Research Review

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ARTICLE

Systematized Review of the Effect of Supplementation on Glycemic Control in Type 1 Diabetes

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Abstract

Despite the rise in the number of diabetics, studies on nutritional supplementation to help improve glycemic control type 1 diabetes can often be lacking. This review systematically collated research on the supplementation of glutamine, vitamin D, and magnesium to analyze what is currently known and what gaps in research can be filled. It was found that glutamine research is severely lacking but shows promise as a supplement to aid in glycemic control. Deficiencies in Vitamin D and magnesium show some relationship to poor glycemic control with some mixed results for supplementation beyond repletion. Data outside of the target population shows that all three supplements show potential promise in maintaining β-cell health in those with residual β-cells. In conclusion, glutamine and magnesium show the most value in improving glycemic control, but the mechanisms behind this are not known. More research is needed in this field to confirm and strengthen assumptions.

Key words :- • "type 1 diabetes", "t1d", "type 1", "diabetes mellitus type 1", "diabetes mellitus" •"supplementary nutrition","supplement" •"vitamin D", "cholecalciferol", "ergocalciferol", "vitamin D3", "vitamin D2"• "magnesium", "Mg" •"glutamine", "glutamate", "Gln", "Q" • "glycemic variability", "glycemic control", "glycemic", "glycemia"

1 | INTRODUCTION

Type 1 Diabetes (T1D) is a chronic disease that manifests because of autoimmune onslaught on β-cells within the pancreas leading to a stark decline of endogenous insulin production and subsequent reliance on exogenous insulin to preserve life [1-3]. The dysfunction of the endoplasmic reticulum (ER) of β-cells is considered a marker for T1D autoimmune onslaught and development [2-3]. As cellular stress induced fragility of the ER membrane leads to subsequent dysfunction and therefore decline of endogenous insulin production, preserving β-cell ER membrane integrity may be a potential method of increasing glycemic control in newly diagnosed diabetics or those with latent function [3-4]. Individuals with persistent β-cell function have been shown to have better glycemic control with less incidents of life-threatening or severe hypoglycemic episodes [4].

Glycemic Control

Improving glycemic control is paramount to the health of those with T1D whether it be through preservation of β-cell function or otherwise. Glycated hemoglobin (HbA1c) is a widely used measure of glycemic control as it can reveal a biological blood sugar average over the course of the lifespan of a blood cell—about three months [5]. Individual measurements of HbA1c have been

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of questionable value [6-7]. Single-measurement HbA1c has a tendency for inaccuracy regarding actual blood sugar averages with it commonly being either under-or overestimated [6]. In addition, HbA1c alone is a weak reflection of a patient's history of or tendency towards hypoglycemia which is acutely dangerous [4,7].

However,despite the relative unreliability associated with single-point measurements of HbA1c,maintaining measures of it are of paramount importance due to it being of immense value for measuring glycemic variability [8-9]. Glycemic variability (GV) is a compilation of data points of HbA1c measures or, in the case of continuous glucose monitoring(CGM), blood glucose measures to track glycemic trends more accurately than single-point measures [8-9].Poor glycemic control is typically defined as higher HbA1c and GV [8-9].Frequent measurements of HbA1c have been associated with lower odds of complications (OR 0.64,0.43-0.97)as wellas glycemic improvements [9]. Higher HbA1c and GV is linked to a higher risk for cardiovascular complications such as cardiovascular disease and cardiac autoimmunity as well as overall mortality [10-11]. Glycemic control also has an impact on brain function with cognitive dysfunction being relatively common among those with poor glycemic control [12].

T1D Statistics

Approximately 1.3 million people in the United States are reported to have T1D [13]. The prevalence of the disease has been increasing, especially in racial minorities, those of lower socioeconomic status, and individuals with SARS-CoV-2 (COVID-19) infection in the past thirty days [14-17]. While incidence of the disease decreases after the age of 14, the overall incidence rate has been increasing yearly with an almost 2% increase annually from 2002 to 2015 [18-19].

This review aims to address how different supplemental nutrients such as glutamine, vitamin D, and magnesium affect glycemic control in T1D. The reviewed interventions involve supplementary nutrition consisting of glutamine, vitamin D, and/or magnesium with the main outcome being glycemic control. Glycemic control, which is measured via HbA1c and, when available, HbA1c variability. Included analysis has measurements made prior to intervention initiation and at least once again at a time span of at least 3 months after initial intervention.

Additional outcomes include key nutrient status, other health markers, and patient satisfaction. Nutrition status would vary per intervention but would consist of any change in serum amount of the nutrient of focus. Measurements of additional outcomes would follow the same or similar time span and frequency of glycemic control measurements.Health markers such as lipid levels are also noted, when applicable and available.

Subgroups are defined by different supplement types utilized, namely glutamine, vitamin D, and magnesium. This review aims to compile available literature to explain how each subgroups affect glycemic control. Each subgroup will conform to the previously recorded investigation methods with some specific changes. Glutamine analysis will also investigate upstream and downstream substrates such as glutamate to glean a better understanding of how it affects glycemic control. Vitamin D analysis and magnesium analysis will more deeply consider the starting nutrition status of the patients involved by demarcating deficiency status. Studies will also be differentiated on the base of dosage, dosage scaling over time, and dosage amount.

2 | METHODS

Protocol and Registration

This systematic review's registration ID is CRD42022313368. The PRISMA 2020 Checklist was used to formulate this review and to help analyze data.

Search Strategy

The review utilized PubMed, Ovid, EBSCO (Academic Search Complete), MEDLINE, and EMBASE to compile research data. The search was restricted to English language and the year span of 2010-2022. Due to the sparse information, modifiers were used liberally or not at all to broaden

the scope of the search. Additionally, the searches were re-run prior to final analysis. Key words used included the following:

- "type 1 diabetes", "t1d", "type 1", "diabetes mellitus type 1", "diabetes mellitus"
- "supplementary nutrition", "supplement"
- "vitamin D", "cholecalciferol", "ergocalciferol", "vitamin D3", "vitamin D2"
- "magnesium", "Mg"
- "glutamine", "glutamate", "Gln", "Q"
- "glycemic variability", "glycemic control", "glycemic", "glycemia"

Eligibility Criteria

The main study types included were randomized controlled trials as they determined the effectiveness of each intervention. Cohort studies were included if they could determine the long-term effect and feasibility of an intervention. Case-control studies were used to supplement the review with additional analysis of cellular mechanisms and dynamics that may be unique in the disease of interest. Qualitative studies were also used to supplement the review by providing information on whether an intervention is practical.

Studies were included in the main analysis if the patients had T1D and no notable comorbid diseases that would affect nutrient dynamics except for vitamin deficiencies or processes associated with the disease of focus. Studies were not setting restricted, but the focus was preferentially in an out-patient context. The main outcomes of included studies measured glycemic control via HbA1c and GV. For the main analysis, those without T1D were excluded. Additional research data outside of the main scope of research—for example, involving those without diabetes—was included to enhance the information derived from directly applicable research. Since the data for specific supplements concerning T1D can be relatively sparse, this additional data is meant to expand upon the mechanisms behind what is available as well as offer additional insight into where the future of T1D nutritional supplement research can go.

Data Extraction and Quality Assessment

Data extraction was completed via Excel© spreadsheet with guidance from the Cochrane Consumers & Communications Review Group Data Extraction template [20]. Data sources were compiled for analysis from the aforementioned research databases. Information analysis included study type, study size, blinding, randomization methods, nutrition deficiency status of participants, frequency of data gathering, HbA1c levels, nutrition status, length of time since diagnosis of T1D, and relevant health history. Purpose was established for each extracted study to ensure the aims matched what the review is intended to cover. The description of the methods, sample group, and study design were compiled to ensure that the studies had adequate power or were otherwise statistically valid. The results were similarly parsed to ensure statistical validity of the research as well as how it may tie into the review's scope. Quality of data was ensured by a combination of risk assessment and determining statistical validity.

The data extracted generally set statistical significance at $p \leq 0.05$ and/or were within 95% confidence intervals. While many studies were blinded, few were explicitly double-blinded. Some were not blinded at all. Research studies were run through a risk of bias assessment and checked for quality. Figure 1 shows the process through which articles were systematically identified, screened, and reviewed.

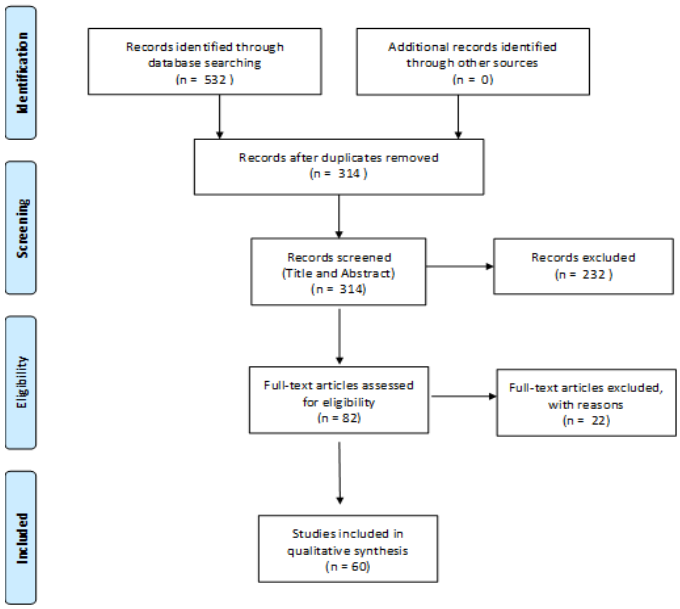

Figure 1. PRISMA Diagram

3 | RESULTS

Glutamine Supplementation

Nocturnal hypoglycemia significantly increased with glutamine supplementation (p=0.03; p=0.045) in adolescents post-exercise [21-22]. One study noted the mechanism behind the hypoglycemia was not significantly associated (p=0.4) to alterations in insulin sensitivity [22]. These studies indicate that glutamine supplementation in T1D patients reduces blood glucose levels but not by increasing insulin sensitivity.

Table 1. *Glutamine Studies in T1D Data Extraction*

Source	Sample/Study Description	Purpose	Results
	Glutamine - Type 1 Diabetes Information		
Mauras, N., Xing, D., Fox, L. A., Englert, K., & Darmaun, D. (2010). Effects of glutamine on glycemic control during and after exercise in adolescents with type 1 diabetes: a pilot study. Diabetes care, 33(9), 1951–1953. https://doi.org/10.2337/dc10-0275	In a randomized crossover controlled trial, 10 adolescent type 1 diabetics were given either a glutamine or placebo drink prior to exercise and bedtime. Exercise consisted of four cycles of 15 minutes on treadmill and 5 minutes resting and occurred at 3PM with drinks for 3 weeks.	To investigate the effect of oral glutamine on postexercise nocturnal hypoglycemia in type 1 diabetic adolescents	Hypoglycemia was more common with glutamine intervention compared to the placebo (P=0.03; P=0.05).
Torres-Santiago, L., Mauras, N., Hossain, J., Weltman, A. L., & Darmaun, D. (2017). Does oral glutamine improve insulin sensitivity in adolescents with type 1 diabetes?. Nutrition (Burbank, Los Angeles County, Calif.), 34, 1–6. https://doi.org/10.1016/j.nut.2016.09.003	In a double-blind, crossover, randomized control trial, 13 adolescent patients with type 1 diabetes performed four cycles of 15-min treadmill/5-min rest twice in a 4 week period. They randomly received glutamine or placebo drink. Blood sugar was tracked.	To investigate if glutamine intervention increases insulin sensitivity in adolescent type 1 diabetics	intervention did not alter insulin sensitivity (P=.4). Overnight hypoglycemia increased after intervention (P=.045)

Supplementary Information

Glutamine supplementation in non-diabetic patients has been shown to significantly attenuate the rise of blood sugar (p=0.007) after consuming a carbohydrate-dense nutritional drink as well as generally slow gastric emptying [23]. However, in type 2 diabetics (T2D), neither insulin secretion nor postprandial glycemic control was significantly improved by glutamine supplementation [24]. Glutamate—an amino acid tied to glutamine in a biological cycle—attenuated ($p<0.05$) rises in blood glucose when carbohydrates were taken in combination with glutamate [25-27]. The glutamate-glutamine cycle is an important aspect of neurotransmission within glutamatergic and GAGAergic neurons [26-27].

Glutamine has also been found to affect the immune system with being stimulated to increase lymphocyte count in anorexic and inflammatory response syndrome patients [28-29]. Glutamine supplementation also has been shown to suppress inflammatory response by decreasing T-cell leukocytes ($p<0.05$) and killer cell ($p<0.01$) count in patients with inflammatory response syndrome [29]. Studies on how glutamine affects cells find that glutamine supplementation promotes proliferation of cells while preventing ER stress-induced apoptosis [30-31]. The research suggests glutamine supplementation might attenuate both inflammatory response and inflammation induced ER membrane stress associated with autoimmune conditions such as T1D.

Table 2. *Glutamine Studies Outside of T1D Data Extraction*

Source	Sample /Study Description	Purpose	Results
	Glutamine - Supplementary Information		
Cetinbas, F., Yelken, B., & Gulbas, Z. (2010). Role of glutamine administration on cellular immunity after total parenteral nutrition enriched with glutamine in patients with systemic inflammatory response syndrome. Journal of critical care, 25(4), 661.e1–661.e6616. https://doi.org/10.1016/j.jcrc.2010.03.011	In this prospective, randomized control trial, 30 SIRS patients were either given 0.4g/[kg d] L-Glutamine or a control for 6 days. C-reactive protein, IgM, IgG, IgA, C3, C4, and lymphocytes were tracked via blood analysis on day 1 and day 6. The Acute Physiologic and Chronic Health Evaluation II score and the Simplified Acute Physiologic II score were used to analyze patients.	To identify the effect of intravenous glutamine intervention on immune state in patients with systemic inflammatory response syndrome (SIRS).	While some changes occurred, most were not at a significant level. intervention significantly decreased leukocyte and killer cell count. On the sixth day, the Simplified Acute Physiologic II score was low in the intervention group but not in the control group. These results generally demonstrate that glutamine intervention may help suppress inflammation.
Crespo, I., San-Miguel, B., Prause, C., Marroni, N., Cuevas, M. J., González-Gallego, J., & Tuñón, M. J. (2012). Glutamine treatment attenuates endoplasmic reticulum stress and apoptosis in TNBS-induced colitis. PloS one, 7(11), e50407. https://doi.org/10.1371/journal.pone.0050407	Male rats had colitis induced via TNBS and were subsequently given glutamine daily for 2 to 7 days. Oxidative stress and ERS markers were tracked alongside other biological markers.	To identify how glutamine affects ER stress and apoptosis in a rat model of experimental IBD	Glutamine helped inhibit the progression and increase of of oxidative stress, ERS, p53, cytochrome c expression, and caspase-9, caspase-8, caspase-3, JNK phosphorylation, and PARP-1 proteolysis. It helped prevent the fall of Bcl-xL expression and Bax/Bcl-2 ratio.
Di Sebastiano, K. M., Bell, K. E., Barnes, T., Weeraratne, A., Premji, T., & Mourtzakis, M. (2013). Glutamate supplementation is associated with improved glucose metabolism following carbohydrate ingestion in healthy males. The British journal of nutrition, 110(12), 2165–2172. https://doi.org/10.1017/S0007114513001633	In this controlled study, 9 patient participated in 4 trials: GLU+CHO, GLU+placebo, CHO+placebo, placebo+placebo (control). Blood was taken at 0 (fasting), 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min.	To investigate how carbs affect glutamate levels and how glutamate levels affect glucose metabolism	Plasma glutamate increased post GLU and GLU+CHO trials. Glucose response was attenuated by higher glutamate levels during GLU+CHO.
Du, Y. T., Piscitelli, D., Ahmad, S., Trahair, L. G., Greenfield, J. R., Samocha-Bonet, D., Rayner, C. K., Horowitz, M., & Jones, K. L. (2018). Effects of Glutamine on Gastric Emptying of Low- and High-Nutrient Drinks in Healthy Young Subjects-Impact on Glycaemia. Nutrients, 10(6), 739. https://doi.org/10.3390/nu10060739	In this randomized crossover control trial, 8 healthy men consumed either 30g of glutamine or no glutamine before partaking in either a low-nutrient beef soup or high-nutrient dextrose drink on four separate occassions. Gastric emptying, blood glucose, and plasma insulin were tracked during each event.	To identify the effect of glutamine on gastric emptying and glycemic response after exposure to drinks of varied nutritional value in healthy males	Glutamine did not significantly affect blood glucose values from the low-nutrient drink. However, it attenuated the typical rise in blood sugar from the high nutrient drink for about 60 minutes (P=0.007). Gastric emptying slowed regardless of drink type with glutamine intervention.
Jiang, Q., Chen, J., Liu, S., Liu, G., Yao, K., & Yin, Y. (2017). l-Glutamine Attenuates Apoptosis Induced by Endoplasmic Reticulum Stress by Activating the IRE1α-XBP1 Axis in IPEC-J2: A Novel Mechanism of l-Glutamine in Promoting Intestinal Health. International journal of molecular sciences, 18(12), 2617. https://doi.org/10.3390/ijms18122617	In this laboratory experiment, intestinal porcine epithelial cell line J2 was exposed to tunicamycin to induce ERS. After observation of the media till after apoptosis, L-glutamine was introduced and observed.	To investigate if L-glutamine can attenuate endoplasmic reticulum stress (ERS) induced apoptosis	L-glutamine promoted cellular proliferation and maintains high GRP78 levels, and helped to prevent apoptosis. This is due to L-glutamine modulating both ERS and CHOP-mediation.
Mansour, A., Mohajeri-Tehrani, M. R., Qorbani, M., Ghamari, M., Larijani, B., & Hosseini, S. (2020). Postprandial glycemia and insulin secretion following glutamine administration: A randomized controlled trial. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition, 90(5-6), 425–429. https://doi.org/10.1024/0300-9831/a000463	In a double-blind randomized controlled trial, 66 patients with T2D either received 30 g/d glutamine or a placebo for 6 weeks. Postprandial C-peptide, insulin, and glucose were tracked from baseline and at the end of the trial at 30 and 90 minutes after consuming a meal	To investigate the effect of glutamine intervention on postprandial glycemial and insulin secretion in type 2 diabetics	intervention did not significantly improve postprandial glycemic control or insulin secretion
Mondello, S., Italiano, D., Giacobbe, M. S., Mondello, P., Trimarchi, G., Aloisi, C., Bramanti, P., & Spina, E. (2010). Glutamine-supplemented total parenteral nutrition improves immunological status in anorectic patients. Nutrition (Burbank, Los Angeles County, Calif.), 26(6), 677–681. https://doi.org/10.1016/j.nut.2009.10.008	In this randomized controlled trial, 36 anorectic patients either received standard PN or PN with glutamine (0.18g/[kg d]) for 20 days. Serum neopterin, IGF-1, and lymphocyte count were tracked at baseline, 10 days, and 20 days.	To investigate the effect of glutamine intervention on the immune system of anorectic patients on total PN	After 10 days, serum neopterin significantly increased in those supplemented (P<0.001). Coupled with an increase in lymphocytes, the intervention of glutamine seems to stimulate the immune system in these patients
Schousboe, A., Scafidi, S., Bak, L. K., Waagepetersen, H. S., & McKenna, M. C. (2014). Glutamate metabolism in the brain focusing on astrocytes. Advances in neurobiology, 11, 13–30. https://doi.org/10.1007/978-3-319-08894-5_2	This is a chapter going over the mechanisms behind glutamate metabolism in the brain with a focus on astrocytes.	To illustrate glutamate metabolism in the brain focusing on astrocytes	The glutamate-glutamine cycle is one aspect of the neutrotransmission system involving astrocytes
Walls, A. B., Waagepetersen, H. S., Bak, L. K., Schousboe, A., & Sonnewald, U. (2015). The glutamine-glutamate/GABA cycle: function, regional differences in glutamate and GABA production and effects of interference with GABA metabolism. Neurochemical research, 40(2), 402–409. https://doi.org/10.1007/s11064-014-1473-1	This article illustrates the glutamine-glutamate/GABA cycle and how it applies to aspects of metabolism in the body	To explain the Glutamine–Glutamate/GABA Cycle	Glutamine is important in both glutamatergic and GAGAergic neurons.

Vitamin D Supplementation

Results on Vitamin D supplementation in patients with T1D tends to be relatively mixed but deficiency in Vitamin D was found to be common in most studies [32-37]. A study of 194 children did not find a significant relationship (p=0.057) between HbA1c and Vitamin D levels despite extensive statistical analysis and both bivariate and multivariate modeling [32]. In an investigation of the supplementation of Vitamin D in both T1D and T2D patients, the study found while Vitamin D effectively decreased HbA1c in T2D patients, the supplement had no significant (p=0.52) decrease in T1D patients [35]. However, the power analysis for this study found the T1D branch was low (7.5% for 88 patients) power while the T2D branch was high (60.4% for 37 patients) power [35]. Repletion of Vitamin D with 20000 UI/week for 6 months in a largely Hispanic and female group did not result in significant changes in either glycemic control (p=0.96) or IL-6 (p=0.85) inflammatory marker levels [37].

In a nonblinded, nonrandomized study with 80 patients, supplementation to replete deficiency was found to lower HbA1c after a 12-week intervention (r=-0.4, p=.001) with univariate and linear analysis of data done [33]. Another study—double-blinded with 39 patients, high doses of Vitamin D (4000 IU/d were found to be effective in lowering both HbA1c (p<0.001) and usage of exogenous insulin (p=0.003-0.039) with increases in serum Vitamin D (p=0.003) and regulatory T-cells (p=0.017) occurring more strongly in male participants [38]. In another case, Vitamin D supplementation significantly (p<0.0001) improved glycemic control in children [34].

Beyond supplementation, different levels of Vitamin D deficiency were correlated to different levels of glycemic control with multivariate regression showing a significant (p<0.01) link between serum levels of Vitamin D and HbA1c level [36]. In a similar vein, interleukin-6 (IL-6) was seen to be significantly higher (p=.026) in those deficient in Vitamin D [37]. When paired with saxagliptin, supplementation might help preserve β-cell function in latent autoimmune diabetes in adults—also known as LADA [39]. Vitamin D seems to be vitally linked to maintaining a healthy baseline levels of IL-6 and glycemia [36-37].

Table 3. *Vitamin D Studies in T1D Data Extraction*

Source	Sample/Study Description	Purpose	Results
	Vitamin D - Type 1 Diabetes Information		
Al Sawah, S., Compher, C. W., Hanlon, A. L., & Lipman, T. H. (2016). 25-Hydroxyvitamin D and glycemic control: A cross-sectional study of children and adolescents with type 1 diabetes. Diabetes research and clinical practice, 115, 54–59. https://doi.org/10.1016/j.diabres.2016.03.002	As part of a cross-sectional study, 25-hydroxyvitamin D and blood sugar were directly measured via non-fasting blood measurements from 197 patients from a children's hospital diabetes center during usual follow-up visit while HbA1c was derived from medical records. Most patients investigated were adolescent, male, and caucasian.	To investigate vitamin D levels and if they have an association with HbA1c in type 1 diabetic children and adolescents	40.6% were deficient in vitamin D and mean HbA1c was 8.6±1.4%. No significant relationship was reached in bivariate or multivariate models but it came close in the bivariate model (P=0.057)
Aljabri, K. S., Bokhari, S. A., & Khan, M. J. (2010). Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. Annals of Saudi medicine, 30(6), 454–458. https://doi.org/10.4103/0256-4947.72265	As part of a prospective, nonblinded, and nonrandomized controlled trial, 4000IU vitamin D3 and 1200 mg/d Ca were given to 80 vitamin D deficient patients with type 1 diabetes. 25-hydroxyvitamin D and HbA1c levels were measured at baseline and at 12 weeks (84 days)	To investigate whether vitamin D repletion would improve glycemic control in vitamin D deficient type 1 diabetes patients	Higher 25-hydroxyvitamin D levels were significantly associated with lower HbA1c at the 12 week follow-up (r=-0.4, P=.001) as well as a significant difference in HbA1c change depending on level of vitamin D repletion (P=.04).
Bogdanou, D., Penna-Martinez, M., Rillmann, N., Chung, T. L., Moran-Auth, Y., Wehrle, J., Cappel, C., Huenecke, S., Herrmann, E., Koehl, U., & Badenhoop, K. (2017). T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential crossover. Diabetes/metabolism research and reviews, 33(3), 10.1002/dmrr.2865. https://doi.org/10.1002/dmrr.2865	As part of a randomized, double-blind, controlled trial with a sequential crossover, 39 type 1 diabetic patients all were given 4000 IU/d cholecalciferol for 3 months. In the following 3 months, half were given placebo while the other half were given a sequential alternative.	To investigate if high dose vitamin D can enhance regulatory T cells and improve metabolism in type 1 diabetics by remedying immune dysfunction which can sometimes be caused by vitamin D deficiency.	Glycemic control improved indicated by lower HbA1c (P<.001) and lower insulin usage (P=.003-.039). Regulatory T cells and median 25-hydroxyvitamin D had stronger increase in men compared to women (P=.017; P=.003). High dose was well tolerated with no observed toxicity.
Mohammadian, S., Fatahi, N., Zaeri, H., & Vakili, M. A. (2015). Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. Journal of clinical and diagnostic research : JCDR, 9(3), SC05–SC7. https://doi.org/10.7860/JCDR/2015/10053.5683	This study followed children with type 1 diabetes who were deficient in vitamin D. 25-hydroxyvitamin D and HbA1c were compared before and after a 3 month intervention consisting of 300000 UI vitamin D3 and two 40mg/kg doses of Ca.	To investigate if vitamin D repletion causes glycemic changes in vitamin D deficient type 1 diabetes patients	Vitamin D3 intervention improved glycemic control for the studied group (P<0.0001)
Nwosu, B. U., & Maranda, L. (2014). The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. PloS one, 9(6), e99646. https://doi.org/10.1371/journal.pone.0099646	A retrospective study was conducted involving 131 patients with either type 1 or type 2 diabetes. 88 were type 1 diabetics while 43 were type 2 diabetics. All were diagnosed with diabetes for greater than 12 months and took vitamin D to treat vitamin D deficiency. These patients had complete data with baseline and follow-up measurements of HbA1c, alanine transaminase, and 25-hydroxyvitamin D.	To investigate the effect of vitamin D intervention on glycemic control and hepatic dysfunction in youths with type 1 diabetes or type 2 diabetes.	Vitamin D intervention had no significant changes in measurements beyond serum levels for type 1 diabetics. In contrast, it significantly decreased BMI and alanine transaminase (P=.015; P=.012) and a clinically significant decrease in HbA1c.
Savastio, S., Cadario, F., Genoni, G., Bellomo, G., Bagnati, M., Secco, G., Picchi, R., Giglione, E., & Bona, G. (2016). Vitamin D Deficiency and Glycemic Status in Children and Adolescents with Type 1 Diabetes Mellitus. PloS one, 11(9), e0162554. https://doi.org/10.1371/journal.pone.0162554	As part of a cross-sectional study, 141 patients with type 1 diabetes who were diagnosed for over 12 months had their fasting glucose, HbA1c, 25-hydroxyvitamin D, and daily insulin studied. 1000 IU/day cholecalciferol was systematically given for those with vitamin D insufficiency (<75 nmol/L)	To investigate 25-hydroxyvitamin D status and its relationship to insulin sensitivity and glycemic control in children with type 1 diabetes	25-hydroxyvitamin D insufficiency was common and there was a significant difference in it between those with different levels of glycemic control (P<0.01). Multivariate regression analysis linked HbA1c and 25-hydroxyvitamin D (P<0.001)
Shih, E. M., Mittelman, S., Pitukcheewanont, P., Azen, C. G., & Monzavi, R. (2016). Effects of vitamin D repletion on glycemic control and inflammatory cytokines in adolescents with type 1 diabetes. Pediatric diabetes, 17(1), 36–43. https://doi.org/10.1111/pedi.12238	In a randomized, prospective, crossover study, 25 vitamin D deficient patients aged 13-21 years diagnosed with type 1 diabetes for at least a year were followed. Most patients were female and hispanic in this study. 20000 UI/wk of vitamin D3 was given for 6 months either immediately or after 6 months of observation without intervention.	To investigate if repleting vitamin D deficiency in type 1 diabetics can improve glycemic control and reduce markers of inflammation	Glycemic control and inflammatory markers did not significantly change in response to intervention. IL-6 was seen to be significantly higher in the deficient group (P=.026)
Zhang, Z., Yan, X., Wu, C., Pei, X., Li, X., Wang, X., Niu, X., Jiang, H., Zeng, X., & Zhou, Z. (2020). Adding vitamin D3 to the dipeptidyl peptidase-4 inhibitor saxagliptin has the potential to protect β cell function in LADA patients: A 1-year pilot study. Diabetes/metabolism research and reviews, 36(5), e3298. https://doi.org/10.1002/dmrr.3298	In a randomized controlled trial, 60 patients with latent autoimmune diabetes in adults (LADA) either received (A) conventional therapy or (B) conventional therapy with saxagliptin (5 mg/day) or (C) conventional therapy vitamin D (2000 UI/day) with saxagliptin (5 mg/day). Fasting and 2-hour postprandial blood glucoses, HbA1c, and C-peptide levels were obtained at baseline as well as at 3, 6, and 12 months	To investigate if vitamin B3 added to DPP-4 inhibitors have a protective effect on β-cell function in LADA patients	The glutamic acid decarboxylase antibody titer levels of Group C decreased significantly (P<.05) while it did not for other groups. Fasting C-peptide, 2-hour postprandial C-peptide, and C-peptide index were maintained since baseline. Fasting C-peptide levels decreased in group B (P<.05) and C-peptide index levels decreased in group A (P<.05). In summary, vitamin D3 may help preserve β-cell function in conjunction with saxagliptin

Supplementary Information

Key markers of inflammation (p=0.19) or glycemic control (p=0.46) did not improve in 6 months with high-dose supplementation of Vitamin D [40]. However, supplementation is generally found to significantly decrease insulin resistance (p<0.001) and thereby improving insulin sensitivity [41-43]. This is linked to decreasing diabetes risk in prediabetics who are deficient in Vitamin D [42]. Supplementation additionally was found to lower fasting blood sugar (p<0.001), fasting insulin (p<0.001), inflammatory markers (p<0.001), and beta cell output (p=0.03) in healthy obese or overweight patients [41]. Along with improving insulin sensitivity (p=0.05), glycemic control (p=0.002), and oxidative stress (p=0.04) were improved compared to the control in elderly patients at 6 months [43]. This research generally concludes Vitamin D supplementation, especially to replenish deficiency, is beneficial to improve general health.

Table 4. *Vitamin D Studies outside T1D Data Extraction*

Source	Sample/Study Description	Purpose	Results
	Vitamin D - Supplementary Information		
Ebadi, S. A., Sharifi, L., Rashidi, E., Ebadi, S. S., Khalili, S., Sadeghi, S., Afzali, N., & Shiri, S. M. (2021). Supplementation with vitamin D and insulin homeostasis in healthy overweight and obese adults: A randomized clinical trial. Obesity research & clinical practice, 15(3), 256–261. https://doi.org/10.1016/j.orcp.2021.03.004	In this randomized control trial, 64 healthy obese or overweight patients either received 50000 IU/weekly vitamin D or a placebo for 8 weeks. Serum vitamin D, fasting blood sugar, fasting insulin, insulin resistance (via HOMA2-IR), beta-cell function (via HOMA3-beta), Insulin sensitivity (via HOMA2-S), and lipid profile were measured per participant.	To identify how vitamin D intervention impacts insulin homeostasis in healthy obese and overweight patients	In the supplement group, fasting blood sugar, fasting insulin, insulin resistance, and beta cell function lowered compared to placebo (P<0.001; P<0.001; P<0.001; P=0.03). Meanwhile insulin sensitivity increased in the supplement group but decreased in the placebo group (P<0.001). No significant changes in other parameters measured.
Miao, J., Bachmann, K. N., Huang, S., Su, Y. R., Dusek, J., Newton-Cheh, C., Arora, P., & Wang, T. J. (2021). Effects of Vitamin D Supplementation on Cardiovascular and Glycemic Biomarkers. Journal of the American Heart Association, 10(10), e017727. https://doi.org/10.1161/JAHA.120.017727	In a secondary analysis of the randomized control trial DAYLIGHT, 289 individuals with low vitamin D had their HOMA-IR, hs-CRP, N-terminal pro-B-type natriuretic peptide, renin, aldosterone, and lipids were tracked from baseline to 6 months. They received low dose (400 IU/d) or high dose (4000 IU/d) vitamin D for 6 months.	To investigate if vitamin D intervention reduces insulin resistance, inflammation, neurohormonal activation, and lipid levels	There were no significant differences between the two groups.
Niroomand, M., Fotouhi, A., Irannejad, N., & Hosseinpanah, F. (2019). Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. Diabetes research and clinical practice, 148, 1–9. https://doi.org/10.1016/j.diabres.2018.12.008	In a double-blinded controlled randomized clinical trial, 83 prediabetics with vitamin D deficiency were given vitamin D3 intervention or a suitable placebo for 6 months. Fasting glucose, 2hr oral glucose tolerance test plasma glucose, HOMA-IR, and glucose tolerance progression rate were tracked.	To investigate how high dose vitamin D affects insulin sensitivity and diabetes risk in those with prediabetes	The intervention improved insulin sensitivity and decreased diabetes risk (P=0.04; P=0.002).
Wenclewska, S., Szymczak-Pajor, I., Drzewoski, J., Bunk, M., & Śliwińska, A. (2019). Vitamin D Supplementation Reduces Both Oxidative DNA Damage and Insulin Resistance in the Elderly with Metabolic Disorders. International journal of molecular sciences, 20(12), 2891. https://doi.org/10.3390/ijms20122891	In a randomized controlled trial, 92 vitamin d deficient elderly patients either were supplemented with 2000IU/day vitamin D or not for 3 months. The patients were stratified based on diabetes risk. Fasting plasma glucose, fasting insulin, HbA1c, lipid fraction, HOMA-IR, and TG/HDL ratio were tracked.	To investigate the effect of vitamin D intervention on metabolism and oxidative DNA damage in elderly people with metabolic disorder	Intervention decreased HOMA-IR, TG/HDL ratio, and HbA1c while increasing HDL. This indicates that the intervention can potentially reduce oxidative DNA stress and improve metabolic markers

Magnesium Supplementation

No correlation was noted between levels of serum magnesium and HbA1c (r=-0.014, p=0.843) in a prospective cohort study [44]. However, other studies contradict this prospective study's findings.
Low serum magnesium was linked to poor glycemic control (p=0.002) with low magnesium being common in those with poor control [45-46]. There was a significantly negative correlation (adjusted r (2) =0.172, p=0.004; r=-0.625, p<0.001) between magnesium and HbA1c [45-46]. Potential health complications such as BMI (r=-0.197, p=0. 04), triglyceride levels (p<0.001), total cholesterol (p<0.001), low-density lipoprotein

(LDL) ($p<0.001$), and duration of diabetes ($p<0.001$) are also negatively correlated with HbA1c and magnesium levels [46-47]. Repletion of magnesium deficiency has been shown to improve both glycemic control ($p<0.001$) and lipid profile in children ($p<0.001$) [48]. In general, low magnesium levels are linked to poor glycemic outcomes as well as decreased overall health quality as measured by key health indicators such as cholesterol.

Table 5. *Magnesium Studies in T1D Data Extraction*

Source	Sample/Study Description	Purpose	Results
Magnesium - Type 1 Diabetes Information			
Galli-Tsinopoulou, A., Maggana, I., Kyrgios, I., Mouzaki, K., Grammatikopoulou, M. G., Stylianou, C., & Karavanaki, K. (2014). Association between magnesium concentration and HbA1c in children and adolescents with type 1 diabetes mellitus. Journal of diabetes, 6(4), 369–377. https://doi.org/10.1111/1753-0407.12118	In a cross-sectional study, 138 youths from age 1.9-20.3 years with type 1 diabetes were assessed. Anthropometrics, HbA1c, serum Mg, ionized Ca, total Ca, P, K, Na, and urinary albumin were measured while estimated glomerular filtration rate was calculated.	To investigate magnesium levels and if they have an association with glycemic control in type 1 diabetic youths	Poor glycemic control was associated with lower magnesium levels (P=0.002). Serum magnesium and Hba1c had a negative correlation (P<0.001) and the two remained significantly associated (adjusted r(2)=0.172; P=0.004) after adjustments for confounding factors. Poor control odds ratio between magnesium concentration quartiles was 0.190 (1.7% HbA1c lowered)
Inácio, I., Azevedo, T., Balsa, A. M., Ferreira, S., Rosinha, P., Alves, M., Dantas, R., & Guimarães, J. (2022). Association Between Serum Magnesium and Glycemic Control, Lipid Profile and Diabetic Retinopathy in Type 1 Diabetes. Cureus, 14(1), e21128. https://doi.org/10.7759/cureus.21128	A retrospective study with ophthalmological evaluation and serum magnesium level determination was conducted involving 105 type 1 diabetic adults split into two groups: low magnesium (≤1.80 mg/dL) or normal magnesium (1.81-2.60 mg/dL).	To investigate the relationship between magnesium level, glycemic control, lipid profile, and diabetic retinopathy	20% of those studied had low magnesium and 26.7% had diabetic retinopathy. Low magnesium individuals had higher HbA1c (P=.014) and trigs (P=.024). Magnesium levels had a negative correlation with HbA1c (r=-.281, P=.004) and BMI (r=-.197, P=.041).
Shahbah, D., El Naga, A. A., Hassan, T., Zakaria, M., Beshir, M., Al Morshedy, S., Abdalhady, M., Kamel, E., Rahman, D. A., Kamel, L., & Abdelkader, M. (2016). Status of serum magnesium in Egyptian children with type 1 diabetes and its correlation to glycemic control and lipid profile. Medicine, 95(47), e5166. https://doi.org/10.1097/MD.0000000000005166	A case-control study involving 71 type 1 diabetics aged 1-18 years were given thorough work-ups every 3 months alongside lipid profile and serum magnesium levels.	To investigate serum magnesium levels in type 1 diabetic children and how it relates to glycemic control and lipid profile	Serum magnesium was often deficient. Positive correlation with HDL (P<.002). Negative correlation with age, HbA1c, trigs, cholesterol, LDL, and disease duration (P<.001).
Shahbah, D., Hassan, T., Morsy, S., Saadany, H. E., Fathy, M., Al-Ghobashy, A., Elsamad, N., Emam, A., Elhewala, A., Ibrahim, B., Gebaly, S. E., Sayed, H. E., & Ahmed, H. (2017). Oral magnesium supplementation improves glycemic control and lipid profile in children with type 1 diabetes and hypomagnesaemia. Medicine, 96(11), e6352. https://doi.org/10.1097/MD.0000000000006352	A case-control study involving 71 type 1 diabetics aged 1-18 years were given thorough work-ups every 3 months alongside lipid profile and serum magnesium levels.	To investigate serum magnesium levels in type 1 diabetic children and how it relates to glycemic control and lipid profile and if intervention changes either	Magnesium repletion was associated with better control and more positive lipid panels. Serum trigs, LDL, and cholesterol lowered post intervention (P<.001) while HDL increased (P<.001). HbA1c was significantly lowered (P<.001)
van Dijk, P. R., Waanders, F., Qiu, J., de Boer, H., van Goor, H., & Bilo, H. (2020). Hypomagnesemia in persons with type 1 diabetes: associations with clinical parameters and oxidative stress. Therapeutic advances in endocrinology and metabolism, 11, 2042018820980240. https://doi.org/10.1177/2042018820980240	A prospective cohort study was conducted with 207 patients with type 1 diabetes with a mean age of 45. HbA1c, magnesium elvels, QOL, and oxidative stress were examined	To investigate the relationship of hypomagnesemia and magnesium with glycemic control and complications	No correlation (r=-.014, P=.843).

Supplementary Information

Non-diabetic metabolic syndrome patients with normal serum magnesium levels experienced an increase ($p=0.003$) in serum Vitamin D as well as a decrease ($p=0.0036$) in HbA1c [49]. This finding was supported in other studies which found magnesium supplementation decreased insulin resistance ($p=0.049$) and cholesterol levels ($p=0.006$) compared to placebo [50-51].

Magnesium has a distinct effect on cells with extracellular magnesium being seen to inhibit ($p \leq 0.05$) membrane fusion by modulating oxidative stress [52]. In magnesium deficient patients without hypertension, supplementation led to improved ($p<0.00005$) β-cell function and better biological handling ($p<0.005$) of

insulin sensitivity variations as measured by the Belfiore index [53]. Supplementation is linked to a decrease in oxidative stress by preventing uptake of SO4- uptake ($p<0.01$ to $p<0.001$) through competitive binding [54]. Through these cellular mechanisms, magnesium is shown to affect cellular metabolism and therefore affect glycemic control.

Table 6. *Vitamin D Studies outside T1D Data Extraction*

Source	Sample/Study Description	Purpose	Results
Magnesium - Supplementary Information			
Afitska, K., Clavel, J., Kisters, K., Vormann, J., & Werner, T. (2021). Magnesium citrate supplementation decreased blood pressure and HbA1c in normomagnesemic subjects with metabolic syndrome: a 12-week, placebo-controlled, double-blinded pilot trial. Magnesium research, 34(3), 130–139. https://doi.org/10.1684/mrh.2021.0489	In this randomized control trial, 24 patients took either 400mg magnesium citrate or placebo for 12 weeks. Blood pressure, HbA1c, blood glucose, serum Mg, serum Ca, blood ionized Mg, cholesterol, trigs, vitamin D, creatinine, IL-6, and C-reactive protein were tracked at baseline and follow-up.	To identify how Mg intervention affects normomagnesmic individuals with metabolic syndrome	Intervention decreased overall blood pressure as well as HbA1c significantly. IT additionally significantly increased serum vitamin D.
Falco, C. N., Grupi, C., Sosa, E., Scanavacca, M., Hachul, D., Lara, S., Sacilotto, L., Pisani, C. F., Ramires, J. A., & Darrieux, F. (2012). Successful improvement of frequency and symptoms of premature complexes after oral magnesium administration. Arquivos brasileiros de cardiologia, 98(6), 480–487. https://doi.org/10.1590/s0066-782x2012005000043	In this randomized double-blind study, 60 patients symptomatic with >240 PVC or PsVC on 24hr Holter monitoring took either a placebo or 3.0g/day MgP for 30 days.	To investigate whether MgP intervention in PVC or PsVC patients can improve symptoms and decrease arrhythmia frequency	There was significant premature complex density reduction in the MgP group. Symptoms also improved significantly ($P<0.001$)
Guerrero-Romero, F., & Rodriguez-Morán, M. (2011). Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. European journal of clinical investigation, 41(4), 405–410. https://doi.org/10.1111/j.1365-2362.2010.02422.x	In a randomized, double-blind, clinical trial, 106 nondiabetic, normotensive, hypomagnesmic patients were divided into the supplemented group and placebo group. 50ml of solution was given daily for 3 months.	To investigate the role of magnesium in β-cell function in non-diabetics	Intervention improved function of β-cells compensating for variations in insulin sensitivity
Ham, J. Y., & Shon, Y. H. (2020). Natural Magnesium-Enriched Deep Sea Water Improves Insulin Resistance and the Lipid Profile of Prediabetic Adults: A Randomized, Double-Blinded Crossover Trial. Nutrients, 12(2), 515. https://doi.org/10.3390/nu12020515	In a double-blinded crossover trial, the patients consumed 440 ML of balanced deep-sea water (BDSW) a day for 8 weeks. Fasting glucose, postprandial glucose, fasting insulin, HOMA-IR, C-peptide, HbA1c, lipid metabolism, and physical metrics were tracked.	To investigate how deep sea water affects prediabetic adults	Fasting insulin, HOMA-IR, cholesterol, LDL-cholesterol significantly decreased for the intervention.
Heidary, Z., Khalili, H., Mohammadi, M., Beigmohammadi, M. T., & Abdollahi, A. (2020). Effect of Magnesium Loading Dose on Insulin Resistance in Patients With Stress-Induced Hyperglycemia: A Randomized Clinical Trial. Journal of intensive care medicine, 35(7), 687–693. https://doi.org/10.1177/0885066618777431	In this randomized control trial, 70 non-diabetic critically ill patients with SIH either intravenously received 7.5g magnesium sulfate in 500mL saline or a placebo over 8 hrs. Serum Mg, intracellular Mg, serum adiponectin, HOMA-IR, and HOMA-AD ratio were tracked.	To investigate the effect of magnesium intervention on insulin resistance in critically ill patients with stress-induced hyperglycemia (SIH) without diabetes	Intervention significantly increased serum and intracellular Mg levels ($P<0.001$). After 3 days, the supplemented group significantly improved in HOMA-IR ($P=0.02$), adiponectin ($P=0.04$), and HOMA-AD ratio ($P<0.001$) compared to the placebo group.
Morabito, R., Remigante, A., & Marino, A. (2019). Protective Role of Magnesium against Oxidative Stress on SO4= Uptake through Band 3 Protein in Human Erythrocytes. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology, 52(6), 1292–1308. https://doi.org/10.33594/000000091	In this laboratory experiment, whole blood samples were exposed to 10mM $MgCl_2$ then treated with H_2O_2 (300 μM, 600 μM and 1 mM) for 30 minutes. For a different protocol, the samples were additionally exposed to NEM (0.5, 1 and 2 mM). SO4-uptake was measured with a turbidimetric method while GSH and membrane-SH was measured through spectrophotometry. Expression of Band 3 protein, P-Tyr, and Syk were measured.	To investigate the role of magnesium in protecting against oxidative stress	The magnesium ion prevented SO4-uptake reduction. P-Tyr and Syk expression remained high.
Rodrigues, A. K., Melo, A. E., & Domingueti, C. P. (2020). Association between reduced serum levels of magnesium and the presence of poor glycemic control and complications in type 1 diabetes mellitus: A systematic review and meta-analysis. Diabetes & metabolic syndrome, 14(2), 127–134. https://doi.org/10.1016/j.dsx.2020.01.015	This systematic review and meta-analysis involved using cross-sectional, cohort or case-control observational studies from the Medline/PubMed, Web of Science, Scopus and Scielo databases	To investigate the link between magnesium levels, glycemic control, and complications	Low magnesium levels were associated with poor glycemic control in most of the studies and data analyzed but further research is needed
Zocchi, M., Béchet, D., Mazur, A., Maier, J. A., & Castiglioni, S. (2021). Magnesium Influences Membrane Fusion during Myogenesis by Modulating Oxidative Stress in C2C12 Myoblasts. Nutrients, 13(4), 1049. https://doi.org/10.3390/nu13041049	C2C12 cells were cultured with $MgSO_4$ at low (0.1mM), physiological (1mM), or high (3, 6, and 10 mM) concentrations. N-Acetylcysteine was used to inhibit reactive oxygen species production for 24 hrs at 10mM.	To investigare how low and high extracellular Mg affects C2C12 myogenic differentiation	The extracellular Mg inhibited myoblast fusion by inducing oxidative stress within the myoblasts

Table 7. *Other Relevant Studies Data Extraction*

Source	Sample/Study Description	Purpose	Results
	Other Information		
Avari, P., Moscardo, V., Jugnee, N., Oliver, N., & Reddy, M. (2020). Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. Journal of diabetes science and technology, 14(3), 567–574. https://doi.org/10.1177/1932296819867688	In this blinded randomized control trial, 40 adult type 1 diabetics were randomly sorted to use either a rtCGM (Dexcom G5) or a iscCGM (Freestyle Libre) for a final total of 16 weeks. Glycemic variability was measured at baseline, 8 weeks, and 16 weeks.	To identify the impact of real-time continuous glucose monitoring (rtCGM) and intermittently scanned continuous glucose monitoring (iscCGM) on glycemic variability in adult type 1 diabetics	The rtCGM improved glycemic variability comparatively especially in regards to reducing the risk of hypoglycemia.
Cutfield, S. W., Derraik, J. G., Reed, P. W., Hofman, P. L., Jefferies, C., & Cutfield, W. S. (2011). Early markers of glycaemic control in children with type 1 diabetes mellitus. PloS one, 6(9), e25251. https://doi.org/10.1371/journal.pone.0025251	In this longitudinal study, 229 type 1 diabetic children less than 15 years of age in the Auckland area were tracked for anthropometrics, living arrangements, socioeconomic status, type 1 diabetes antibody titre, venous pH, venous bicarbonate, HbA1c, and insulin dose	To identify factors that may be associated with HbA1c level	Higher HbA1c was associated with female sex (P<.05), lower socioeconomics status (P<.01), non-european ethnicity (P<.01), Pacific Islander ethnicity (P<.001), not living with both biological parents (P<.05) and greater BMI (P<.05)
Nansel, T. R., Lipsky, L. M., & Liu, A. (2016). Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. The American journal of clinical nutrition, 104(1), 81–87. https://doi.org/10.3945/ajcn.115.126136	In a randomized clinical trial, 136 type 1 diabetic patients completed a 3 day diet record at baseline then at 3, 6, 9, 12, and 18 months. Continuous glucose monitoring data was obtained from Medtronic iPro. HbA1c was measured every 3 months while 1,5 anhydroglucitol was measured every 6 months	To investigate the longitudal relationship between dietary intake and glycemic control	HbA1c was inversely associated with carbohydrates and sugar but was positively associated with protein and unsaturated fat. More glycemic control was associated with unsaturated fat, low glycemic index, natural sugars, carbohydrate, fiber, whole plant food density, and higher scores on Healthy Eating Index-2005
Rama Chandran, S., Tay, W. L., Lye, W. K., Lim, L. L., Ratnasingam, J., Tan, A., & Gardner, D. (2018). Beyond HbA1c: Comparing Glycemic Variability and Glycemic Indices in Predicting Hypoglycemia in Type 1 and Type 2 Diabetes. Diabetes technology & therapeutics, 20(5), 353–362. https://doi.org/10.1089/dia.2017.0388	In this retrospective observational study, 60 T1D and 100T@D were tracked via CGM and self-monitored glucose for 3-6 days.	To investigate the predictive value of glycemic variability and other glycemic indices	Hypoglycemia occurred more often in T1D and HbA1c was a weak predictor of hypoglycemia. Low Blood Glucose Index, Glycemic Risk Assessment Diabetes Equation (GRADE) Hypoglycemia, and Hypoglycemia Index calculated from CGM data were good predictors. %CV from either data source was the most robust predictor
Sousa, G. R., Pober, D., Galderisi, A., Lv, H., Yu, L., Pereira, A. C., Doria, A., Kosiborod, M., & Lipes, M. A. (2019). Glycemic Control, Cardiac Autoimmunity, and Long-Term Risk of Cardiovascular Disease in Type 1 Diabetes Mellitus. Circulation, 139(6), 730–743. https://doi.org/10.1161/CIRCULATIONAHA.118.038068	This longitudintal study sourced data from a number of pre-existing studies in order to track cardiac antibodies, HbA1c, coronary artery calcification, high-sensitivity C-reactive protein, and cardiovascular disease events.	To investigate how poor glycemic control relates to cardiovascular disease (CVD) risk	Poor glycemic control was associated with cardiac risk associated with autoimmunity. Positivity for cardiac autoantibodies substantially increased risk for cardiovascular disease (4 of 6; hazard ratio, 16.1; 95% CI, 3.0-88.2)
Freese, J., Al-Rawi, R., Choat, H., Martin, A., Lunsford, A., Tse, H., Mick, G., & McCormick, K. (2021). Proinsulin to C-Peptide Ratio in the First Year After Diagnosis of Type 1 Diabetes. The Journal of clinical endocrinology and metabolism, 106(11), e4318–e4326. https://doi.org/10.1210/clinem/dgab463	In a randomized, double-blind, controlled trial, 99 new-onset type 1 diabetics were followed for a year. 30 were in the placebo group. C-peptide, proinsulin, glucose, and HbA1c were measured at baseline, 5 months, and 12 months after a liquid mixed meal tolerance test.	To investigate and track the changes in the proinsulin to c-peptide ratio and its relationship to residual β-cell function in new-onset type 1 diabetics	β-cell endoplasmic reticulum stress is increased indicated by increasing proinsulin to C-peptide ratios (fasting P=.0003; stimulated P=.00008). A higher baseline proinsulin level was correlated with steeper C-peptide decline (P=.004). The lower the age of diagnosis, the higher the ratio (P=.04). Higher ratios indicate increased stress and lower glycemic control.
Gubitosi-Klug, R. A., Braffett, B. H., Hitt, S., Arends, V., Uschner, D., Jones, K., Diminick, L., Kaiger, A. B., Patterson, A. D., Roshandel, D., Marcovina, S., Lachin, J. M., Steffes, M., Palmer, J. P., & DCCT/EDIC Research Group (2021). Residual β-cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. The Journal of clinical investigation, 131(3), e143011. https://doi.org/10.1172/JCI143011	Serum C-peptide was measured in 944 participants during a 4 hr mixed-meal tolerance test. Depending on the result, the patients were stratified into groups: nonresponder (<0.003 nmol/L), low responders (≥ 0.003 to ≤0.03 nmol/L), intermediate responders (>0.03 to ≤0.2 nmol/L), and high responders (>0.2 nmol/L).	To investigate residual β-cell function in diabetics with an average 35 year duration of type 1 diabetes	Residual C-peptide concentration was not associated with HbA1c and did not ameliorate the manifestations of complications. Severe hypoglycemia was less in those with more residual C-peptide (P=.0001). β-cell function can have residual persistence long after initial diagnosis
Sims, E. K., Chaudhry, Z., Watkins, R., Syed, F., Blum, J., Ouyang, F., Perkins, S. M., Mirmira, R. G., Sosenko, J., DiMeglio, L. A., & Evans-Molina, C. (2016). Elevations in the Fasting Serum Proinsulin-to-C-Peptide Ratio Precede the Onset of Type 1 Diabetes. Diabetes care, 39(9), 1519–1526. https://doi.org/10.2337/dc15-2849	Information was gathered from TrialNet Pathway to Prevention participants about 12 months prior to investigation. 60 developed diabetes while 58 did not and the two groups were compared in terms of PI:C ratio.	To investigate if elevation in proinsulin to C-peptide (PI:C) ratio is associated with type 1 diabetes progression	Dysfunction of the β-cell endoplasmic reticulum indicated by PI:C ratio increases precedes type 1 diabetes onset and is most pronounced in the younger patients. Logistic regression analysis adjusted for age and BMI indicates higher odds of progression for higher natural log PI:C ratios (1.44)
Wang, S., Flibotte, S., Camunas-Soler, J., MacDonald, P. E., & Johnson, J. D. (2021). A New Hypothesis for Type 1 Diabetes Risk: The At-Risk Allele at rs3842753 Associates With Increased Beta-Cell INS Messenger RNA in a Meta-Analysis of Single-Cell RNA-Sequencing Data. Canadian journal of diabetes, 45(8), 775–784.e2. https://doi.org/10.1016/j.jcjd.2021.03.007	Human islet single-cell RNA sequencing data from the year 2020 was aligned to reference genome GRCh38.98 and genotyped rs3842753. 2315 β-cells and 1223 β-like cells from protected, heterozygous, and at-risk donor groups were integrated.	To investigate the effect of genetic variation at rs3842753 on insulin mRNA at the cellular level	Hereditary type 1 diabetes may be related to elevated, inborn insulin production leading to β-cell endoplasmic reticulum stress and subsequent death. β-cells with rs3842753 C allele (high risk allele) had higher endoplasmic reticulum stress markers compared to the A allele (low risk).

Risk of bias was assessed following the Risk of Bias assessment template developed by the Cochrane Consumers & Communication Review Group [20]. This assessment was adapted from Table 8.5.c in chapter 8 of the Cochrane Handbook [20]. This is a reflection of data quality outside of statistics and, in particular to research directly applicable to T1D, reflects the quality of the diabetes supplement research found for this review. Risk was often unclear and high risk was often associated with blinding, randomization, and allocation concealment. Low risk was most often associated with outcome data and reporting. Table 8 shows the risk of bias assessments.

Table 8. *Risk of Bias Assessment*

Source	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Magnesium - Type 1 Diabetes Information						
Galli-Tsinopoulou, A., Maggana, I., Kyrgios, I., Mouzaki, K., Grammatikopoulou, M. G., Stylianou, C., & Karavanaki, K. (2014). Association between magnesium concentration and HbA1c in children and adolescents with type 1 diabetes mellitus. Journal of diabetes, 6(4), 369–377. https://doi.org/10.1111/1753-0407.12118	Unclear Risk	Low Risk	High Risk	Unclear Risk	Low Risk	Low Risk
Inácio, I., Azevedo, T., Balsa, A. M., Ferreira, S., Rosinha, P., Alves, M., Dantas, R., & Guimarães, J. (2022). Association Between Serum Magnesium and Glycemic Control, Lipid Profile and Diabetic Retinopathy in Type 1 Diabetes. Cureus, 14(1), e21128. https://doi.org/10.7759/cureus.21128	High Risk	Unclear Risk	Unclear Risk	High Risk	Low Risk	Low Risk
Shahbah, D., El Naga, A. A., Hassan, T., Zakaria, M., Beshir, M., Al Morshedy, S., Abdalhady, M., Kamel, E., Rahman, D. A., Kamel, L., & Abdelkader, M. (2016). Status of serum magnesium in Egyptian children with type 1 diabetes and its correlation to glycemic control and lipid profile. Medicine, 95(47), e5166. https://doi.org/10.1097/MD.0000000000005166	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Shahbah, D., Hassan, T., Morsy, S., Saadany, H. E., Fathy, M., Al-Ghobashy, A., Elsamad, N., Emam, A., Elhewala, A., Ibrahim, B., Gebaly, S. E., Sayed, H. E., & Ahmed, H. (2017). Oral magnesium supplementation improves glycemic control and lipid profile in children with type 1 diabetes and hypomagnesaemia. Medicine, 96(11), e6352. https://doi.org/10.1097/MD.0000000000006352	High Risk	High Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
van Dijk, P. R., Waanders, F., Qiu, J., de Boer, H., van Goor, H., & Bilo, H. (2020). Hypomagnesemia in persons with type 1 diabetes: associations with clinical parameters and oxidative stress. Therapeutic advances in endocrinology and metabolism, 11, 2042018820980240. https://doi.org/10.1177/2042018820980240	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk

Magnesium - Supplementary Information						
Afitska, K., Clavel, J., Kisters, K., Vormann, J., & Werner, T. (2021). Magnesium citrate supplementation decreased blood pressure and HbA1c in normomagnesemic subjects with metabolic syndrome: a 12-week, placebo-controlled, double-blinded pilot trial. Magnesium research, 34(3), 130–139. https://doi.org/10.1684/mrh.2021.0489	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Falco, C. N., Grupi, C., Sosa, E., Scanavacca, M., Hachul, D., Lara, S., Sacilotto, L., Pisani, C. F., Ramires, J. A., & Darrieux, F. (2012). Successful improvement of frequency and symptoms of premature complexes after oral magnesium administration. Arquivos brasileiros de cardiologia, 98(6), 480–487. https://doi.org/10.1590/s0066-782x2012005000043	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Guerrero-Romero, F., & Rodríguez-Morán, M. (2011). Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. European journal of clinical investigation, 41(4), 405–410. https://doi.org/10.1111/j.1365-2362.2010.02422.x	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ham, J. Y., & Shon, Y. H. (2020). Natural Magnesium-Enriched Deep-Sea Water Improves Insulin Resistance and the Lipid Profile of Prediabetic Adults: A Randomized, Double-Blinded Crossover Trial. Nutrients, 12(2), 515. https://doi.org/10.3390/nu12020515	High Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk
Heidary, Z., Khalili, H., Mohammadi, M., Beigmohammadi, M. T., & Abdollahi, A. (2020). Effect of Magnesium Loading Dose on Insulin Resistance in Patients With Stress-Induced Hyperglycemia: A Randomized Clinical Trial. Journal of intensive care medicine, 35(7), 687–693. https://doi.org/10.1177/0885066618777431	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Morabito, R., Remigante, A., & Marino, A. (2019). Protective Role of Magnesium against Oxidative Stress on SO4= Uptake through Band 3 Protein in Human Erythrocytes. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology, 52(6), 1292–1308. https://doi.org/10.33594/000000091	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk

Rodrigues, A. K., Melo, A. E., & Domingueti, C. P. (2020). Association between reduced serum levels of magnesium and the presence of poor glycemic control and complications in type 1 diabetes mellitus: A systematic review and meta-analysis. Diabetes & metabolic syndrome, 14(2), 127–134. https://doi.org/10.1016/j.dsx.2020.01.015	High Risk	Unclear Risk	High Risk	High Risk	Low Risk	Low Risk
Zocchi, M., Béchet, D., Mazur, A., Maier, J. A., & Castiglioni, S. (2021). Magnesium Influences Membrane Fusion during Myogenesis by Modulating Oxidative Stress in C2C12 Myoblasts. Nutrients, 13(4), 1049. https://doi.org/10.3390/nu13041049	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Glutamine - Type 1 Diabetes Information						
Mauras, N., Xing, D., Fox, L. A., Englert, K., & Darmaun, D. (2010). Effects of glutamine on glycemic control during and after exercise in adolescents with type 1 diabetes: a pilot study. Diabetes care, 33(9), 1951–1953. https://doi.org/10.2337/dc10-0275	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Torres-Santiago, L., Mauras, N., Hossain, J., Weltman, A. L., & Darmaun, D. (2017). Does oral glutamine improve insulin sensitivity in adolescents with type 1 diabetes?. Nutrition (Burbank, Los Angeles County, Calif.), 34, 1–6. https://doi.org/10.1016/j.nut.2016.09.003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Glutamine - Supplementary Information						
Cetinbas, F., Yelken, B., & Gulbas, Z. (2010). Role of glutamine administration on cellular immunity after total parenteral nutrition enriched with glutamine in patients with systemic inflammatory response syndrome. Journal of critical care, 25(4), 661.e1–661.e6616. https://doi.org/10.1016/j.jcrc.2010.03.011	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Crespo, I., San-Miguel, B., Prause, C., Marroni, N., Cuevas, M. J., González-Gallego, J., & Tuñón, M. J. (2012). Glutamine treatment attenuates endoplasmic reticulum stress and apoptosis in TNBS-induced colitis. PloS one, 7(11), e50407. https://doi.org/10.1371/journal.pone.0050407	High Risk	High Risk	Unclear Risk	High Risk	Low Risk	Low Risk

Di Sebastiano, K. M., Bell, K. E., Barnes, T., Weeraratne, A., Premji, T., & Mourtzakis, M. (2013). Glutamate supplementation is associated with improved glucose metabolism following carbohydrate ingestion in healthy males. The British journal of nutrition, 110(12), 2165–2172. https://doi.org/10.1017/S0007114513001633	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Du, Y. T., Piscitelli, D., Ahmad, S., Trahair, L. G., Greenfield, J. R., Samocha-Bonet, D., Rayner, C. K., Horowitz, M., & Jones, K. L. (2018). Effects of Glutamine on Gastric Emptying of Low- and High-Nutrient Drinks in Healthy Young Subjects-Impact on Glycaemia. Nutrients, 10(6), 739. https://doi.org/10.3390/nu10060739	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Jiang, Q., Chen, J., Liu, S., Liu, G., Yao, K., & Yin, Y. (2017). l-Glutamine Attenuates Apoptosis Induced by Endoplasmic Reticulum Stress by Activating the IRE1α-XBP1 Axis in IPEC-J2: A Novel Mechanism of l-Glutamine in Promoting Intestinal Health. International journal of molecular sciences, 18(12), 2617. https://doi.org/10.3390/ijms18122617	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Mansour, A., Mohajeri-Tehrani, M. R., Qorbani, M., Ghamari, M., Larijani, B., & Hosseini, S. (2020). Postprandial glycemia and insulin secretion following glutamine administration: A randomized controlled trial. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition, 90(5-6), 425–429. https://doi.org/10.1024/0300-9831/a000463	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Mondello, S., Italiano, D., Giacobbe, M. S., Mondello, P., Trimarchi, G., Aloisi, C., Bramanti, P., & Spina, E. (2010). Glutamine-supplemented total parenteral nutrition improves immunological status in anorectic patients. Nutrition (Burbank, Los Angeles County, Calif.), 26(6), 677–681. https://doi.org/10.1016/j.nut.2009.10.008	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Schousboe, A., Scafidi, S., Bak, L. K., Waagepetersen, H. S., & McKenna, M. C. (2014). Glutamate metabolism in the brain focusing on astrocytes. Advances in neurobiology, 11, 13–30. https://doi.org/10.1007/978-3-319-08894-5_2	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk

Walls, A. B., Waagepetersen, H. S., Bak, L. K., Schousboe, A., & Sonnewald, U. (2015). The glutamine-glutamate/GABA cycle: function, regional differences in glutamate and GABA production and effects of interference with GABA metabolism. Neurochemical research, 40(2), 402–409. https://doi.org/10.1007/s11064-014-1473-1	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Vitamin D - Type 1 Diabetes Information						
Al Sawah, S., Compher, C. W., Hanlon, A. L., & Lipman, T. H. (2016). 25-Hydroxyvitamin D and glycemic control: A cross-sectional study of children and adolescents with type 1 diabetes. Diabetes research and clinical practice, 115, 54–59. https://doi.org/10.1016/j.diabres.2016.03.002	Unclear Risk	High Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Aljabri, K. S., Bokhari, S. A., & Khan, M. J. (2010). Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. Annals of Saudi medicine, 30(6), 454–458. https://doi.org/10.4103/0256-4947.72265	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Bogdanou, D., Penna-Martinez, M., Filmann, N., Chung, T. L., Moran-Auth, Y., Wehrle, J., Cappel, C., Huenecke, S., Herrmann, E., Koehl, U., & Badenhoop, K. (2017). T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential crossover. Diabetes/metabolism research and reviews, 33(3), 10.1002/dmrr.2865. https://doi.org/10.1002/dmrr.2865	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Mohammadian, S., Fatahi, N., Zaeri, H., & Vakili, M. A. (2015). Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. Journal of clinical and diagnostic research : JCDR, 9(3), SC05–SC7. https://doi.org/10.7860/JCDR/2015/10053.5683	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Nwosu, B. U., & Maranda, L. (2014). The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. PloS one, 9(6), e99646. https://doi.org/10.1371/journal.pone.0099646	High Risk	Unclear Risk	Unclear Risk	High Risk	Low Risk	Low Risk

Savastio, S., Cadario, F., Genoni, G., Bellomo, G., Bagnati, M., Secco, G., Picchi, R., Giglione, E., & Bona, G. (2016). Vitamin D Deficiency and Glycemic Status in Children and Adolescents with Type 1 Diabetes Mellitus. PloS one, 11(9), e0162554. https://doi.org/10.1371/journal.pone.0162554	High Risk	Unclear Risk	High Risk	High Risk	Low Risk	Low Risk
Shih, E. M., Mittelman, S., Pitukcheewanont, P., Azen, C. G., & Monzavi, R. (2016). Effects of vitamin D repletion on glycemic control and inflammatory cytokines in adolescents with type 1 diabetes. Pediatric diabetes, 17(1), 36–43. https://doi.org/10.1111/pedi.12238	Low Risk	High Risk	Unclear Risk	High Risk	Low Risk	Low Risk
Zhang, Z., Yan, X., Wu, C., Pei, X., Li, X., Wang, X., Niu, X., Jiang, H., Zeng, X., & Zhou, Z. (2020). Adding vitamin D3 to the dipeptidyl peptidase-4 inhibitor saxagliptin has the potential to protect β-cell function in LADA patients: A 1-year pilot study. Diabetes/metabolism research and reviews, 36(5), e3298. https://doi.org/10.1002/dmrr.3298	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk
Vitamin D - Supplementary Information						
Ebadi, S. A., Sharifi, L., Rashidi, E., Ebadi, S. S., Khalili, S., Sadeghi, S., Afzali, N., & Shiri, S. M. (2021). Supplementation with vitamin D and insulin homeostasis in healthy overweight and obese adults: A randomized clinical trial. Obesity research & clinical practice, 15(3), 256–261. https://doi.org/10.1016/j.orcp.2021.03.004	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Miao, J., Bachmann, K. N., Huang, S., Su, Y. R., Dusek, J., Newton-Cheh, C., Arora, P., & Wang, T. J. (2021). Effects of Vitamin D Supplementation on Cardiovascular and Glycemic Biomarkers. Journal of the American Heart Association, 10(10), e017727. https://doi.org/10.1161/JAHA.120.017727	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Niroomand, M., Fotouhi, A., Irannejad, N., & Hosseinpanah, F. (2019). Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. Diabetes research and clinical practice, 148, 1–9. https://doi.org/10.1016/j.diabres.2018.12.008	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Wenclewska, S., Szymczak-Pajor, I., Drzewoski, J., Bunk, M., & Śliwińska, A. (2019). Vitamin D Supplementation Reduces Both Oxidative DNA Damage and Insulin Resistance in the Elderly with Metabolic Disorders. International journal of molecular sciences, 20(12), 2891. https://doi.org/10.3390/ijms20122891	Low Risk	High Risk	Low Risk	High Risk	Low Risk	Low Risk
Other Information						
Avari, P., Moscardo, V., Jugnee, N., Oliver, N., & Reddy, M. (2020). Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes. Journal of diabetes science and technology, 14(3), 567–574. https://doi.org/10.1177/1932296819867688	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Cutfield, S. W., Derraik, J. G., Reed, P. W., Hofman, P. L., Jefferies, C., & Cutfield, W. S. (2011). Early markers of glycaemic control in children with type 1 diabetes mellitus. PloS one, 6(9), e25251. https://doi.org/10.1371/journal.pone.0025251	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk
Nansel, T. R., Lipsky, L. M., & Liu, A. (2016). Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. The American journal of clinical nutrition, 104(1), 81–87. https://doi.org/10.3945/ajcn.115.126136	Low Risk	Low Risk	Unclear Risk	High Risk	Low Risk	Low Risk
Rama Chandran, S., Tay, W. L., Lye, W. K., Lim, L. L., Ratnasingam, J., Tan, A., & Gardner, D. (2018). Beyond HbA1c: Comparing Glycemic Variability and Glycemic Indices in Predicting Hypoglycemia in Type 1 and Type 2 Diabetes. Diabetes technology & therapeutics, 20(5), 353–362. https://doi.org/10.1089/dia.2017.0388	High Risk	Unclear Risk	High Risk	High Risk	Low Risk	Low Risk
Sousa, G. R., Pober, D., Galderisi, A., Lv, H., Yu, L., Pereira, A. C., Doria, A., Kosiborod, M., & Lipes, M. A. (2019). Glycemic Control, Cardiac Autoimmunity, and Long-Term Risk of Cardiovascular Disease in Type 1 Diabetes Mellitus. Circulation, 139(6), 730–743. https://doi.org/10.1161/CIRCULATIONAHA.118.036068	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk

Freese, J., Al-Rawi, R., Choat, H., Martin, A., Lunsford, A., Tse, H., Mick, G., & McCormick, K. (2021). Proinsulin to C-Peptide Ratio in the First Year After Diagnosis of Type 1 Diabetes. The Journal of clinical endocrinology and metabolism, 106(11), e4318–e4326. https://doi.org/10.1210/clinem/dgab463	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Gubitosi-Klug, R. A., Braffett, B. H., Hitt, S., Arends, V., Uschner, D., Jones, K., Diminick, L., Karger, A. B., Paterson, A. D., Roshandel, D., Marcovina, S., Lachin, J. M., Steffes, M., Palmer, J. P., & DCCT/EDIC Research Group (2021). Residual β cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. The Journal of clinical investigation, 131(3), e143011. https://doi.org/10.1172/JCI143011	High Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Sims, E. K., Chaudhry, Z., Watkins, R., Syed, F., Blum, J., Ouyang, F., Perkins, S. M., Mirmira, R. G., Sosenko, J., DiMeglio, L. A., & Evans-Molina, C. (2016). Elevations in the Fasting Serum Proinsulin-to-C-Peptide Ratio Precede the Onset of Type 1 Diabetes. Diabetes care, 39(9), 1519–1526. https://doi.org/10.2337/dc15-2849	High Risk	Low Risk	Unclear Risk	High Risk	Low Risk	Low Risk
Wang, S., Flibotte, S., Camunas-Soler, J., MacDonald, P. E., & Johnson, J. D. (2021). A New Hypothesis for Type 1 Diabetes Risk: The At-Risk Allele at rs3842753 Associates With Increased Beta-Cell INS Messenger RNA in a Meta-Analysis of Single-Cell RNA-Sequencing Data. Canadian journal of diabetes, 45(8), 775–784.e2. https://doi.org/10.1016/j.jcjd.2021.03.007	Unclear Risk	Unclear Risk	Unclear Risk	High Risk	Low Risk	Low Risk

4 | DISCUSSION

Despite mixed research findings, the reviewed supplement all show potential value in T1D patients. Data outside of the target population will be analyzed to better inform what is known.

Glutamine Supplementation

Only two relevant glutamine supplementation studies directly concerning T1D were found for use in this systemized review. Both studies had relatively small sample sizes but had statistically sound analysis [21-22]. The lack of connection to insulin sensitivity implies the mechanism is

potentially linked to something such as β-cell activity [22]. The fact the two studies utilizes adolescent diabetics is important to note especially in the context of findings from research on glutamine outside of T1D because young T1D patients may have residual β-cells [21-22].

Studies on non-diabetic patients supported glutamine supplementation has a distinct effect on glucose metabolism and supports the findings in the previous studies involving T1D patients [23, 25]. While glutamine does not appear to affect insulin sensitivity or secretion, glutamine may aid in maintaining residual β-cell integrity rather than enhancing cellular capabilities [22, 24]. Of note is how glutamine affects cellular dynamics through its modulation of ER membrane stress since apoptotic mechanism has been implicated as a key factor in T1D onset [2-3, 31].

While the research into how glutamine may affect T1D patients is not available, research outside of the scope of T1D alone seems to suggest the mechanism behind its value is linked to the preservation of β-cell function [2-3, 31]. Since the patients in the two T1D glutamine studied mentioned are adolescents, the change in glycemic trends may be linked to residual β-cells improving function—outputting insulin—and leading to hypoglycemia due to the combination of exogenous and endogenous insulin now being in excess [2-3,21-22,31]. While this is speculation, it is a valuable potential research hypothesis to potentially pursue.

Vitamin D Supplementation

The research on Vitamin D supplementation is mixed in terms of results and quality. Since the mechanism behind how Vitamin D supplements may affect T1D is not established, little can be gleaned from the research on why the findings are so mixed. However, since Vitamin D deficiency is seen to be common in T1D patients, supplementation may still be of value even if it may not have a direct effect on glycemic control [32-37].

Based on research outside of T1D, more insight can be gained on why the findings for T1D are so foggy. While Vitamin D supplementation does not seem to directly affect glycemic control in many instances, Vitamin D seems to have a distinct effect on insulin resistance and, potentially, oxidative stress [40-43]. By improving insulin sensitivity, β-cells may experience less stress leading to improved insulin dynamics for those with functional β-cells—such as LADA patients [39, 41,43]. Improving insulin resistance may also generally help T1D patients even without residual β-cells due to it decreasing the required exogenous insulin [41]. However, since insulin resistance and residual β-cells are not a universal experience for those with T1D, results of Vitamin D supplementation are understandably mixed.

The findings from this review agree with published advice given by the American Diabetes Association (ADA). The ADA notes the benefits of additional Vitamin D supplementation are not clear, but supplementation may reduce risk for developing T1D in childhood [55].

Magnesium Supplementation

Information on T1D and magnesium supplementation have a strong lean towards promoting supplementation and especially repletion of magnesium deficiency [45-48]. A prior meta-analysis of available research supported a link between low magnesium levels and poor glycemic control [56]. Research outside the confines of T1D alone reveals magnesium supplementation may have a link to glycemic control due to its effect on insulin resistance and β-cell function [50-51, 53-54].

While the ADA does not have noted recommendations regarding magnesium, the National Center for Complementary and Integrative Health (NIH) provides recommendations that agree with this review's findings. The NIH notes deficiency in magnesium can raise the chances of developing diabetes and that supplementation can aid those who have the condition [57]. However, the NIH does not specify if this specifically affects T1D and mentions that the studies for this information are lacking in power [57].

Quality and Risk Assessment

Research for T1D and each supplement reviewed is mixed in quality and risk. Unclear risk was common, especially regarding randomization, allocation concealment, and blinding. This indicates data may suffer from the placebo effect or unintended effects on habits affecting glycemic control—such as potentially changing insulin doses, food, or other such things. Much of the investigated research did not deeply address the mechanisms behind the observations. This is likely due to the sparseness in pool of available sources concerning T1D and these specific supplements.

Strengths and Limitations

One of the clearest things in this review is the lack of robust research pertaining to how supplementation of any of the reviewed supplements affects people with T1D. There was a sparse amount of data concerning T1D and the specific subgroups of supplements focused on in this review. The reviewed studies tended to have small sample sizes and low power. A lack of blinding or randomization was also common. While the related research that does not directly concern T1D tended to be of good quality, there is only so much data outside of the interest group can do to inform the conversation of how the reviewed supplements affect T1D patients. The research outside of T1D allows for greater insight into what the limited research for T1D supplementation may mean but research that does not directly involve patients with T1D cannot inform any recommendation until research is done to confirm or deny assumptions.

Application for Practitioner

The application of all the supplements, in a clinical setting, is a bit clouded by both mixed data and lacking data. Most value can be gleaned from how each supplement may help preserve β-cell integrity in those with residual cells or those who are newly diagnosed. While there is limited research on how supplementation of all three reviewed supplements may affect β-cells in T1D, the research outside of the T1D interest group analyzed suggest each supplement may have significant clinical value to pursue preservation of cells via supplementary nutrition. For those with residual cells or are newly diagnosed, supplementation of magnesium, vitamin D, and glutamine may be of value [2-3,21-22,31,39, 41,43,50-51,53]. In general,remedying nutritional deficiencies is advisable even if the effect is not directly on glycemic control.

2 | CONCLUSION

Glutamine for T1D research is still relatively new and would serve better with more data prior to any form of general recommendation for it [21-22]. Glutamine supplementation in T1D would benefit from more research purely based on the scarceness of what is available in comparison to the other reviewed supplements. Glutamine may have value in those with residual β-cells [2-3, 31]. While Vitamin D has the most robust selection of data directly relevant to T1D in this review, the mixed results of the vitamin's effects prevent the development of a definitive conclusion on its effectiveness [32-37]. Magnesium has a strong lean towards value as a supplement for T1D and deficiency in it should be considered paramount to remedy [45-48].

Research that investigates how these supplements affect the β-cells of those with T1D would be valuable and would better inform of their effectiveness. The focus on preservation of β-cells in any T1D patient with residual β-cells is of particular value and, as all the reviewed supplements show some influence on β-cell health, each should be reviewed for its cellular effects [2-3,21-22,31,39,41,43,50-51,53].

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