Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com

ISSN 2230-8407 [LINKING]

L-Tryptophan Supplementation Improves Glycemic Control and Sleep Quality in Uncontrolled Diabetes Patients: A Randomized double blinded Trial."

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How to cite: S.Parthasarathy[1], M Arun[2], M.R Suchitra[3]. **L-Tryptophan Supplementation Improves Glycemic Control and Sleep Quality in Uncontrolled Diabetes Patients: A Randomized double blinded Trial."** International Research Journal of Pharmacy, 2025,16:4:6-14.

Doi: http://doi.org/10.56802/irjp.2025.v16.i04.pp6-14

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Abstract:

Background: Diabetes mellitus is a growing worldwide health issue marked by sustained hyperglycemia. Present-day treatment plans center on drug therapy, lifestyle changes, and diet regimens. Emerging evidence indicates that the amino acid tryptophan is involved in glycemic

control. Objective: To evaluate the effect of L-tryptophan supplementation on glycemic control in patients who have uncontrolled diabetes mellitus (HbA1c > 7.0%).

Methods: A double-blind, placebo-controlled, randomized trial was done with 60 subjects (30 in Group T who received 500 mg of L-tryptophan and 30 in Group C who received placebo) between the ages of 30-70 years. Ethical clearance was received (STH – IHEC – 106/2023 dated 05/02/2023). Glycemic control was checked by measuring HbA1c levels at baseline and at three months. Adherence was checked by weekly calls, and compliance >75% was considered successful. Statistical analysis comprised the use of Student's t-test and chi-square tests, set at $p < 0.05$.

Results: Demographics between groups were similar ($p > 0.05$). The baseline HbA1c for Group T was 8.33 ± 0.733%, falling to 7.47 ± 0.56% at three months ($p < 0.001$). For Group C, the HbA1c fell from 8.23 ± 0.74% to 8.09 ± 0.66%. Improvements in sleep quality were experienced by 25 people in Group T and 5 people in Group C.

Conclusion: L-tryptophan supplementation markedly enhances glycemic control in patients with poorly controlled diabetes, making it a promising adjunctive treatment. The participants also had better sleep quality. More research with larger populations is needed to confirm these findings and assess different dosages in different populations.

Keywords: diabetes, uncontrolled, HbA1C, nutraceutical, tryptophan

Introduction:

Diabetes mellitus, a metabolic disease that involves persistent hyperglycemia, is a major health problem globally with increasing prevalence rates that burden healthcare systems and place high societal costs. Existing control measures are largely aimed at glycemic control using pharmacologic treatments, lifestyle interventions, and diet management. Nonetheless, optimal glycemic goals and the avoidance of complications continue to be a problem for most patients. New findings point towards the possible contribution of food components to diabetes control, with a specific focus on the amino acid tryptophan.

Tryptophan, a vital amino acid, is a precursor to various bioactive molecules, such as serotonin and melatonin, which have been associated with metabolic control and insulin secretion modulation. Recent evidence indicates that tryptophan could have positive effects on glucose metabolism and insulin sensitivity through modulation of gut microbiota and the related short-

chain fatty acids. Nonetheless, evidence on its efficacy and safety as an adjunct therapy in diabetes treatment is still limited.[1-3]

This randomized trial tests the impact of tryptophan supplementation in patients with diabetes mellitus. Through assessment of glycemic control, metabolic markers, and patient-reported outcomes, we aim to discover if incorporating tryptophan into standard treatment for diabetes can improve outcomes. Our results may add to the existing literature that looks for alternative, diet-related methods for the improvement of diabetes treatment and the quality of life in patients.

Methodology

Design This randomized, double-blinded, placebo-controlled trial was conducted to determine the impact of L-tryptophan supplementation on glycemic control in subjects with uncontrolled diabetes mellitus (HbA1c >7.0%). Ethical approval from the [Institution Name] Institutional Review Board was obtained, and written informed consent was obtained prior to enrolment in the study. STH – IHEC – 106/2023 dated 05/02/2023

Participants included 60 males and females aged 30 to 70 years with a diagnosis of type 2 diabetes mellitus and HbA1c greater than 7.0%. Participants were randomly assigned to either the group receiving the intervention, L-tryptophan, or the group that received placebo.

Exclusion criteria: A previous hypersensitivity to L-tryptophan or any study excipient. A past severe psychiatric disorder, or currently on medications that affect mood or cognitive function. A clinically significant renal or hepatic impairment. Patients currently taking antidepressants or other mood-modifying medications. Pregnant or breastfeeding patients.

Intervention Patients were randomly assigned (1:1 ratio) to either a group receiving L-tryptophan, at a dose of 500 mg (group T) nightly, or a placebo control (group C) for the duration of three months. Randomization was achieved by a computer-generated sequence of random numbers. Both the participants and investigators remained blind to the group assignments during the entire trial period.

Participants and the investigators were both blinded to group allocation (either the L-tryptophan or the placebo group). This implies that the patients under treatment did not know whether they were on L-tryptophan or a placebo, and similarly, the healthcare workers making

assessments and gathering data also did not know the group assignments. This two-blinding is aimed at reducing performance bias, whereby participants' or researchers' expectations might distort treatment outcomes.

Preparation for Intervention: L-tryptophan and placebo capsules were made to be visually identical in terms of size, shape, and color. This makes the participants unable to determine which group they are in according to the appearance of the capsules, upholding the blinding condition throughout the trial.

Randomization Process: Randomization was done by means of a computer-generated list of random numbers, creating a 1:1 assignment to the intervention (L-tryptophan) or control (placebo) group. Randomization by this method ensures that confounding variables are distributed evenly between the two groups, thus further ensuring the validity of comparisons of outcomes.

Data Monitoring and Collection: The study protocol adherence was monitored on a weekly basis through telephone calls during the course of the trial. The telephone calls, however, were done in such a way that it did not break the blinding to the group assignment either for the participants or the investigators. Outcome measure collection staff, who were not participating in the supplementation administration, were given the task of collecting outcome measures (like HbA1c values and self-reported sleep quality) without knowing whether participants were receiving the active supplement or placebo.Glycemic control was assessed by measuring HbA1c levels at baseline and after three months of intervention. The principal investigator monitored all patients for adherence to the study protocol by calling each participant weekly, during which time adherence to the nightly dose and side-effect assessment had occurred. Compliance of greater than 75% in taking the study medication was deemed a successful intervention. All adverse events and side effects were recorded and reviewed throughout the study. Participant were asked to report any unexpected symptoms or reactions, and at the end of the study safety monitoring was done. Statistical analyses were performed. The mean and SD were calculated and a student t test was performed for the data while for the sex values the chi square test was done and a p value of less than 0.05 was considered significant.

Results:

The present study recruited sixty participants with uncontrolled diabetes mellitus, thus completing a study of planned analyses as specified in the protocol. The groups had comparable demographic characteristics and baseline parameters and as expressed in Table 1, there were

no significant differences in age or sponsored distribution. Group T mean age was 54.66 with 21 males and 9 females, and Group C mean age was 53.26 with 20 males and 10 females. in fact, the entire array of p-values for these demographic variables was greater than 0.05, thus statistically equal between the two groups.

At baseline, mean HbA1c levels were similar between both groups, with Group T having an average HbA1c of 8.33 ± 0.733%, compared to 8.23 ± 0.74% for Group C. The p value calculated for this comparison was 0.45 and showed there was no significant difference between groups for glycemic control finding at the start of this study. Over the three-month intervention both groups had reduced HbA1c levels, but the reductions were significantly larger in Group T. Following the intervention, HbA1c level in Group T fell to 7.47 ± 0.56% and the HbA1c level for Group C fell to 8.09 ± 0.66%. The difference in the change of HbA1c between groups was statistically significant, with a p value of <0.001, indicating that L-tryptophan supplementation resulted in a clinically meaningful change in metabolic control in the study subject population. Moreover, while there were no significant side effects in either group, subjects in Group T reported an unexpected improvement in the quality of sleep they experienced. Although improved sleep was not a variable measured at the outset of the study, it was reported frequently in follow-up interviews as a noted benefit of L-tryptophan supplementation. Twenty five out of thirty in Group T and 5 out of 30 in Group C reported better sleep. (see table 1)

Table 1 showing the details of the study variables with p values.

	Group T (tryptophan)	Group C (control)	P value
Age in years	54.66	53.26	0.4
Male: female	21/9	20/10	0.6
Hba1c (basal)	8.33 ± 0.733	8.23 ±0.74	0.45
HbA1c (after 3 months)	7.47 6± 0.56	8.09 ± 0.66	< **0.001**

This study demonstrated that L-tryptophan supplementation significantly reduced HbA1c levels in patients with uncontrolled diabetes, outperforming placebo in efficacy. The findings

highlight the potential of dietary supplements, such as L-tryptophan, as adjunctive strategies in the management of diabetes, especially considering the reported improvement in sleep quality,

The study showed that L-tryptophan supplementation significantly decreased the HgbA1c levels in adults with uncontrolled diabetes compared to placebo. The findings were noteworthy and demonstrate the potential of dietary supplements like L-tryptophan as adjunct strategies to control diabetes, especially since all subjects reported improved sleep quality.

Discussion:

There has been growing interest in the relationship of dietary factors, most significantly amino acids (including tryptophan) and diabetes management in recent years. This paper summarizes findings from various studies regarding the effects and mechanisms of action of tryptophan and its metabolites, and their potential for regulating insulin secretion, glucose metabolism and diabetes health outcomes. Dietary management is an integral component of diabetes treatment and care; dietary interventions promote glycemic control and reduce complications. Dietary guidelines recommend a balanced diet focusing on macronutrient distribution, which includes total fat (less than 30%), saturated fat (less than 10%), and moderation of carbohydrates and protein, as well as certain supplements, such as L-carnitine, α-lipoic acid, and ω-3 fatty acids that may enhance metabolic health. Differences in amino acid metabolism, and in particular the metabolism of essential amino acids such as tryptophan, are increasingly acknowledged to influence diabetes risk and management. Research investigating the physiological effects of tryptophan have shown that tryptophan supplementation can improve pancreatic function, specifically through stimulating C-peptide and glucagon secretion, which are important factors in the regulation of insulin. Increased C-peptide levels indicate increased insulin produced by the body. This suggests that it is possible tryptophan has a positive role to enhance the secretion of insulin in someone living with diabetes. The reported decreases in plasma glucose post tryptophan consumption suggest glycemic control might be achieved with tryptophan consumption. These findings support previous findings that recommend tryptophan for modulating glucose metabolism due to the increased availability of tryptophan after foods with large glycemic response. [4-7]Furthermore, longitudinal studies examining specific amino acids, including tryptophan, have begun to examine their effects on insulin and resistance, and noted specific amino acids may predict risk for diabetes over long periods of time. Interestingly, within a large sample of more than 5,000 participants, several amino acids were strongly associated with lower insulin secretion and increased glucose levels. This showed that some

dysregulation of amino acids, may have an important role in the etiological developments of type 2 diabetes diabetes. This relationship between amino acid profiles and systems metabolic responses provide good rational, to conduct further investigations into specific dietary patterns of optimal amino acid intake, especially for those at risk for insulin resistance or diabetes.

As important as the role insulin dynamics play is the effect of tryptophan on cognitive function. Diabetic patients that exhibited lower levels of plasma tryptophan has been associated with co-morbidities of cognitive impairment and may be related to the complications of insulin resistance affecting the brain. This relationship also suggests how tryptophan affects metabolic processes for brain function The serotonergic system is involved in both the central and peripheral processes impacting diabetes management, and since most of serotonin is synthesized in the gut, stored in platelets, and acts in the central nervous system (C NS) and systemic levels - the relationship implications are concerning to feeding behaviors and mood. Presently, this relationship exists whether serotonin itself can affect blood glucose levels, and complications of diabetes such as possibly neuropathic and macroangiopathic effects. Hence, pharmacological avenues aimed at enhancing serotoninergic activity is the next line of possible medications for management of diabetes,[7-8] as achieving benefits on glycemic control and mood stabilization in the same therapy is an interesting avenue. Several studies have shown the beneficial effect of tryptophan on sleep quality which goes with our findings. [9-11]

To summarize, the utilization of tryptophan in diabetes management remains a valuable approach which deserves further investigation. It is well established that dietary changes, especially those related to the amino acid composition of foods, can have an impact on insulin dynamics, metabolic physiology, and metabolic health. Additionally, the possible cognitive improvements associated with tryptophan consumption adds to the necessity for dietary approaches in diabetes management. As we learn more about the relationships between diet, metabolism, and cognitive processing, it will be important to ensure clinical practice reflects the current understanding of the importance of diet in people with diabetes and concurrent impacts on overall health. Further research will be needed to untangle the mechanistic pathways produced by tryptophan and perhaps other amino acids to allow for targeted dietary interventions for people with diabetes.

Limitations:

While this study is informative regarding the effects of L-tryptophan supplementation on glycemic control in patients with diabetes, there are some limitations to be discussed. First,

with a sample size of limited a of sixty participants, generalizability of results may be limited as a larger sample size could provide more definitive findings with more statistical power. Also, the three-month duration of treatment may not be adequate to assess the long-term effects of L-tryptophan supplementation, and sustainablility of glycemic control identified in this study. Secondly, the study relied on self-reported adherence assessment called through weekly telephone calls, which could result in bias could under report compliance. The use of a more objective measure of adherence, for example, pill counts and/or biochemical validation could potentially produce results with more reliability. Thirdly, this study solely used one dose of an L-tryptophan supplementation (500 mg) and did not consider individual variations to the elements of dosage. Finally, although the participants stated they had improvements with sleep quality, sleep quality was not a primary endpoint assessed in this study and could bias how the interpretation of the effects of tryptophan was interpreted in this study on glycemic control. Finally, the findings in this study is on a specific population and further studies exploring the effects of L-tryptophan supplementation in different populations and across different types of diabetes would further our understanding of the role of L-tryptophan supplementation on glycemic control. In future studies, consideration needs to be given to these aspects of practice to refine and deepen our understanding of the effects of L-tryptophan supplementation on glycemic control. We could not clearly prove that a better sleep pattern has produced better reduction in HbA1C levels.

Conclusion:

In summary, this trial has shown that supplementation with L-tryptophan, may be beneficial in improving glycemic control in those with uncontrolled diabetes and used as an adjunctive therapy to usual care. In addition, in the current study some participants claimed improved quality of sleep suggesting added potential benefits from tryptophan beyond just related to glycemic state. Given the limitations of our current size and short duration findings provide impetus for further research into dietary approaches to diabetes including as we have done with amino acids such as tryptophan. Future large investigations evaluating different dose of tryptophan in various populations will help advance our understanding and clinical efforts to enhance care of those with diabetes.

Ethical issues – approved

Patient consent – Yes

There is no conflict of interest

There is no external financial aid from any source including companies manufacturing L tryptophan

The corresponding author (on behalf of all the authors) declared that the manuscript is original and is not published or communicated for publication elsewhere either in part or full.

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