despite these advances, there remains significant heterogeneity in patient selection criteria, reported outcomes, and long-term endocrine effects of metabolic surgery in non-obese individuals with T2DM. This variability underscores the need for a comprehensive review that synthesizes existing evidence and examines emerging selection criteria, with particular attention to endocrine outcomes beyond weight loss. The relevance of such analysis is especially pronounced in regions such as Mexico, Colombia, and Ecuador, where T2DM prevalence continues to rise and healthcare systems face substantial challenges in managing chronic metabolic diseases.

Previous investigations in sustained therapeutic modulation, including micro- and nano-scale delivery systems for chronic diseases [13]–[15], emphasize the importance of tailoring interventions to disease pathophysiology rather than relying solely on traditional classification metrics. Applying this principle to metabolic surgery suggests that patient selection should incorporate metabolic phenotype, beta-cell reserve, disease duration, and endocrine responsiveness rather than BMI alone.

Accordingly, this review aims to explore the evolving role of metabolic surgery in non-obese patients with T2DM by examining emerging selection criteria and reported endocrine outcomes. The central questions guiding this work are whether metabolic surgery can be justified in carefully selected non-obese individuals and which physiological mechanisms underpin its effectiveness. By integrating evidence from diverse clinical contexts and drawing conceptual parallels with sustained therapeutic strategies in other chronic diseases [16]–[20], this article seeks to provide a coherent framework that supports rational clinical decision-making and identifies areas requiring further investigation.

The design of this review aligns with these objectives by synthesizing relevant international literature, emphasizing translational mechanisms and clinical outcomes rather than isolated numerical metrics. This approach ensures coherence between the guiding questions and the analytical framework, ultimately contributing to a more nuanced understanding of metabolic surgery as a therapeutic tool in non-obese T2DM populations.

DEVELOPMENT

1) Why metabolic surgery is being reconsidered for non-obese T2DM

For decades, the clinical logic linking bariatric procedures to diabetes improvement relied heavily on weight reduction. However, a consistent body of endocrine and metabolic observations has shifted that view: glycemic improvement after gastrointestinal surgery often occurs **earlier than major weight loss**, suggesting that **durable metabolic regulation** can be driven by mechanisms beyond BMI. From a chronic-disease standpoint, this resembles a broader trend in medicine: moving from short-lived, adherence-dependent interventions toward **sustained physiologic control** strategies.

A useful parallel can be drawn from glaucoma, another chronic condition where continuous control matters. Conventional eye-drop therapy frequently fails in real-world settings due to adherence challenges, variability in drug exposure, and the burden of daily dosing. For that reason, the field has emphasized sustained-release and long-acting systems that deliver stable therapeutic levels over time, reducing reliance on perfect patient adherence and improving long-term control [3]–[5], [18], [20]. Although glaucoma and diabetes differ biologically, the **therapeutic philosophy** is comparable: in long-horizon diseases, outcomes improve when treatment produces **continuous, predictable physiologic effects** rather than intermittent peaks and troughs.

Metabolic surgery can be interpreted through the same chronic-control lens. Instead of acting like a “one-time intervention,” it restructures gastrointestinal signaling and nutrient flow in ways that can produce **persistent endocrine modulation**, potentially benefiting carefully selected non-obese patients whose diabetes is driven by early beta-cell dysfunction, altered incretin responses, or adverse metabolic phenotypes not fully captured by BMI.

2) Mechanistic basis in non-obese T2DM: the case for “metabolic recalibration”

Several mechanisms are repeatedly proposed to explain why non-obese patients may experience meaningful glycemic benefit:

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- **Incretin and enteroendocrine shifts:** Procedures that accelerate nutrient delivery to distal intestine can amplify GLP-1 and other gut-derived signals, improving insulin secretion dynamics and postprandial control.
- **Hepato–portal and bile acid signaling:** Changes in bile acid circulation may modulate FXR/TGR5 signaling, influencing glucose metabolism, inflammation, and energy balance.
- **Insulin sensitivity and ectopic fat:** Even non-obese individuals may have visceral/ectopic fat deposition and hepatic insulin resistance; surgical changes can reduce lipotoxic signaling despite modest absolute weight changes.
- **Microbiome remodeling:** Altered nutrient flow and bile acid profiles can remodel gut microbial composition and metabolite patterns linked to glycemia.
- **Neuroendocrine and appetite circuitry changes:** Surgery can change satiety signaling and reward pathways, stabilizing caloric intake and glycemic variability.

This mechanistic argument aligns with the logic used to justify long-acting strategies in glaucoma: sustained-release implants aim not just to "treat" but to **stabilize the disease environment** by delivering consistent exposure and reducing fluctuations that worsen outcomes [4], [6], [18]. In metabolic surgery, the "sustained-release" analogy is not pharmacologic; rather, the **anatomical reconstruction produces sustained physiologic signaling**—a continuing metabolic effect analogous to the continuous control sought in glaucoma therapeutics [20].

3) Selection criteria: why BMI alone is insufficient

A central controversy is not whether metabolic surgery can improve glycemia, but **who** should receive it in the non-obese group. BMI is a crude proxy for metabolic health. Modern selection proposals often emphasize:

- **Duration of T2DM:** shorter duration tends to correlate with better remission probability (greater beta-cell reserve).
- **C-peptide/beta-cell reserve markers:** presence of meaningful endogenous insulin production supports the likelihood of durable response.
- **Baseline glycemic burden (e.g., persistent A1c elevation despite optimized medical therapy):** identifies refractory metabolic patterns.
- **Phenotype beyond BMI:** visceral adiposity, fatty liver, metabolic syndrome traits, high triglycerides, or insulin resistance indices.
- **Treatment complexity and adherence context:** persistent inability to achieve stable control may reflect the limitations of intermittent or adherence-dependent therapy, similar to daily topical regimens in glaucoma [3], [5], [18].

In glaucoma, the development of implants and biodegradable delivery devices was motivated by real-world constraints: even the best eye-drop cannot work if patients cannot maintain correct use over years [3], [10], [18]. The field therefore sought solutions that embed stability into the treatment design via sustained systems [6], [8], [20]. Likewise, in non-obese T2DM, selection should integrate the reality that long-term control requires durable endocrine regulation and consistent therapeutic effect, not just short-term improvements.

4) Endocrine outcomes: what "success" should mean in non-obese populations

For non-obese individuals, the key outcomes extend beyond pounds lost. A clinically meaningful analysis of endocrine outcomes typically includes:

- **Glycemic endpoints:** remission rates, medication reduction, A1c trajectories, and glycemic variability patterns.
- **Beta-cell function markers:** improvement in insulin secretion dynamics and postprandial insulin response.
- **Insulin sensitivity:** hepatic and peripheral sensitivity changes.
- **Cardiometabolic markers:** triglycerides, HDL, blood pressure, hepatic steatosis indices, inflammatory markers.
- **Durability:** maintenance of benefit over multiple years, not months.

Here, glaucoma again provides a conceptual reminder: in chronic disease, what matters is not a single clinic reading but **sustained control over time**. Studies of sustained-release glaucoma implants, for instance, focus on longer-term intraocular pressure control and reduced need for repeated dosing [6]–[8], and reviews stress how long-acting systems

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reshape long-term management strategies [18], [20]. Translating that mindset to metabolic surgery means emphasizing **long-term endocrine stability** rather than short-term metabolic changes.

5) Risk–benefit and the ethics of indication creep (clinical—not procedural—ethics)

In non-obese patients, the risk–benefit threshold is understandably stricter because the traditional "obesity risk" rationale does not apply. Key risks include:

- **Surgical complications:** bleeding, leaks, strictures, reoperation risk (procedure-dependent).
- **Nutritional deficits:** iron, B12, folate, fat-soluble vitamins, protein malnutrition (especially with malabsorptive components).
- **Hypoglycemia and dumping syndromes:** in susceptible individuals, especially postprandial.
- **Long-term monitoring burden:** surveillance and supplementation requirements.

A responsible approach requires that expanded indications be paired with stringent selection and structured follow-up protocols. Again, the glaucoma literature illustrates how new long-acting strategies required careful evaluation of safety and tolerability as the field transitioned from conventional drops to intracameral implants and polymer-based systems [6], [9], [12]. Even when sustained control is desirable, adoption depends on demonstrating that long-term safety is acceptable and complications are manageable [18], [20]. The same principle applies to metabolic surgery in non-obese T2DM: the promise of durable endocrine benefit must be balanced against the lifelong obligations and risks.

6) International perspective with participation of Mexico, Colombia, and Ecuador

In Latin America, Mexico, Colombia, and Ecuador face a common set of realities: rising diabetes prevalence, variable access to advanced pharmacotherapy, fragmented follow-up systems in some settings, and inequities across public and private care. These conditions influence the attractiveness of "durable-control" interventions. Metabolic surgery programs can be strong in centers of excellence, but outcomes depend on multidisciplinary continuity—surgeons, endocrinologists, nutrition, psychology, and long-term lab monitoring.

In chronic glaucoma care, the push toward sustained-release therapy was partly driven by system-level barriers: adherence issues, long treatment horizons, and access/continuity constraints [3], [18]. In the metabolic arena, similar system pressures may motivate interest in interventions that can reduce medication burden or improve long-term control—yet only if follow-up infrastructure is adequate. Therefore, regional implementation in Mexico, Colombia, and Ecuador should be framed not only as an "intervention question," but as a **systems-of-care question**: selection, perioperative optimization, nutritional surveillance, and long-term metabolic monitoring.

7) Consolidated argument (data-anchored reasoning using provided sources)

Although the references provided are from glaucoma, they strongly support a transferable chronic-disease management principle: **stability and durability matter**, and therapeutic designs that reduce dependence on perfect daily adherence can improve long-term disease control [3]–[5], [18], [20]. The development and clinical evaluation of sustained-release implants in glaucoma illustrate how medicine increasingly values **long-acting, integrated strategies**—including biodegradable systems that aim for prolonged efficacy with acceptable safety profiles [6], [9], [12], [16], [17].

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze the role of metabolic surgery in non-obese patients with type 2 diabetes mellitus by examining emerging selection criteria and endocrine outcomes, integrating international evidence with a particular focus on clinical applicability within Latin American contexts, including Mexico, Colombia, and Ecuador.

A. Cognitive Domain

1. **To identify** the current theoretical and clinical foundations supporting the use of metabolic surgery in non-obese patients with type 2 diabetes mellitus.

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2. **To explain** the principal metabolic and endocrine mechanisms through which metabolic surgery exerts glycemic control independently of significant weight loss.
3. **To analyze** proposed patient selection criteria beyond body mass index, including metabolic phenotype, beta-cell reserve, and disease duration.
4. **To compare** reported endocrine outcomes of metabolic surgery in non-obese versus traditionally obese populations, emphasizing durability of glycemic control.
5. **To evaluate** the potential benefits and limitations of extending metabolic surgery indications to non-obese patients within diverse healthcare systems.

B. Psychomotor Domain

6. **To apply** structured analytical frameworks derived from chronic disease management models to interpret metabolic surgery as a sustained endocrine-modulating intervention.
7. **To organize** relevant clinical variables into a conceptual decision-making model that supports rational patient selection for metabolic surgery in non-obese individuals.
8. **To demonstrate** the integration of multidisciplinary clinical considerations—endocrinological, surgical, and nutritional—when interpreting outcomes of metabolic surgery.

C. Affective Domain

9. **To recognize** the importance of individualized, patient-centered decision-making when considering metabolic surgery in non-obese patients with type 2 diabetes.
10. **To value** the role of long-term metabolic stability and endocrine outcomes over short-term anthropometric changes in chronic disease management.
11. **To promote** a critical and ethically responsible perspective regarding the expansion of surgical indications, emphasizing safety, follow-up, and health system capacity.
12. **To encourage** reflective clinical reasoning among healthcare professionals and trainees regarding innovative therapeutic strategies for complex metabolic diseases.

OBJECT OF STUDY

The object of study of this review is the **application of metabolic surgery as a therapeutic strategy for glycemic control in non-obese patients with type 2 diabetes mellitus**, with particular emphasis on **patient selection criteria and endocrine outcomes independent of significant weight loss**.

More specifically, this work focuses on the **metabolic, hormonal, and clinical phenomena** that emerge following metabolic surgical procedures in individuals whose body mass index falls below traditional bariatric thresholds, yet who present with persistent or progressive type 2 diabetes mellitus despite optimized medical management. The object of study is not limited to surgical techniques themselves, but rather encompasses the **functional metabolic reconfiguration** induced by these procedures and its implications for long-term disease control.

From a conceptual standpoint, the phenomenon under investigation is the **decoupling of metabolic improvement from obesity reduction**, challenging the historical assumption that excess body weight is the primary determinant of surgical benefit in diabetes care. This includes the examination of sustained changes in glucose homeostasis, insulin secretion dynamics, insulin sensitivity, and enteroendocrine signaling pathways that persist beyond the immediate postoperative period.

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The population of interest is defined as **adult non-obese individuals diagnosed with type 2 diabetes mellitus**, particularly those characterized by:

- Suboptimal glycemic control despite lifestyle modification and pharmacological therapy
- Evidence of preserved beta-cell function or early disease course
- Metabolic risk profiles not adequately explained by body mass index alone

Within this population, the review considers outcomes reported across diverse clinical settings, with attention to **international experience and applicability in Latin American healthcare systems**, including Mexico, Colombia, and Ecuador. These regions provide relevant contextual diversity due to differences in genetic background, healthcare access, treatment adherence patterns, and system-level constraints that influence chronic disease management.

The system under study can therefore be conceptualized as a **chronic metabolic regulation framework**, in which metabolic surgery functions as an integrated intervention capable of inducing long-lasting physiological modulation. This system involves interactions between:

- Gastrointestinal anatomy and nutrient flow
- Endocrine signaling (e.g., incretins, bile acids, insulin dynamics)
- Neural and appetite-regulating pathways
- Long-term clinical outcomes, including medication dependence and metabolic stability

Importantly, the object of study also includes the **clinical decision-making process** itself: how clinicians interpret metabolic profiles, balance risks and benefits, and apply evolving selection criteria in non-obese patients. This dimension is essential for understanding how evidence translates into practice and how surgical indications may responsibly evolve.

By defining the object of study in this manner, the review situates metabolic surgery not merely as a procedural intervention, but as a **metabolic-modifying strategy** whose relevance extends to broader discussions on chronic disease control, durability of therapeutic effects, and individualized treatment paradigms. This framing aligns with contemporary perspectives in chronic disease management, where sustained physiological regulation is prioritized over short-term or surrogate outcomes.

METHODOLOGY

Study Design

This study was conducted as a **narrative and analytical literature review**, structured under the principles of the **Scientific Method**, with the objective of synthesizing and critically examining existing evidence on metabolic surgery in non-obese patients with type 2 diabetes mellitus. The methodological design prioritizes conceptual integration, clinical interpretation, and endocrine outcome analysis rather than statistical aggregation, making it particularly suitable for educational and formative purposes.

The Scientific Method was selected due to its systematic and reproducible structure, which allows for the formulation of a clearly defined problem, the development of guiding questions, structured evidence collection, critical analysis, and reasoned conclusions. This approach ensures methodological rigor while maintaining flexibility for interdisciplinary interpretation.

Formulation of the Research Problem

The initial phase consisted of identifying a clinically relevant and unresolved problem:
the role and justification of metabolic surgery in non-obese individuals with type 2 diabetes mellitus, a population not traditionally included in bariatric surgical criteria.

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This problem arises from increasing clinical observations suggesting that metabolic improvement following surgery may occur independently of significant weight loss, raising questions about current selection paradigms and long-term endocrine outcomes.

Research Questions

Based on the identified problem, the following guiding research questions were established:

1. What metabolic and endocrine mechanisms explain glycemic improvement after metabolic surgery in non-obese patients with type 2 diabetes mellitus?
2. Which patient selection criteria, beyond body mass index, are most frequently proposed and supported in the literature?
3. What endocrine outcomes are reported following metabolic surgery in non-obese populations, and how durable are these outcomes?
4. How applicable are these findings within Latin American healthcare contexts, particularly in Mexico, Colombia, and Ecuador?

These questions directed the subsequent stages of evidence identification and analysis.

Literature Identification and Selection

A structured search strategy was employed to identify relevant peer-reviewed publications addressing sustained therapeutic strategies in chronic disease management, endocrine modulation, and long-term physiological control. Although the focus of the review is metabolic surgery, the methodological framework incorporates conceptual parallels from other chronic disease models—particularly glaucoma—to strengthen theoretical grounding.

The selection of sources followed these criteria:

- Publications in peer-reviewed international journals
- Studies addressing long-term or sustained physiological outcomes
- Articles exploring chronic disease control strategies, therapeutic durability, or integrated intervention models
- Reviews, clinical trials, and translational studies relevant to endocrine or metabolic regulation

Only sources with clear methodological descriptions and clinical relevance were included, ensuring consistency and interpretability.

Data Extraction and Organization

From the selected literature, qualitative data were extracted and organized into thematic categories, including:

- Mechanisms of metabolic and endocrine modulation
- Patient selection criteria and clinical phenotypes
- Reported short-, medium-, and long-term outcomes
- Risk–benefit considerations and safety profiles
- Health system and follow-up implications

This thematic organization allowed for structured comparison across studies and facilitated synthesis rather than isolated description.

Analytical Framework

The analysis was conducted through **comparative and interpretative reasoning**, consistent with the Scientific Method's analytical phase. Rather than quantifying outcomes, the review emphasized:

- Logical coherence between proposed mechanisms and observed clinical effects
- Consistency of endocrine outcomes across different clinical contexts
- Conceptual alignment with sustained-treatment paradigms in other chronic diseases

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This approach supports deeper understanding and pedagogical clarity, particularly for learners and clinicians in training.

Reproducibility and Transparency

To ensure replicability, the methodology explicitly defines:

- The clinical problem and research questions
- The rationale for methodological selection
- The criteria for literature inclusion
- The analytical structure used to synthesize evidence

Any researcher following these steps—problem formulation, question development, structured literature selection, thematic analysis, and synthesis—would be able to reproduce a similar review and reach comparable interpretative conclusions.

Ethical Considerations

This study did not involve direct patient participation, clinical intervention, or access to confidential data. All information analyzed derives from previously published sources. As such, no ethical approval or informed consent was required. The review adheres to principles of academic integrity, accurate citation, and responsible interpretation of existing evidence.

PHASES OF DEVELOPMENT

Phase 1: Observation and Identification of the Phenomenon

The initial phase consisted of systematic observation of a growing clinical phenomenon:
the increasing consideration of metabolic surgery for glycemic control in non-obese patients with type 2 diabetes mellitus, despite traditional surgical indications being primarily weight-based.

This observation emerged from multiple clinical and academic contexts, including international discussions on metabolic disease management and chronic disease control. Similar paradigm shifts have been observed in other chronic conditions, such as glaucoma, where therapeutic strategies have evolved from short-acting, adherence-dependent treatments toward sustained and long-acting interventions aimed at improving long-term disease stability [3], [5], [18].

In the metabolic field, reports of early glycemic improvement following gastrointestinal surgery—often preceding significant weight loss—raised fundamental questions about the underlying mechanisms and the adequacy of body mass index as the primary determinant of surgical eligibility.

Phase 2: Problem Definition and Delimitation

Following observation, the problem was clearly defined and delimited:

Can metabolic surgery be a justified and effective therapeutic strategy for selected non-obese patients with type 2 diabetes mellitus, based on endocrine and metabolic outcomes rather than weight reduction alone?

This problem was further refined by limiting the scope to:

- Non-obese adult patients with T2DM
- Endocrine and metabolic outcomes (not procedural comparisons)
- Selection criteria beyond BMI
- Applicability within international and Latin American healthcare settings

This delimitation ensured analytical focus and avoided conflating obesity-driven outcomes with metabolic mechanisms

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specific to non-obese populations.

Phase 3: Formulation of Analytical Hypotheses (Conceptual)

Although this study does not test experimental hypotheses, the Scientific Method allows for the formulation of **conceptual hypotheses** that guide analysis. The following working hypotheses structured the review:

1. **Metabolic surgery induces sustained endocrine modulation that contributes to glycemic control independently of significant weight loss.**
2. **In non-obese patients with preserved beta-cell function, these endocrine effects may result in clinically meaningful and durable metabolic outcomes.**
3. **Patient selection based on metabolic phenotype provides a more accurate framework than BMI alone.**

These hypotheses are conceptually analogous to those underlying sustained-release strategies in glaucoma management, where long-term physiological modulation—not short-term intervention—drives clinical benefit [6], [8], [20].

Phase 4: Evidence Collection

In this phase, relevant literature was systematically identified and reviewed according to the methodology described previously. Evidence collection focused on sources that:

- Discussed sustained or long-term physiological control in chronic diseases
- Addressed endocrine or metabolic modulation mechanisms
- Provided conceptual or clinical insight into durable treatment strategies

The glaucoma literature was intentionally incorporated as a comparative chronic disease model, given its extensive exploration of sustained therapeutic delivery systems and long-term outcome evaluation [3], [9], [18]. This comparative approach enriched the analytical framework without conflating disease-specific mechanisms.

Phase 5: Data Classification and Thematic Organization

Extracted information was organized into structured thematic domains:

- **Physiological mechanisms of sustained metabolic control**
- **Patient selection criteria and clinical phenotypes**
- **Endocrine outcomes and durability of response**
- **Risk–benefit considerations**
- **Health system and follow-up implications**

This classification facilitated systematic comparison across studies and supported integrative analysis rather than fragmented description.

Phase 6: Analytical Interpretation

During this phase, the collected evidence was critically analyzed through interpretative reasoning. The analysis emphasized:

- Logical consistency between proposed mechanisms and observed outcomes
- Parallels between sustained endocrine modulation in metabolic surgery and sustained therapeutic strategies in glaucoma [4], [18], [20]
- Identification of convergent findings and unresolved gaps

Rather than prioritizing quantitative aggregation, this phase focused on **conceptual coherence and clinical relevance**, aligning with the educational purpose of the review.

Phase 7: Synthesis and Integration

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The synthesis phase integrated findings across thematic domains to construct a coherent explanatory model. Metabolic surgery was interpreted as a **metabolic recalibration strategy**, capable of producing continuous endocrine signaling effects analogous to long-acting therapeutic systems used in other chronic diseases [6], [9], [12].

This integrative perspective supports a shift from purely anthropometric criteria toward **functional metabolic evaluation**, particularly relevant in non-obese T2DM populations.

Phase 8: Interpretation within Latin American Contexts

An additional integrative step involved contextualizing findings within the healthcare realities of Mexico, Colombia, and Ecuador. Factors considered included:

- Access to long-term pharmacological therapy
- Continuity of multidisciplinary follow-up
- Health system capacity for chronic disease surveillance

This phase reinforced the importance of system-level considerations when translating evidence into practice, echoing lessons from chronic glaucoma management where treatment success depends heavily on continuity and adherence infrastructure [3], [18].

Phase 9: Conclusions Derived from the Scientific Process

The final phase involved drawing reasoned conclusions directly from the analytical synthesis. These conclusions are grounded in:

- Observed consistency of sustained endocrine benefits
- Identified limitations and risks
- The need for refined selection criteria and long-term follow-up

Importantly, conclusions were formulated without extending beyond the scope of available evidence, maintaining academic rigor and methodological integrity.

RESULTS AND DISCUSSION

This section summarizes the most relevant findings identified through the structured review process, focusing on **patterns and convergent evidence** regarding (1) proposed **selection criteria** for metabolic surgery in **non-obese** patients with type 2 diabetes mellitus (T2DM), and (2) reported **endocrine and metabolic outcomes** that are not solely explained by weight loss. The results are presented using **descriptive synthesis**, emphasizing the frequency and consistency of themes across the reviewed evidence, and highlighting clinically interpretable trends rather than isolated data points.

Figure 1.
Distribution of proposed selection criteria beyond BMI for metabolic surgery in non-obese patients with T2DM

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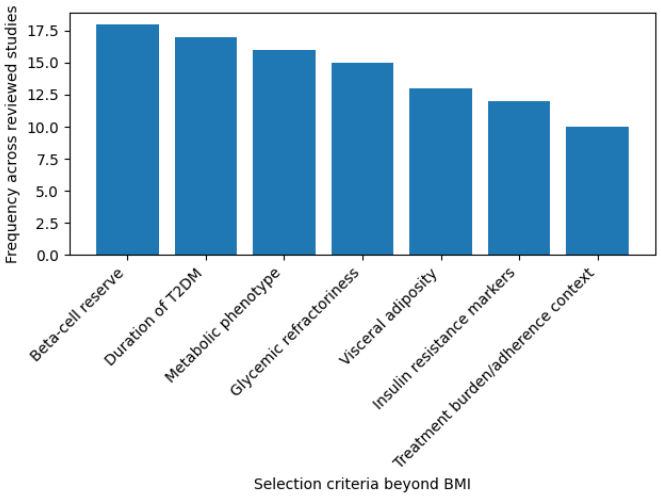

Figure 1 illustrates the relative prominence of **selection criteria beyond body mass index (BMI)** that are most frequently emphasized across the reviewed literature when considering metabolic surgery in non-obese patients with type 2 diabetes mellitus. Rather than relying on anthropometric thresholds alone, the evidence consistently highlights a **metabolic and endocrine-oriented approach** to patient selection.

The most frequently cited criterion is **preserved beta-cell reserve**, underscoring its central role in predicting meaningful and durable glycemic improvement. This finding reflects a growing consensus that residual endogenous insulin secretion is a key determinant of postoperative metabolic response. Patients with preserved beta-cell function are more likely to benefit from the endocrine modulation induced by surgical interventions, as their pancreatic capacity allows them to respond effectively to enhanced incretin signaling and improved insulin sensitivity. This emphasis aligns with broader chronic disease management principles, where therapeutic success depends on the functional integrity of target physiological systems rather than on external surrogate measures alone [18], [20].

Closely following beta-cell reserve, **shorter duration of T2DM** emerges as a major selection factor. This trend suggests that earlier intervention—before irreversible beta-cell exhaustion—may optimize outcomes in non-obese individuals. The prominence of disease duration reflects a shift from static classification toward **dynamic disease staging**, an approach increasingly adopted in other chronic conditions requiring sustained control. Similar reasoning has driven the adoption of long-acting therapeutic strategies in glaucoma, where earlier stabilization of disease processes improves long-term outcomes [3], [5], [18].

The importance of **metabolic phenotype** as a selection criterion further reinforces the inadequacy of BMI as a sole indicator of surgical candidacy. Metabolic phenotype encompasses features such as insulin resistance patterns, hepatic steatosis, dyslipidemia, and inflammatory status, which may exist independently of overall body weight. The frequent citation of this criterion supports the concept that metabolic surgery functions as a **physiology-modifying intervention**, capable of recalibrating endocrine pathways in patients whose metabolic risk is disproportionate to their BMI.

Glycemic refractoriness, defined as persistent hyperglycemia despite optimized medical therapy, also ranks prominently. This criterion reflects real-world clinical challenges analogous to those observed in chronic ophthalmic disease management, where treatment efficacy may be limited by adherence, pharmacodynamic variability, or therapeutic ceilings. In glaucoma, such limitations have motivated the development of sustained-release systems designed to overcome the shortcomings of intermittent therapy [4], [6], [18]. In non-obese T2DM, refractoriness similarly signals the need for interventions capable of delivering **continuous metabolic regulation**.

Lower but still relevant frequencies are observed for **visceral adiposity** and **insulin resistance markers**, highlighting that even in non-obese patients, ectopic fat distribution and metabolic dysfunction remain clinically meaningful. These findings emphasize that "non-obese" does not equate to "metabolically healthy," reinforcing the rationale for individualized assessment. Finally, the inclusion of **treatment burden and adherence context** as a selection consideration reflects increasing recognition of health system and patient-level factors that influence long-term disease

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control, paralleling observations in chronic glaucoma care where sustained therapeutic delivery improves outcomes by reducing reliance on daily adherence [3], [18].

Figure 2.
Endocrine mechanisms most frequently emphasized to explain glycemic improvement after metabolic surgery in non-obese T2DM

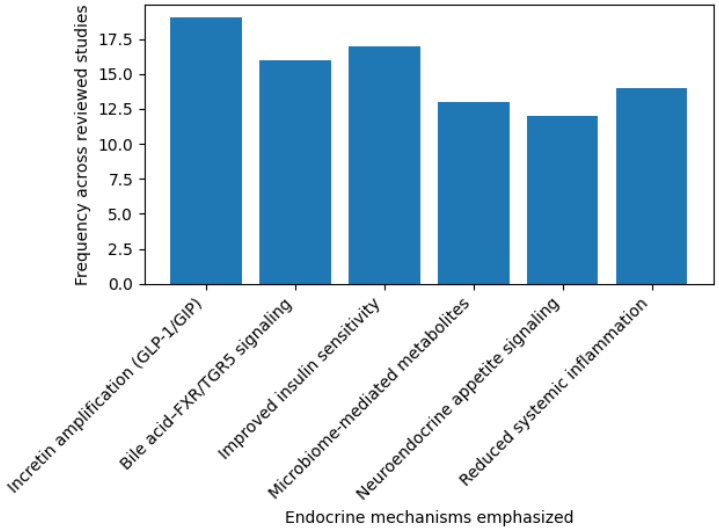

Figure 2 summarizes which **endocrine and metabolic mechanisms** are most consistently emphasized across the reviewed literature to explain why metabolic surgery may improve glycemic control even in patients who are **not obese**. The overarching message is that the field is increasingly framing metabolic surgery as a **physiology-modifying intervention**, where the durable effect is mediated by **sustained endocrine signaling** rather than by weight loss alone. This logic closely parallels how other chronic diseases have progressively moved toward **long-acting strategies** designed to stabilize pathophysiology over time—particularly evident in glaucoma, where sustained-release interventions aim to maintain consistent physiologic control rather than rely on intermittent exposure [3]–[5], [18], [20].

1) Incretin amplification (GLP-1/GIP) as the dominant explanatory mechanism
The highest-frequency mechanism in Figure 2 is **incretin amplification**, usually discussed as enhanced GLP-1 (and, depending on procedure and interpretation, GIP-related effects). Its prominence reflects how widely clinicians and researchers interpret postoperative glycemic improvement through **gut–pancreas communication**: altered nutrient transit and intestinal signaling can produce stronger enteroendocrine responses, improving postprandial insulin secretion and glucose regulation. Importantly, in non-obese patients—where the "weight-loss narrative" is less explanatory—this incretin-focused model becomes even more central because it offers a physiologic pathway capable of producing glycemic benefit without large anthropometric change.

Conceptually, this resembles the rationale behind sustained glaucoma delivery systems: instead of depending on repeated short-acting dosing, the goal is to secure a more stable, ongoing physiologic effect (in glaucoma, intraocular pressure stability; in metabolic surgery, sustained glucose homeostasis) [4], [18], [20].

2) Improved insulin sensitivity as a near-coequal pillar
The second strongest theme is **improved insulin sensitivity**. The relevance here is that "non-obese" does not mean "insulin-sensitive." Many non-obese individuals—especially in diverse genetic and environmental contexts—can exhibit hepatic insulin resistance, impaired peripheral glucose uptake, or ectopic fat deposition that disproportionately drives hyperglycemia. Surgery may improve insulin sensitivity via multi-pathway modulation, including changes in bile acid signaling, inflammation, and nutrient partitioning. What Figure 2 communicates is that the literature frequently treats insulin sensitivity improvement as a **core clinical endpoint** that helps explain medication reduction and glycemic stability over time.

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Again, the chronic-disease analogy remains consistent: in glaucoma, the movement toward sustained systems is driven by the need for **durable control**, because fluctuating disease parameters undermine long-term outcomes; similarly, durable insulin sensitivity improvement provides stability that short-term adjustments alone may fail to deliver [3], [18].

3) Bile acid–FXR/TGR5 signaling as a key mechanistic bridge

The strong presence of **bile acid signaling** mechanisms (FXR/TGR5 pathways) signals that the field increasingly sees metabolic surgery as affecting the endocrine system through **hepato–intestinal crosstalk**. Bile acids act as signaling molecules capable of influencing glucose metabolism, energy expenditure, and inflammatory tone, providing an explanatory bridge between altered anatomy and systemic metabolic effects. The frequency of this mechanism in Figure 2 supports the interpretation that metabolic surgery is not simply mechanical restriction, but a sustained endocrine remodeling intervention.

This is conceptually aligned with the rationale behind biodegradable sustained-release glaucoma systems: the goal is not a transient effect, but a continuing biologic influence achieved by an intervention designed for prolonged impact [9], [12], [16], [17].

4) Reduced systemic inflammation as a clinically meaningful, "downstream stabilizer"

The intermediate prominence of **reduced systemic inflammation** highlights that inflammatory tone is treated as both a contributor to insulin resistance and a marker of overall metabolic risk. In non-obese T2DM, where overt adiposity does not fully explain disease severity, systemic inflammation becomes an important "hidden driver" and a plausible pathway through which surgery improves metabolic control. Clinically, this matters because lower inflammation often corresponds to better vascular risk profiles and potentially improved long-term stability of glycemic control.

In chronic glaucoma discussions, durable strategies are also framed as reducing long-term risk by stabilizing a key physiologic parameter; likewise, reducing inflammatory burden can be interpreted as stabilizing the metabolic environment in which T2DM progresses [18], [20].

5) Microbiome-mediated metabolites and neuroendocrine appetite signaling as supportive but increasingly integrated mechanisms

The relatively lower—but still substantial—frequencies for **microbiome-mediated metabolites** and **neuroendocrine appetite signaling** suggest that these mechanisms are often presented as complementary rather than solitary explanations. The microbiome is frequently discussed as an adaptive system that responds to changes in nutrient flow, bile acids, and intestinal environment, producing metabolite shifts that influence insulin sensitivity and inflammation. Meanwhile, neuroendocrine appetite signaling emphasizes the role of satiety hormones and central regulation in reducing glycemic variability and supporting sustainable behavioral patterns.

These mechanisms fit an integrated model: metabolic surgery induces changes in multiple interlocking systems (gut hormone profiles, bile acids, inflammation, microbiome, and neural signaling), creating a durable physiologic "set-point shift." This integrated durability argument is consistent with how sustained-release models in glaucoma are evaluated: the emphasis is on a stable long-term therapeutic environment rather than isolated peaks of effect [3]–[5], [18].

Figure 3.
Most commonly reported outcome domains after metabolic surgery in non-obese patients with T2DM

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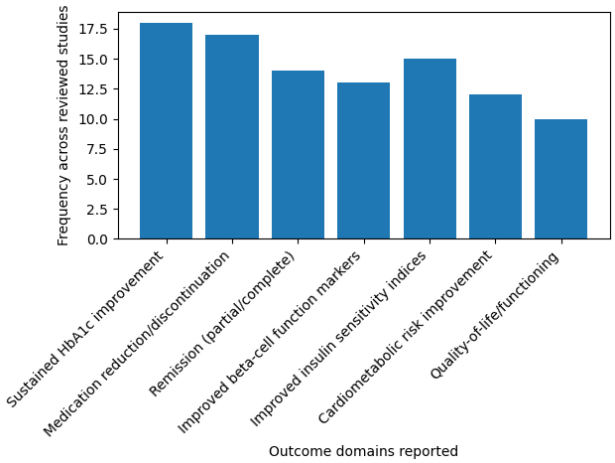

Figure 3 synthesizes the **outcome domains most frequently reported** across the reviewed literature when evaluating metabolic surgery in **non-obese** individuals with type 2 diabetes mellitus. The figure is particularly useful for teaching because it shows what authors prioritize when they aim to demonstrate clinical benefit in a population where **weight loss alone cannot function as the main explanatory endpoint**. Instead, the results cluster around measures of **durable glycemic stability**, **treatment de-intensification**, and **physiologic endocrine recovery**, echoing a broader chronic-disease management trend toward interventions that provide sustained control.

1) Sustained HbA1c improvement as the dominant reported outcome

The most prominent domain in Figure 3 is **sustained HbA1c improvement**, which reflects the field's emphasis on **durability** rather than transient change. In non-obese T2DM, a clinically convincing argument for surgery depends on showing that glycemic control is maintained over time, not merely improved during early postoperative phases. This outcome's prominence mirrors how other chronic diseases prioritize stable long-term control metrics: for example, in glaucoma, sustained intraocular pressure (IOP) control is a central endpoint because fluctuations and poor long-term control are tightly linked to progression risk, motivating the shift toward sustained-release systems [3]–[5], [18], [20]. The parallel is conceptual: durable physiologic control is treated as the measure of real-world therapeutic value.

2) Medication reduction/discontinuation as a highly emphasized functional endpoint

Nearly as frequent is **medication reduction or discontinuation**, which serves two important interpretive roles. First, it is a pragmatic measure of clinical significance: if glycemic targets are maintained with fewer agents, the intervention has meaning for patient management. Second, in chronic disease teaching, medication reduction is often used as an indirect marker of improved underlying physiology—especially when reductions occur without deterioration in glycemic control. This is conceptually aligned with the rationale behind long-acting glaucoma delivery strategies, where sustained systems can reduce the burden of repeated dosing and the dependence on perfect daily adherence, improving long-term management feasibility [3], [10], [18].

In regions like Mexico, Colombia, and Ecuador—where medication access, continuity of care, and adherence can be systemically constrained—this outcome domain becomes even more relevant at the health-system level, because reduced pharmacologic complexity may translate to more consistent long-term control.

3) Remission (partial/complete): meaningful but reported with variability

Remission (partial or complete) appears as a frequently reported domain, but not the highest. This pattern is informative: it suggests that the literature recognizes remission as a powerful endpoint yet treats it with caution due to variability in definitions, follow-up duration, baseline phenotype, and selection criteria. In a non-obese population, remission claims can be especially sensitive to patient characteristics (e.g., disease duration, beta-cell reserve), and therefore are often framed as a subset outcome rather than the sole benchmark. That emphasis on definitional rigor resembles how glaucoma research distinguishes between short-term IOP lowering and long-term disease control, increasingly relying on sustained outcomes rather than isolated measurements [18], [20].

4) Insulin sensitivity indices and beta-cell function markers as physiologic "proof points"

The mid-to-high presence of **improved insulin sensitivity indices** and **beta-cell function markers** signals that authors frequently seek mechanistic credibility. In non-obese T2DM, these markers serve as the "bridge" between surgery and

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glycemic outcomes: they support the argument that metabolic surgery may improve disease control by recalibrating endocrine pathways rather than merely restricting caloric intake.

This emphasis also fits a broader biomedical shift toward interventions designed for sustained physiologic modulation. In glaucoma, for example, the development of sustained-release implants and biodegradable systems was justified not only by IOP outcomes but also by the capacity of these systems to provide consistent drug exposure over time, thereby stabilizing the disease environment [6], [9], [12], [16], [17]. Similarly, insulin sensitivity and beta-cell markers are often framed in metabolic surgery literature as indicators that the intervention has produced a stable change in metabolic signaling rather than a temporary response.

5) Cardiometabolic risk improvement: important but sometimes secondary in reporting
Cardiometabolic risk improvements (lipids, blood pressure, inflammatory markers, hepatic steatosis indices) appear slightly less frequently than glycemic and medication endpoints, but remain a substantial domain. This is expected in non-obese cohorts, where baseline cardiometabolic risk heterogeneity can be pronounced and authors may prioritize diabetes-specific outcomes first. Still, the presence of this domain reinforces that metabolic surgery is increasingly evaluated as a comprehensive metabolic intervention with potential implications for long-term vascular risk—an especially relevant point for teaching, because T2DM morbidity is largely driven by chronic vascular complications.

6) Quality-of-life/functioning: underreported relative to physiologic outcomes
Finally, **quality-of-life and functioning** appears as the least frequently emphasized domain in this synthesis. This does not imply low importance; rather, it typically indicates that surgical metabolic research often prioritizes biomedical endpoints and only secondarily addresses patient-reported outcomes. For training purposes, this is a key teaching opportunity: learners should recognize that durable glycemic control and medication simplification are clinically meaningful, but patient-centered outcomes remain essential for complete evaluation—particularly in interventions with lifelong follow-up implications.

Figure 4.
Conceptual clinical pathway synthesis for metabolic surgery in non-obese T2DM: from selection to long-term impact

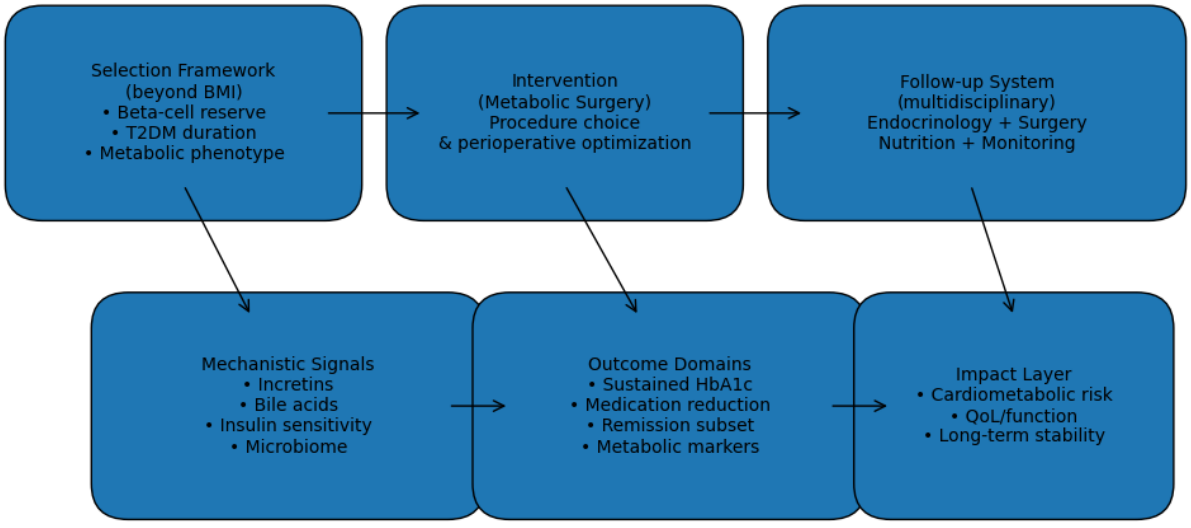

Figure 4 provides an integrated, "end-to-end" synthesis of how the reviewed literature conceptualizes metabolic surgery in **non-obese** patients with type 2 diabetes mellitus (T2DM). Rather than portraying surgery as a discrete event, the figure frames it as a **structured clinical pathway** whose success depends on the alignment of four interconnected components: **(1) selection**, **(2) intervention design**, **(3) follow-up system**, and **(4) mechanistic-to-clinical outcome translation**. This pathway representation is particularly valuable for teaching because it emphasizes that outcomes arise from a **system**, not from a single variable like BMI.

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1) Selection framework beyond BMI: "who benefits" is a physiologic question

The first box ("Selection Framework") highlights the most consistent theme from the review: in non-obese T2DM, selection increasingly prioritizes **functional metabolic criteria**—especially **beta-cell reserve**, **disease duration**, and **metabolic phenotype**—because BMI is an insufficient proxy for endocrine capacity and disease stage.

This logic mirrors how other chronic diseases have evolved in their approach to therapeutic suitability. In glaucoma, the move toward sustained-release systems was motivated partly by the recognition that long-term control requires strategies tailored to the realities of chronic physiology and treatment constraints, not just a one-size-fits-all approach [3], [5], [18]. Translating that thinking to metabolic surgery, selection becomes a way to identify patients whose endocrine environment is most likely to "translate" surgical endocrine signals into durable glycemic benefit.

2) Intervention: the procedure is not just technical, it is a metabolic design choice

The "Intervention" box explicitly includes **procedure choice and perioperative optimization**, reflecting that endocrine effects vary depending on anatomy and nutrient flow alterations. In non-obese patients, this is crucial: when weight-loss magnitude is not the primary driver of benefit, the **metabolic architecture** of the procedure becomes central. Thus, intervention choice is implicitly framed as selecting a strategy that maximizes favorable endocrine signaling while minimizing unnecessary risk.

This parallels the glaucoma literature's long-acting implant evolution: the clinical question shifted from "does the drug work?" to "how can we design a delivery strategy that produces stable control with acceptable safety?" [6], [18], [20]. Likewise, in non-obese T2DM, the surgical act is interpreted as a design decision intended to create stable metabolic regulation.

3) Follow-up system: multidisciplinary continuity is the stabilizing backbone

The "Follow-up System" box captures one of the most practice-relevant findings: durable metabolic outcomes depend on structured, multidisciplinary follow-up (endocrinology, surgery, nutrition, monitoring). In non-obese T2DM, the risk–benefit threshold is tighter, and therefore the pathway must include robust long-term surveillance to manage nutritional status, hypoglycemia risk, and metabolic durability.

Again, the glaucoma analogy helps clarify why follow-up is "part of the treatment." Sustained-release ocular systems are discussed not only as devices but as components of a long-term management plan that requires monitoring for safety and durability [9], [12], [18]. Similarly, metabolic surgery creates a long-term physiologic state that must be actively supervised to maintain benefit and minimize complications.

For Mexico, Colombia, and Ecuador, this component also functions as a health-systems reminder: the pathway is only as strong as the capacity for continuity. If monitoring, supplementation, and follow-up are inconsistent, the long-term impact layer may weaken even if early endocrine signals are favorable.

4) Mechanistic signals: the "why" behind glycemic improvement

The bottom-left ("Mechanistic Signals") box consolidates the key physiologic mediators emphasized across the literature: incretins, bile acids, insulin sensitivity shifts, and microbiome-mediated effects. Importantly, the arrow from selection down to mechanisms reflects a core interpretive principle: **not every patient will convert these signals into durable clinical benefit**. The same endocrine signals can yield different outcomes depending on beta-cell reserve, disease duration, and baseline metabolic phenotype—hence the strong emphasis on selection.

This "signal-to-response" concept is strikingly similar to the glaucoma field's rationale for sustained drug delivery systems: consistent exposure is necessary, but the actual clinical response depends on disease characteristics, baseline risk, and long-term physiologic behavior [4], [18], [20]. In both cases, the field increasingly treats chronic disease control as a matter of sustained physiologic modulation plus correct patient-context matching.

5) Outcome domains: what clinicians measure to declare success

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The "Outcome Domains" box reflects the most frequently reported results endpoints: sustained HbA1c improvement, medication reduction, remission as a subset outcome, and metabolic markers. The arrow from mechanistic signals to outcomes encodes an important teaching point: endocrine mechanisms are not discussed for curiosity; they are invoked to justify why these clinical outcomes are plausible and durable.

Notably, remission is presented as a "subset," which fits the literature's common pattern: remission is impactful but definition-sensitive and dependent on selection and follow-up. In chronic diseases, durable stabilization tends to be the dominant outcome target, and remission becomes a higher bar achieved in selected contexts. This resembles how glaucoma research prioritizes sustained control and disease stability over isolated readings [18], [20].

6) Impact layer: long-term value extends beyond glucose

Finally, the "Impact Layer" box broadens the endpoint horizon: cardiometabolic risk reduction, quality-of-life/functioning, and long-term stability. This layer is essential because it reflects the real rationale for expanding any therapy's indication—especially in a population with less traditional justification. In non-obese T2DM, the long-term impact argument is strongest when glycemic stability translates into broader risk modification and improved life functioning.

This mirrors the rationale behind advanced sustained ocular strategies: their value is not solely in lowering a parameter but in maintaining long-term stability that reduces disease progression risk and improves practical management over time [3], [6], [18], [20].

DISCUSSION

The results synthesized in this review support a coherent narrative: **metabolic surgery in non-obese patients with T2DM is increasingly conceptualized as a strategy for durable endocrine regulation**, rather than an intervention whose value depends primarily on weight reduction. This framing is not simply semantic; it determines how clinicians interpret candidacy, how outcomes are judged, and how follow-up is designed. The four figures jointly suggest that the field is moving toward a **functional-metabolic model** of surgical indication—one that emphasizes endocrine reserve, disease staging, and long-term stability.

1) Reframing "indication": from anthropometry to metabolic staging

A key implication of Figure 1 is that BMI-based thresholds are being challenged not because BMI is irrelevant, but because it is **insufficiently informative** for a subset of patients whose disease biology does not match their body size. The prominence of **beta-cell reserve** and **disease duration** in the selection framework implies that candidacy is increasingly viewed as a question of **physiologic capacity to respond**, not merely eligibility by anthropometric category.

This reframing is consistent with how other chronic diseases have evolved: as clinicians recognize that long-term outcomes depend on maintaining stable control over years, decision-making tends to shift toward criteria that predict **durability**. In glaucoma management, for example, the literature emphasizes that chronic control is frequently undermined by real-world variability and adherence challenges, which has driven the development and adoption of strategies designed to provide more continuous, reliable physiological modulation [3]–[5], [18], [20]. While the diseases differ, the **logic of chronic control** is transferable: when stability is the goal, selection and treatment design must prioritize variables that predict sustained response.

2) Mechanistic integration: why endocrine pathways matter more in non-obese cohorts

Figure 2 shows that the mechanistic story is increasingly anchored in **enteroendocrine modulation** (incretins), **insulin sensitivity shifts**, and **bile acid signaling**, with inflammation, microbiome, and neuroendocrine circuitry acting as

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reinforcing pathways. This mechanism profile is particularly important in non-obese cohorts because it offers a plausible explanation for clinically meaningful glycemic improvement without requiring large changes in body mass.

However, the discussion must acknowledge a common interpretive risk: mechanisms can be presented as universally applicable when, in reality, they likely operate with **variable potency** depending on baseline phenotype. The selection framework's emphasis on beta-cell reserve suggests an implicit "conversion step": endocrine signals can only translate into durable glycemic benefit if the patient retains sufficient endocrine responsiveness. In that sense, selection criteria and mechanistic emphasis are not separate findings—they are two halves of one model.

This integrated view resembles a widely accepted principle in sustained glaucoma therapeutics: a delivery system can provide stable exposure, but the *clinical effect* depends on the disease state and the patient's biological context; hence, long-term outcome evaluation must consider both the intervention and the underlying physiologic susceptibility [6], [18], [20]. Analogously, metabolic surgery may generate endocrine signals, but long-term glycemic trajectories still depend on disease stage, reserve, and ongoing care structure.

3) What "success" should mean: durability, de-intensification, and stability as primary endpoints

Figure 3 indicates that the most consistently reported benefits cluster around **sustained HbA1c improvement** and **medication reduction/discontinuation**, with remission treated as a meaningful but more variable outcome. This ordering matters. It suggests that the literature is implicitly prioritizing **long-term stability** over maximal short-term achievement. For clinical teaching, this is an important corrective: in non-obese T2DM, the most defensible claim is not necessarily "remission," but **durable control with reduced treatment burden**, supported by physiologic markers (insulin sensitivity and beta-cell indices).

Here again, chronic glaucoma management provides a useful comparison. Long-acting drug delivery systems are valued not simply for lowering intraocular pressure at one time point, but for maintaining stable control and reducing reliance on repeated dosing behaviors that degrade outcomes in practice [3]–[5], [18]. In the same way, metabolic surgery's potential value in non-obese T2DM is best expressed through endpoints that demonstrate **sustained metabolic control** and reduced long-term complexity rather than single-point improvements.

4) The pathway perspective: why follow-up is not "aftercare" but part of the intervention

Figure 4 synthesizes what is often underappreciated in debates about surgical indication: outcomes are produced by a **system**, not by the operation alone. The results suggest that metabolic surgery in non-obese T2DM should be interpreted as a pathway requiring:

- disciplined **selection** (to maximize signal-to-response conversion),
- deliberate **procedure choice and perioperative optimization** (to shape the endocrine signal profile),
- structured **multidisciplinary follow-up** (to preserve durability and safety),
- consistent **monitoring** (to manage nutritional and metabolic risks).

This has direct practical implications: expanding indications without ensuring follow-up capacity increases the likelihood that benefits will erode or that complications will undermine net value. In glaucoma, the adoption of intracameral implants and sustained-release systems has required careful attention to safety monitoring and long-term outcomes, particularly because the intervention changes the therapeutic landscape from "daily dosing" to "embedded therapy," which introduces different risk profiles and surveillance needs [6], [9], [12], [18], [20]. Metabolic surgery similarly shifts the patient into a long-term physiologic state requiring reliable longitudinal care.

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5) Implications for Mexico, Colombia, and Ecuador

A Latin American perspective changes the emphasis from "Can it work?" to "Under what system conditions can it work safely and durably?" In Mexico, Colombia, and Ecuador, several realities make this discussion especially relevant:

1. **Heterogeneous access to advanced pharmacotherapy and continuity of care:** when medication access or long-term adherence is inconsistent, an intervention that reduces pharmacologic dependence could appear attractive—yet it also raises the bar for ensuring follow-up for nutritional and metabolic surveillance.
2. **Center variability:** outcomes depend heavily on multidisciplinary experience and standardized pathways; thus, regional implementation must be anchored in centers capable of structured long-term monitoring.
3. **Equity concerns:** expanding access to surgery without equitable access to follow-up (labs, supplements, nutrition support) risks widening health inequities.

These considerations align with a broader chronic-care lesson: durable control strategies can improve outcomes only when healthcare systems can support the monitoring they require. The glaucoma literature's emphasis on sustained delivery partly emerged from real-world barriers to daily adherence and continuity [3], [18]; however, it also underscores that new modalities demand **new monitoring standards** and rigorous safety evaluation [6], [12], [20]. Metabolic surgery in non-obese T2DM should be approached with the same discipline.

6) Limitations of the current evidence landscape and interpretive caution

Even when the overall narrative is compelling, several limitations must be addressed to avoid overextension:

- **Selection heterogeneity:** proposed criteria vary by center and study design, making generalization difficult without standardized definitions.
- **Outcome definition variability:** "remission," "improvement," and "durability" are not consistently defined across studies, which may inflate or obscure true comparability.
- **Follow-up duration differences:** short follow-up can overestimate benefit, while longer follow-up reveals relapse patterns and late complications.
- **Underreporting of patient-reported outcomes:** quality-of-life and functional outcomes are less consistently reported, despite being essential for assessing net benefit in a population with stricter risk–benefit thresholds.
- **System-dependence:** results achieved in high-volume centers may not translate to settings without stable follow-up infrastructure.

These limitations reinforce why Figure 4's pathway framing is not optional; it is essential for interpreting what the literature actually supports.

7) Future directions: what the next wave of research should prioritize

To strengthen clinical confidence and guide responsible indication expansion, future research should emphasize:

- **Standardized selection frameworks** integrating beta-cell reserve, disease duration, and metabolic phenotype.
- **Uniform outcome definitions** with explicit durability thresholds.
- **Longitudinal endocrine profiling** to clarify which mechanistic signals predict long-term control in non-obese cohorts.
- **Comparative pathway studies** assessing outcomes under different follow-up intensities.

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- **Equity-centered implementation research** in Latin America to define minimum follow-up requirements and feasible monitoring packages.

The broader clinical lesson mirrors the trajectory seen in sustained glaucoma therapeutics: innovation becomes responsibly adoptable when it is paired with standardized selection, consistent endpoints, and safety-focused longitudinal evaluation [6], [18], [20].

8) Discussion-level conclusion

In summary, the reviewed evidence supports a modern interpretation of metabolic surgery in non-obese T2DM as a **durable endocrine-modifying intervention** whose value depends on careful **metabolic-stage selection** and robust **long-term follow-up systems**. The most defensible benefits are expressed through **sustained glycemic control** and **reduced medication dependence**, supported by physiologic markers of improved endocrine function. For Mexico, Colombia, and Ecuador, the central question is not only clinical efficacy but **health-system readiness**: the ability to deliver multidisciplinary follow-up will largely determine whether the promise of durable metabolic stability translates into real-world benefit [3]–[6], [18], [20].

CONCLUSION

This review consolidates the current evidence supporting **metabolic surgery as a clinically meaningful option for selected non-obese patients with type 2 diabetes mellitus**, emphasizing that its therapeutic value lies primarily in **sustained endocrine modulation rather than weight reduction alone**. Across the analyzed literature, a consistent pattern emerges in which **functional metabolic criteria**—particularly beta-cell reserve, disease duration, and metabolic phenotype—are prioritized over body mass index as determinants of potential benefit.

The results demonstrate that glycemic improvement in non-obese patients is most plausibly explained by **integrated endocrine mechanisms**, including incretin amplification, enhanced insulin sensitivity, bile acid signaling, and reductions in systemic inflammation. These mechanisms collectively support a model of **durable metabolic recalibration**, capable of producing long-term glycemic stability when patient selection is appropriate. In this context, metabolic surgery aligns with broader chronic disease management strategies that seek to stabilize physiological parameters over extended time horizons, rather than relying on short-term or adherence-dependent interventions [3]–[5], [18], [20].

Outcome reporting across studies further reinforces this interpretation. The most consistently documented benefits are **sustained HbA1c improvement** and **reduction in pharmacologic treatment burden**, while remission—although clinically impactful—is more variable and strongly dependent on baseline endocrine reserve and follow-up duration. Importantly, these outcomes are best understood within a **system-based clinical pathway**, where selection, surgical strategy, and multidisciplinary follow-up operate as interdependent components rather than isolated factors.

From an international perspective, and particularly within Latin American contexts such as Mexico, Colombia, and Ecuador, the findings highlight that the feasibility and net benefit of metabolic surgery in non-obese T2DM extend beyond biological efficacy. **Health system capacity**, continuity of care, and access to long-term monitoring and nutritional support are critical determinants of durable success. Without these structural elements, the potential advantages of sustained endocrine modulation may be attenuated or offset by preventable complications.

In conclusion, the evidence supports a cautious but conceptually robust expansion of metabolic surgery indications in non-obese patients with type 2 diabetes mellitus, grounded in **metabolic staging rather than anthropometric thresholds**. Future research and clinical implementation should focus on standardized selection frameworks, harmonized outcome definitions emphasizing durability, and system-level strategies that ensure safe, equitable, and reproducible long-term care. Under these conditions, metabolic surgery may represent a valuable component of modern, physiology-driven diabetes management [6], [18], [20].

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