Anecdote Meets Evidence: The Ivermectin-Diabetes Hypothesis

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Abstract: This letter reviews a case series of four diabetic patients whose HbA1c improved with daily administration of ivermectin over a period of several months up to two years. Furthermore, the limited epidemiological and mechanistic available evidence is evaluated within the framework of the Bradford Hill criteria/guidelines.

Keywords: ivermectin, diabetes, insulin resistance, FXR

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1. Introduction

Interest in the potential repurposing of ivermectin (IVM), a well-established antiparasitic agent, for metabolic conditions such as diabetes has grown in recent years, although rigorous clinical evidence remains limited. This paper explores anecdotal experiences and the limited scientific literature regarding IVM's possible effects on glycemic control. We provide an overview of the evidence from various studies, including mechanistic in vitro studies, animal research and clinical observations, highlighting IVM's potential role and the limitations of current knowledge.

Cadegiani [**1**] reported a case involving a couple in their 70s (hereafter patients A and B) who first attended his clinic at the start of the COVID-19 pandemic. Both individuals had Type 2 diabetes, with initial HbA1c readings of 9.9% and 8.7%, respectively. Owing to pandemic-related lockdowns in 2020 and 2021, the couple was unable to visit their doctor and remained isolated, continuing their medications and maintaining a stable diet. During this period, they were administered IVM daily at a dose of 0.2 mg/kg for two consecutive years. Notably, neither individual received COVID-19 vaccinations, nor did they contract the virus. After two years of consistent IVM use, the HbA1c for patient A decreased from 9.9% to 6.3%, and for patient B from 8.7% to 6.6%. No long-term side effects were reported. In fact, for patient A, a normalization of alanine transaminase (ALT) levels from 87 to 22 U/L was observed, indicating the reversal of liver injury. Likewise, for patient B, ALT levels decreased from 37 to 17 U/L.

Encouraged by this report, an acquaintance from Japan (hereafter patient C) reported improved blood glucose control following off-label use of IVM, both for himself and his wife (hereafter patient D) in personal communication with the corresponding author (CA). Patient C was 67 years old during 2025. Until January 2024, he was diagnosed with Type 2 diabetes. In January 2024, patient C started taking IVM daily at 0.4 mg/kg per day. As a result, his HbA1c level decreased from 8.9% (in January 2024) to 7.5% (in July 2024) and further to a normal level of 5.6% in September 2024. Since then, his blood sugar levels have remained within the normal range, despite gradually reducing his use of other diabetes medications.

Patient D is 54 years old and has been living with diabetes for the past 10 years using insulin continuously. Although originally diagnosed with Type 2 diabetes, the diagnosis was revised to Type 1 diabetes in 2023. Patient D was initially skeptical about taking IVM; however, after seeing the pattern of improvement in patient's C condition, she started taking 0.4 mg/kg daily in December 2024. Her HbA1c decreased from $\sim$ 9% (in December 2024) to $\sim$ 8% (in February 2025) and more recently to 7.6% (in May 2025).

While these accounts remain anecdotal, they underscore the need for a critical evaluation of the literature and a deeper exploration of possible mechanisms of action. This letter assesses these anecdotal accounts

and examines the current evidence surrounding IVM's metabolic effects, particularly concerning diabetes management. The growing global prevalence of diabetes, along with the limited success of conventional therapies in many patients, calls for an open-minded yet evidence-based assessment of all potential treatment options, including those outside mainstream paradigms.

2. Literature review

A preliminary Deep Research search for literature on the impact of IVM on diabetes was conducted using ChatGPT 4.0. As this is an emerging research question, only 10 articles [**2–11**] and one patent application [**12**] were found. Regardless of the limited number of peer-reviewed articles, a Totality of Evidence-based medicine (T-EBM) Wheel (Fig. 1) representing the literature was derived [**13**]. It shows moderate to strong evidence from laboratory-based studies, which has led to cautious expert review. There have been no clinical trials carried out on human participants.

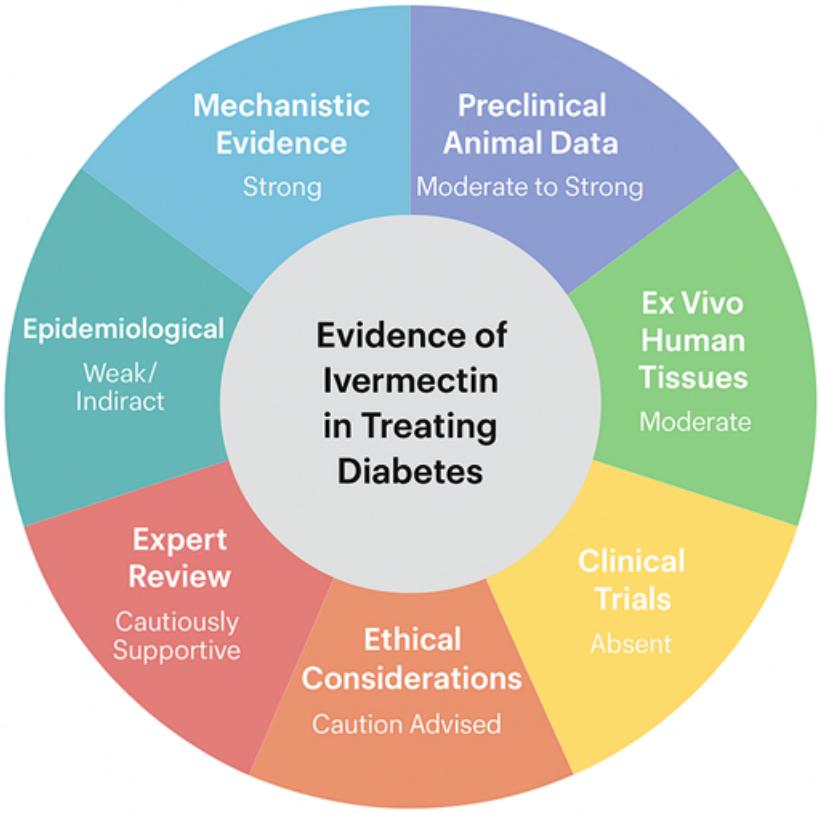

Figure 1: Totality of evidence-based medicine wheel for articles linking ivermectin to glycemic control.

3. Direct evidence from the anecdotal case series

From the reported four case reports, we can make a weak claim of some direct evidence under the Bradford Hill criteria/guidelines framework as amended by Howick and colleagues [**14, 15**]. Because the full recovery of HbA1c followed the daily administration of IVM, one may claim suggestive evidence of temporality. This evidence is very weak for patients A and B, because HbA1c was reported only at baseline and after two years.

However, the temporality evidence for patients C and D is stronger because positive responses were reported within shorter periods of three-month or six-month increments. The temporality evidence would have been stronger for all patients if at least month by month measurements were available.

Furthermore, we note that there is some suggestive evidence of biological gradient: patients A and B used a 0.2 mg/kg IVM daily dose resulting in transition from diabetic to prediabetic levels of HbA1c over a period of two years. On the other hand, starting from a similar baseline, patient C used an increased IVM daily dose of 0.4 mg/kg resulting in a more dramatic transition from diabetic to normal levels over a much shorter period of nine months. Furthermore, the average rate of improvement for patients C and D, both of whom received the same increased IVM dose, is consistent over the first six months, and coincidentally both have approximately equal HbA1c levels at about six months after starting IVM administration (7.5% and 7.6% respectively). Of note, for patient C, the average rate of improvement over the first six months was -0.2% per month and accelerated over the subsequent three months to an average improvement rate of -0.36% per month over the entire period of nine months. These are both conservative underestimates of the improvement rate using the total number of months for the denominator. Finally, for patients A and B, who used the lower IVM dose, the average rate of improvement was slower, at -0.15% and -0.08% per month, respectively. However, there is more uncertainty associated with these numbers as they were calculated over a longer two-year interval.

Unfortunately, it is not possible to claim strength of association without a larger sample size and a control group. Likewise, the small sample size is also a severe limitation towards claiming temporality and biological gradient. Nevertheless, it is encouraging that this limited data is not inconsistent with the hypothesis of a causal relation between daily IVM administration and the normalization of HbA1c levels.

4. Mechanistic evidence – Preclinical Studies

Researchers have been exploring the repurposing of IVM for metabolic diseases, including diabetes, due to unexpected effects on metabolic pathways. Early clues came from studies on nuclear receptors. Farnesoid X Receptor (FXR), a regulator of bile acid, lipid, and glucose homeostasis, was identified as a molecular target of IVM [**2**]. This finding opened avenues to investigate IVM's impact on insulin resistance, glucose metabolism, pancreatic β-cell function, and inflammation, all key factors in diabetes.

4.1. FXR Activation and Metabolic Effects

An important finding in the repurposing of IVM for metabolic disease was its identification as a novel ligand for the Farnesoid X Receptor (FXR), a nuclear receptor involved in bile acid, lipid, and glucose homeostasis [**2**]. FXR (NR1H4) is predominantly expressed in the liver, intestine, kidneys, and adrenal glands, where it functions as a ligand-activated transcription factor regulating gene expression in response to specific endogenous or exogenous molecules. Its natural ligands include bile acids, particularly chenodeoxycholic acid, but it can also be activated by synthetic or repurposed agents such as IVM.

FXR plays a key regulatory role in several physiological processes: (a) it maintains bile acid homeostasis by downregulating bile acid synthesis via negative feedback [**16, 17**]; (b) it modulates lipid metabolism by inhibiting lipogenesis and promoting fatty acid oxidation [**16**]; (c) it influences glucose metabolism by enhancing insulin sensitivity and suppressing hepatic gluconeogenesis [**16**]; (d) it contributes to cholesterol regulation by maintaining HDL/LDL balance [**18**]; (e) and it exerts anti-inflammatory effects in the gut and liver [**19**].

Jin and colleagues [**2**], through high-throughput screening followed by X-ray crystallography, identified IVM as a direct FXR agonist. In their study using diabetic mice, treatment with IVM led to significant improvements in metabolic parameters, including reductions in blood glucose and cholesterol, in wild-type mice, but not in FXR-knockout mice, confirming that these effects were FXR-dependent. Laing [**4**] had observed improved insulin sensitivity, supporting the hypothesis that FXR activation enhances insulin action.

These outcomes are consistent with previous knowledge that FXR agonism improves both hyperglycemia and hyperlipidemia in diabetic models [**20**].

As a result, IVM has emerged as a potential insulin sensitizer and glucose-lowering agent through its activation of FXR. This positions FXR as a compelling therapeutic target in type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), both of which are characterized by dysregulated lipid and glucose metabolism.

These findings are preclinical, with data derived primarily from rodent models. FXR has complex and context-dependent roles, and chronic activation in humans may have unintended consequences not observed in animal studies. Therefore, while the FXR-IVM axis represents a promising area of investigation, further research, including translational and clinical studies, is essential to clarify its therapeutic potential and safety profile in human populations.

Follow-up research reinforced IVM's role in metabolic regulation. Jin's group [**3**] tested avermectin analogues (chemically related to IVM) in a non-alcoholic fatty liver disease model, aiming for selective FXR targeting. They found that certain analogues improved fatty liver and metabolic profiles, supporting FXR as the key mediator. Consistently, other studies show IVM has *"cholesterol-reducing, insulin-resistance-improving, and fatty-liver-ameliorating properties"* in rodent models [**5**]. For example, Yang and colleagues [**5**] screened 12 common insecticides in a cell model of fatty liver and identified IVM as uniquely beneficial to hepatic metabolism. In steatotic HepG2 liver cells overloaded with fatty acids, IVM decreased triglyceride accumulation while upregulating FXR and fatty-acid oxidation genes [**5**]. By inhibiting lipogenesis-related genes and enhancing lipid oxidation, IVM opposed the development of non-alcoholic fatty liver disease (NAFLD) in this in vitro model [**5**].

These mechanistic studies, whether in hepatocyte cell lines or high-fat-fed mice, provide controlled insights but lack the complexity of human diabetes (e.g. they often examine isolated pathways or acute treatment).

4.2. Pancreatic β-Cell Function and Insulin Secretion

Beyond its effects on peripheral insulin sensitivity, IVM may directly influence pancreatic islet function, particularly β-cell insulin secretion. A pivotal study by Marcheva and colleagues [**6**] identified a novel insulinotropic action of IVM through a high-throughput screen of approximately 2 600 drug compounds aimed at restoring insulin secretion in dysfunctional β-cells. Using a model of circadian clock impairment, an established contributor to β-cell failure, the researchers found that IVM significantly enhanced glucose-stimulated calcium influx and insulin release.

Mechanistic analysis revealed that this effect is mediated by the $P2Y_1$ purinergic receptor, a G-protein-coupled receptor (GPCR) predominantly responsive to extracellular adenosine diphosphate (ADP). $P2Y_1$ is expressed in various tissues, including platelets, endothelial and smooth muscle cells, the brain, and, critically, pancreatic β-cells. In β-cells, $P2Y_1$ facilitates insulin exocytosis by coupling to proteins and triggering intracellular Ca^{2+} mobilization, a key signal for insulin granule release [**6**].

IVM appears to act as an allosteric modulator of $P2Y_1$, effectively restoring insulin secretory function in β-cells with disrupted circadian gene expression. This finding suggests that IVM may help overcome secretion deficits where normal glucose-stimulated insulin release is impaired. Validation experiments in both mouse and human cadaveric islets, combined with electrophysiological studies and CRISPR-mediated knockout of $P2Y_1$, confirmed the specificity of this mechanism [**6**].

While this represents an important step in understanding IVM's broader metabolic effects, the findings are currently limited to *ex vivo* islet models under specific conditions (i.e., circadian dysfunction). It remains uncertain whether similar benefits would be observed in typical diabetic patients, where insulin resistance and partial β-cell dysfunction are more common. The translational impact of enhanced insulin secretion via $P2Y_1$ modulation by IVM, particularly regarding long-term glycemic control and safety, requires further investigation in *in vivo* and clinical settings.

4.3. Effects on Lipid Metabolism and Weight

IVM's influence on lipid metabolism is closely intertwined with glucose metabolism. As noted, IVM via FXR can reduce serum cholesterol and triglycerides in mice [**2**]. In diet-induced or chemically induced models of metabolic syndrome, IVM has shown protective effects. A study in rats with valproic acid-induced metabolic derangements (valproate causes weight gain and fatty liver) found that a five-day course of IVM significantly lowered plasma triglyceride and cholesterol levels and attenuated hepatic fat accumulation [**7**]. Histological examination confirmed reduced steatosis in IVM-treated rats, suggesting a hepatoprotective effect against fatty liver disease [**7**]. Similarly, multiple rodent studies report prevention of diet-induced obesity or hepatic fat build-up with IVM treatment [**12**]. Some patent literature even claims IVM and its derivatives can *"balance blood glucose, blood lipid, and cholesterol"* in diabetic/obese mouse models, reducing weight gain, though such claims await peer-reviewed validation [**12**]. Taken together, these findings indicate IVM favorably alters energy balance and lipid storage, which could indirectly aid glycemic control by reducing ectopic fat and improving liver insulin sensitivity.

Most of these studies are short-term interventions in animals. The doses of IVM used (e.g. up to 10-50 μM in cell culture [**5**] or higher-than-standard antiparasitic doses in animals) may exceed typical human exposure, raising questions about feasibility and safety in a chronic setting. Additionally, effects on body weight in humans are unknown, no trials have tested whether IVM can prevent weight gain or improve obesity-related metrics in people.

4.4. Anti-Inflammatory and Immunomodulatory Actions

Chronic inflammation is a known contributor to insulin resistance and β-cell stress in type 2 diabetes. Interestingly, IVM appears to have anti-inflammatory properties that could be relevant to diabetes control. Research in a mouse model of atopic dermatitis (a T-cell-mediated skin inflammation) showed that IVM treatment led to significant reductions in T-cell activation, proliferation, and cytokine production [**4**]. The drug produced marked clinical improvement in this inflammatory condition, suggesting it can modulate immune pathways. While the exact mechanism was not FXR-dependent in that context [**4**], the general immune dampening effect of IVM could translate to lower systemic inflammation. In metabolic terms, this might mean less adipose tissue inflammation or reduced inflammatory signaling (e.g. lower tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6)) that drives insulin resistance. Indeed, given that inflammation links obesity to insulin resistance, any anti-inflammatory action of IVM might help improve insulin sensitivity. Additionally, a recent study on liver fibrosis found that IVM can suppress hepatic stellate cell activation and fibrogenesis [**8**]. In a carbon tetrachloride injury mouse model, IVM-treated mice had attenuated liver fibrosis, likely due to reduced inflammatory and fibrotic signaling in the liver. NAFLD and NASH (non-alcoholic steatohepatitis) are often accompanied by liver inflammation; thus, IVM's anti-fibrotic and anti-inflammatory effect in the liver could be an added benefit in metabolic disease settings.

It is also worth noting the immunomodulatory context of parasitic infections themselves. Helminth infections are known to skew immune responses and sometimes protect against metabolic disorders (the *"hygiene hypothesis"* in diabetes). IVM's primary use, clearing parasites, might remove this immunomodulatory influence. A cluster-randomized trial in Indonesia [**9**] illustrated that deworming can affect metabolic parameters. In communities with endemic helminths, repeated anthelmintic treatment (albendazole in that case) led to increased insulin resistance in individuals who had been infected, compared to those left untreated [**9**]. The postulated reason was that helminth infections induce regulatory immune responses (eosinophils, IgE, Th2 cytokines) that incidentally improve insulin sensitivity, so removing the infection reverses this benefit [**9**]. This finding, while not about IVM per se, is a reminder that the net effect of antiparasitic therapy on metabolism might be complex. In diabetics who are chronically infected with worms, treating the infection with IVM could theoretically lead to a loss of any protective immune effect on metabolism. On the other hand, this also means that if one observes in diabetic patients with a concurrent parasitic infection an association between the recovery of HbA1c levels and the long-term administration of

ivermectin, then the observed recovery cannot be confounded with the resolution of the underlying parasitic infection. In non-infected individuals, IVM's direct anti-inflammatory actions (as observed in other models) would be more likely to prevail as a positive factor.

The anti-inflammatory effects of IVM have mostly been demonstrated in acute or specific inflammatory models. Diabetes involves chronic, multi-organ inflammation (in fat, liver, pancreas); we do not yet know if IVM effectively tempers these processes long-term. Moreover, the immune effects of IVM can be pleiotropic, it may suppress some pathways but also, by killing parasites, alter immune homeostasis in other ways.

5. Studies in Humans and Clinical Evidence

Despite encouraging preclinical findings, human evidence for IVM in diabetes control is very limited. To date, there are no large clinical trials specifically evaluating IVM as a glycemic control medication in people with diabetes. A few clues and indirect pieces of evidence exist:

5.1. Case Reports/Small Series

There is scarce mention of IVM use in diabetic patients outside of infection treatment. Most human use has been in the context of parasitic disease management. No peer-reviewed studies have reported improvements in blood sugar control in diabetic patients taking IVM for parasites. Such outcomes, if any, have not been systematically recorded.

5.2. Observational Insights

A study in Australian First nation peoples found that diabetics responded less well to IVM treatment for strongyloidiasis [**10**]. Importantly, this was about parasitological cure rates, not metabolic outcomes. It underscores that diabetes can alter IVM's efficacy for infections, possibly due to immune dysfunction or pharmacokinetics in diabetic individuals. It does not provide evidence that IVM improves or worsens glycemic control in those patients (their diabetes management was not the focus).

5.3. COVID-19 Trials

During the COVID-19 pandemic, IVM was tested in several trials (often combined with other drugs like metformin or as a standalone) to see if it improved viral outcomes [**21, 22**]. Some of these trials incidentally involved patients with diabetes (since diabetes is a common COVID comorbidity). However, no published data from those studies indicate any effect on glucose or insulin metrics. A review on managing COVID-19 in diabetic patients noted that preclinical work showed IVM's glucose-lowering potential, but *"no data substantiated such observation in humans"* to date [**11**]. In other words, even though laboratory studies suggest IVM can lower blood sugar, this has not been confirmed in clinical practice or trials. For example, the COVID-OUT trial [**23**] (which tested IVM, metformin, and others for preventing severe COVID) did not report any improvements in HbA1c or fasting glucose from IVM; its focus was on infection outcomes. Furthermore, an observable improvement in HbA1c levels is unlikely given the low dose and the short three-day duration of IVM treatment studied in the COVID-OUT trial.

5.4. Meta-analyses and Reviews

There are currently no meta-analyses of randomized trials examining IVM for diabetes control, because the clinical trials have not been done. However, comprehensive reviews of IVM's pharmacology echo the gap between animal studies and human evidence. A 2017 review [**4**] highlighted IVM's metabolic benefits in mice (improved glycemia and insulin sensitivity via FXR) and proposed it as a *"potential novel diabetic therapy,"* but also emphasized that this is speculative without clinical trials.

5.5. Safety Considerations

Any attempt to use IVM chronically for diabetes would need to consider safety and dosage. IVM is generally safe at antiparasitic doses as a one-time or short-course therapy [**24**], but chronic use at higher doses (if required for metabolic effect) has not been studied. Side effects like liver enzyme elevations, interactions with other medications, and the potential for neurotoxicity at high doses would be important considerations [**25,26**]. Also, individuals with diabetes might be on multiple drugs, raising interaction concerns (IVM is metabolized by CYP3A4 [**27**] and could interfere with or be affected by other medications).

6. Conclusions and Future Directions

The four case reports presented in this paper suggest an association between the long-term administration of IVM and the resolution of HbA1c levels in diabetic patients. Within the framework of the Bradford Hill criteria/guidelines [**14, 15**], there is some very limited promising support for temporality and biological gradient but not for strength of association.

A growing body of peer-reviewed research suggests that IVM can modulate key pathways involved in diabetes: it improves insulin sensitivity, alters glucose metabolism, and promotes insulin secretion in animal and cellular models [**4, 6**]. Mechanistically, IVM's actions have been traced to nuclear receptor activation (FXR), G-protein-coupled receptor modulation ($P2Y_1$), and anti-inflammatory effects, leading to lower blood glucose, improved lipid profiles, and reduced fat accumulation in preclinical studies [**2, 5**]. These multifaceted actions imply that IVM (or analogues derived from it) could be repurposed as a metabolic drug. Notably, the drug showed efficacy in lowering hyperglycemia and cholesterol in diabetic mice [**2**] and even ameliorated insulin resistance and fatty liver in rodent models of obesity [**8**]. Within the framework of the Bradford Hill criteria/guidelines [**14, 15**] such findings are promising mechanistic evidence, however because they cannot corroborate a complete causal chain between IVM administration and diabetes mitigation in humans, they contribute mostly towards the *coherence* criterion rather than towards *biological plausibility*.

Future research should address these gaps. Well-designed clinical trials (perhaps small Phase II studies) could test whether IVM added to standard diabetes therapy improves glycemic control or insulin sensitivity in humans. To generate biological gradient evidence, clinical trials could consider comparing patients on 0.2 mg/kg daily IVM against patients on 0.4 mg/kg daily IVM over a period of one year, in addition to making comparisons against a placebo control group, with at least monthly monitoring of HbA1c levels. Participants should continue to be monitored for another year to determine whether the improvement in HbA1c levels persists after the discontinuation of ivermectin administration. To generate stronger temporality evidence, one might explore the effect on HbA1c and glucose levels of a short 10-day IVM administration at the higher 0.6 mg/kg dose, which was used for the treatment of the delta COVID-19 variant [**28, Table 1**], with biomarker measurements at baseline, day 5, and day 10. Such trials should monitor safety closely and might start with populations that have both parasitic infections and diabetes, to observe metabolic changes upon IVM treatment. Furthermore, regularly monitoring a broader range of biomarkers throughout all such trials could yield additional evidence needed to identify complete causal chains connecting IVM administration to diabetes mitigation in humans, which would then lend support towards the Bradford Hill *biological plausibility* criterion. Additionally, research into IVM analogues (like those targeting FXR without other off-target effects) may yield compounds better suited for chronic use in metabolic diseases. The dual actions of IVM on the liver (improving metabolism) and the pancreas (enhancing insulin release) present an attractive therapeutic profile if they can be harnessed safely.

In conclusion, IVM has demonstrated potential to impact diabetes-related pathways in the lab, improving insulin resistance, modulating glucose and lipid metabolism, protecting pancreatic function, and reducing inflammation. These benefits were seen across a variety of study types, from in vitro mechanistic assays to animal models of diabetes and NAFLD. However, clinical translation is still needed. We have a compelling example of drug repurposing research: an antiparasitic agent showing *"new tricks"* that could one day supplement our arsenal against diabetes [**4**]. For now, the role of IVM in diabetes control is an intriguing

scientific prospect that warrants deeper investigation, cautious optimism, and a clear recognition of the need for more data.

Key limitations of the current evidence include the lack of human trial data and the early-stage nature of many studies. To date, no clinical trial has proven that IVM can improve diabetes control in patients, and some authors explicitly note the absence of human data despite positive animal results [**4**]. All mechanistic studies, while insightful, have limitations in methodology, for instance, supra-physiological concentrations of IVM in vitro, or genetically modified animal models that might not mimic typical type 2 diabetes. The long-term safety of using IVM for metabolic indications remains unknown.

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