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Impact of Gut Microbiota Transplant Capsules versus Metformin on HbA1c Reduction in Newly Diagnosed Type 2 Diabetics: A Narrative Review

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a growing global health burden characterised by insulin resistance and progressive beta-cell dysfunction. Metformin remained the first-line pharmacotherapy due to its robust efficacy in lowering glycated haemoglobin (HbA1c) levels and its favourable safety profile. Emerging evidence suggests that gut microbiota dysbiosis contributes to T2DM pathogenesis, and gut microbiota transplant capsules offer a novel approach to restoring metabolic health through microbial reconstitution. This narrative review compared the impact of gut microbiota transplant capsules versus metformin therapy on HbA1c reduction in newly diagnosed type 2 diabetics. A narrative synthesis of published literature was conducted, evaluating mechanisms of action, efficacy in HbA1c reduction, safety profiles, practical considerations, and future directions of both interventions. Metformin lowers HbA1c by an average of 1–1.5% through reduced hepatic gluconeogenesis and enhanced insulin sensitivity, with additional benefits on weight and cardiovascular risk. Gut microbiota transplant capsules have shown promising HbA1c reductions of 0.4–0.8% in early trials by restoring microbial diversity, enhancing short-chain fatty acid production, and improving insulin sensitivity. While metformin's efficacy is well established, FMT capsule evidence remained preliminary, with questions surrounding durability, optimal dosing, and long-term safety. Both interventions are generally well tolerated, though metformin carries gastrointestinal side effects, and FMT capsules require rigorous donor screening and standardisation. Gut microbiota transplant capsules present a promising complementary approach to metformin for HbA1c reduction in T2DM. Larger, longer-term trials are warranted to define their role in routine diabetes management.

Keywords: Gut microbiota transplant capsules**,** Metformin**,** Type 2 diabetes mellitus**,** HbA1c reduction**,** Microbiota modulation therapy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a rapidly escalating global health challenge, affecting over 500 million people worldwide and accounting for significant morbidity, mortality, and economic burden [1, 2]. The disease is primarily characterised by chronic hyperglycaemia resulting from insulin resistance and progressive pancreatic beta-cell dysfunction. Effective glycaemic control in newly diagnosed patients is paramount to reducing microvascular and macrovascular complications and achieving durable metabolic improvements.

Metformin, an oral biguanide, remains the first-line pharmacological therapy for newly diagnosed T2DM due to its well-established efficacy in lowering glycated haemoglobin (HbA1c) levels, favourable safety profile, low risk of hypoglycaemia, and cost-effectiveness [3, 4]. It exerts its glucose-lowering effects predominantly by reducing

hepatic gluconeogenesis and improving peripheral insulin sensitivity. Despite its proven benefits, a significant proportion of patients experience suboptimal response, intolerance due to gastrointestinal side effects, or gradual loss of effectiveness over time.

In parallel, emerging evidence suggests that gut microbiota composition plays a pivotal role in glucose metabolism, insulin sensitivity, and systemic inflammation, implicating dysbiosis as a potential contributor to T2DM pathogenesis [5, 6]. Faecal microbiota transplantation (FMT), traditionally administered via colonoscopy or enema, has evolved into convenient oral capsule formulations designed to restore eubiosis safely and non-invasively. Early pilot studies have demonstrated promising results indicating that microbiota transplantation may improve insulin sensitivity, modulate metabolic pathways, and reduce HbA1c levels in metabolic syndrome and T2DM. This narrative review critically examines and compares the impact of gut microbiota transplant capsules versus metformin therapy on HbA1c reduction in newly diagnosed type 2 diabetics. It synthesises current evidence on mechanisms of action, efficacy, safety profiles, practical considerations, and future directions to guide researchers, clinicians, and policymakers in optimising early diabetes management strategies.

Mechanisms of Action

i. **Metformin:** Metformin lowers blood glucose primarily by inhibiting hepatic gluconeogenesis through activation of AMP-activated protein kinase (AMPK) [7]. This reduces glucose output from the liver and enhances insulin-mediated glucose uptake in peripheral tissues, particularly skeletal muscle. Metformin has also been shown to decrease intestinal glucose absorption and exert modest effects on weight reduction. Interestingly, recent studies have highlighted that metformin's glucose-lowering effects are partly mediated through modulation of the gut microbiota. Metformin alters the gut microbial community, increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria and reducing endotoxin-producing species, thereby improving intestinal barrier integrity and systemic insulin sensitivity [8, 9].

ii. **Gut Microbiota Transplant Capsules:** Gut microbiota transplant capsules deliver processed donor faecal microbiota in a freeze-dried, encapsulated form to the small intestine [10]. This approach aims to correct dysbiosis by reintroducing a diverse and balanced microbial community. The restored microbiota promotes production of SCFAs such as butyrate and propionate, which modulate glucose homeostasis by enhancing incretin secretion, regulating gut hormone release, improving intestinal barrier function, and reducing systemic inflammation. In T2DM, altered gut microbiota composition is associated with increased intestinal permeability, low-grade inflammation, and insulin resistance. By shifting the microbiome towards a more eubiotic state, gut microbiota transplant capsules hold potential to indirectly influence glucose metabolism and reduce HbA1c levels.

Evidence of Efficacy in HbA1c Reduction

i. **Metformin:** Numerous randomised controlled trials have demonstrated metformin's efficacy in lowering HbA1c by 1–1.5% on average in newly diagnosed T2DM patients [11, 12]. The UK Prospective Diabetes Study (UKPDS) remains a landmark trial, showing that intensive glycaemic control with metformin significantly reduces HbA1c, lowers the risk of diabetes-related endpoints, and decreases cardiovascular mortality. Metformin's glycaemic benefits are generally maintained for several years, although progressive beta-cell decline often necessitates treatment intensification. Long-term cohort studies confirm that early initiation of metformin slows disease progression and may contribute to diabetes remission in a subset of patients, particularly when combined with lifestyle interventions.

ii. **Gut Microbiota Transplant Capsules:** The evidence base for gut microbiota transplant capsules in T2DM is limited but growing. Small pilot trials and proof-of-concept studies have reported modest reductions in HbA1c ranging from 0.4% to 0.8% in patients receiving oral FMT capsules compared to placebo [13]. Mechanistic studies suggest that responders typically exhibit significant shifts in gut microbial diversity, increased SCFA production, and improved insulin sensitivity indices such as HOMA-IR. A notable pilot study demonstrated that FMT capsules from lean donors improved peripheral insulin sensitivity and reduced HbA1c at 6 to 12 weeks, although the effect waned over time without repeated dosing or sustained dietary support [14, 15]. The inter-individual variability in response highlights the importance of donor selection, microbiota engraftment success, and baseline gut microbiota composition.

Safety Profile and Tolerability

i. **Metformin:** Metformin is generally well tolerated but commonly causes gastrointestinal side effects such as diarrhoea, bloating, and abdominal discomfort in up to 30% of patients, occasionally leading to discontinuation [16]. Rare but serious adverse effects include lactic acidosis, particularly in patients with renal impairment or severe heart failure. Long-term use has also been associated with vitamin B12 deficiency, necessitating periodic monitoring.

ii. **Gut Microbiota Transplant Capsules:** Gut microbiota transplant capsules are considered safe when derived from rigorously screened donors and produced under stringent quality standards [17, 18]. Reported side effects are typically mild and transient, such as bloating or mild diarrhoea. Unlike colonoscopic FMT, capsules carry a negligible risk of procedural complications. However, concerns remain about potential transmission of undetected pathogens or long-term alterations to host immunity and metabolism. Regulatory frameworks vary across countries, influencing their clinical use.

Practical Considerations

i. **Administration and Adherence:** Metformin is easy to prescribe and administer as a once- or twice-daily oral tablet [19]. Extended-release formulations have improved gastrointestinal tolerability for many patients. Adherence, however, may decline due to side effects, perceived ineffectiveness, or pill burden when combined with other agents over time. Gut microbiota transplant capsules are non-invasive and administered orally, avoiding the discomfort and logistical challenges of colonoscopic delivery. However, optimal dosing regimens, frequency, and maintenance strategies are not yet standardised. Repeat dosing or booster capsules may be required to sustain engraftment and metabolic effects.

ii. **Patient Selection and Individualisation:** Metformin remains the universal first-line therapy for most newly diagnosed T2DM patients unless contraindicated [20]. It is particularly effective in patients with overweight or obesity due to its weight-neutral or modest weight-lowering effect. Gut microbiota transplant capsules may hold promise for patients with marked dysbiosis, metabolic syndrome, or those who poorly tolerate metformin. However, patient stratification tools to identify likely responders are still under development.

Impact on Metabolic Parameters Beyond HbA1c

i. **Metformin:** Beyond HbA1c reduction, metformin favourably influences lipid profiles, promotes mild weight loss, and has demonstrated cardiovascular benefit in high-risk populations [21, 22]. It also possesses anti-inflammatory properties, with emerging evidence supporting its potential role in cancer prevention and healthy ageing.

ii. **Gut Microbiota Transplant Capsules:** Early studies indicate that microbiota transplant capsules may favourably alter body weight, lipid metabolism, and inflammatory markers in addition to HbA1c. Some trials report modest reductions in body mass index (BMI) and visceral adiposity. However, the durability of these effects and their translation to meaningful cardiovascular benefit remain to be established.

Limitations and Challenges

i. **Metformin:** While effective, metformin monotherapy often becomes insufficient over time as beta-cell function declines, necessitating combination therapy with other glucose-lowering agents. Additionally, contraindications such as advanced renal impairment limit its use in certain populations.

ii. **Gut Microbiota Transplant Capsules:** FMT research is still in its infancy for T2DM [23]. Studies have small sample sizes, short follow-up durations, and heterogeneous methodologies. Long-term safety and sustainability of metabolic improvements are unclear. Furthermore, regulatory uncertainty, donor standardisation, and manufacturing consistency remain hurdles to widespread clinical adoption.

Future Directions

The potential synergy between metformin and gut microbiota modulation is of great interest. Studies exploring the combined use of metformin and FMT capsules suggest additive or even synergistic effects on metabolic parameters, likely due to overlapping and complementary mechanisms on the gut ecosystem. Future trials with larger cohorts and longer follow-up are warranted to define optimal patient selection, dosing schedules, and maintenance protocols for sustained HbA1c reduction.

Advances in microbiome profiling and precision medicine may enable the development of tailored FMT capsules or next-generation probiotics targeting specific dysbiotic patterns in T2DM [24]. Synthetic microbiota consortia or

engineered bacterial strains are also under investigation to deliver targeted metabolic benefits with greater reproducibility and regulatory compliance.

CONCLUSION

In conclusion, metformin remains the gold standard first-line pharmacological therapy for newly diagnosed type 2 diabetes, with robust evidence demonstrating its capacity to reduce HbA1c by 1–1.5% on average and confer long-term metabolic and cardiovascular benefits. Despite its limitations, including gastrointestinal intolerance and gradual decline in monotherapy durability, its cost-effectiveness and safety profile ensure its continued central role in diabetes care. Gut microbiota transplant capsules represent an innovative, biologically plausible strategy for improving glucose metabolism by restoring a healthy gut microbial ecosystem. Early trials suggest a modest but promising impact on HbA1c reduction and insulin sensitivity, with good safety and tolerability. However, the evidence base remains preliminary, and significant questions persist regarding long-term efficacy, patient selection, standardisation, and scalability. Ultimately, gut microbiota transplantation and metformin should not be viewed as mutually exclusive. Their complementary mechanisms suggest that integrated approaches leveraging microbiome modulation alongside established pharmacotherapy could unlock new avenues for durable glycaemic control and metabolic health in T2DM. Rigorous clinical trials and translational research will be critical to realising this potential and guiding evidence-based integration into routine diabetes management.

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