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FRUCTOSE AND ITS IMPACT ON URIC ACID LEVELS IN HUMANS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL TRIALS FROM PUBMED DATABASE

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ABSTRACT

Worldwide fructose consumption continues to increase annually. It is well-established that high-dose fructose consumption can lead to metabolic disorders in humans. One of the indicators affected is uric acid, with several studies reporting increased uric acid levels following fructose intake. This study employs a systematic literature review and meta-analysis approach. We conducted a literature search exclusively in the PubMed database using keywords related to hyperuricemia, uric acid, fructose, and human health. The search was based on the PICO strategy: human health (population), fructose (intervention), glucose (comparison), uric acid (outcome). Nine eligible documents were analyzed for meta-analysis out of 81 documents retrieved from the PubMed database. Based on the Random Effects model (RE), the Standardized Mean Difference (SMD) value was -0.37 (95% CI; -1.34 to 0.59). The RE value crosses the vertical 0 line. Across various clinical studies, fructose consumption did not significantly show negative effects. Although some studies demonstrated dynamic changes, they remained within the normal range. However, these conclusions cannot be directly generalized due to limited knowledge on the long-term effects of fructose. Additionally, aspects such as dosage, duration, type of fructose, anthropometry, and subject characteristics need further attention and analysis in each fructose-related study, as they may be significant factors contributing to variations in study outcomes.

Keywords: *fructose, uric acid, human, clinical trial*

INTRODUCTION

Global fructose consumption continues to increase every year. It is well known that high doses of daily fructose consumption can direct to metabolic disorders in humans (1). One of the indicators of health related to fructose consumption is uric acid levels. Several studies have shown an increase in uric acid levels with fructose administration. However, other studies also show variations in findings regarding uric acid levels. Differences in dosage, duration, and subjects may contribute to these variations, which need to be reviewed in more detail. Therefore, it is important to scientifically and collectively examine these findings using a comprehensive approach.

In-depth analyses have been conducted in various studies on fructose at the clinical trial level. For instance, there are currently many scientific reports in PubMed demonstrating the use of fructose in clinical trial experiments. Unfortunately, so far, evaluations and analyses of these clinical trial publications on fructose have not been conducted. This is despite the fact that there's a wealth of high important of information about the use of fructose as a sweetener.

In this study, an analysis will be conducted using literature review approach. The limitation of this study is that the references are restricted to clinical trial publications in PubMed. The results of this study will provide important and stronger information about the impact of fructose on human uric acid levels in a more comprehensive manner.

It is crucial to evaluate the impact of fructose on humans. Caliceti and their colleagues performed a review study on fructose intake, serum uric acid, and also cardiometabolic disorders, which conducted a review but did not include tabulated reporting (2). The most recent clinical trial review study was conducted in 2021, but only 47 documents were analyzed.

Research Question

The study will focus on analyzing the outcomes of the effects of fructose in uric acid levels. The following are the research questions (RQs) for this study:

1. Can fructose significantly impact uric acid levels?
2. Is there a difference in uric acid levels between fructose and glucose interventions?

MATERIAL & METHODS

This study followed the Cochrane Handbook for Systematic Reviews of Interventions (3) for conducting our systematic review and also meta-analysis and transparently reported of our results are following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (4). The study protocol is registered at OSF (Open Science Framework) with registration number 10.17605/OSF.IO/W3NRC.

Search Strategy and Data Source

We used a literature search of the PubMed database, focusing on hyperuricemia, uric acid, fructose, and human health as subjects. The search was based on our PICO strategy: human health (population), fructose (intervention), glucose (comparison), and uric acid (outcome). Boolean operators were used to optimize the search for relevant literature. The search strategy was created to capture more studies published in English from the inception of the journal to 2024 in Pubmed. We also used an assessment framework to make sure the quality of basic research studies conduct and methodological approach considerations in the analysis and publication of observational studies.

Search String: ("fructose"[MeSH Terms] OR "fructose"[All Fields] OR "fructoses"[All Fields]) AND ("uric acid"[MeSH Terms] OR ("uric"[All Fields] AND "acid"[All Fields]) OR "uric acid"[All Fields]) AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]).

Study Selection

This study included randomized intervention trials in humans of all must health backgrounds and ages, with arm intervention periods in days. The screening, study selection, and data extraction were undertaken by two independent authors (BA, LH). Disagreements were resolved through discussion and, if required, by involving a fourth author (BA) to reach a final decision. We assessed the clinical and methodological

heterogeneity across the studies and included meta-analyses whenever these were performed.

Data Extraction

For data extraction the two reviewers (BA and LH) independently extracted data from all eligible studies. Relevant information included the food source of fructose-containing sugars, number of participants on arm, participant health status, study design, randomization declare, comparator intervention, type of fructose-containing sugars, and outcome data. In the data extraction process, we used Microsoft Excel, Nested Knowledge web-based software, and R Studio program.

Risk of Bias Assessment

Included studies were assessed for risk of bias (RoB) independently using the latest update of the JBI quantitative critical appraisal tool (5). The final reporting of RoB is presented as a traffic light summary.

Outcomes

The primary outcome was uric acid concentration in mg/dL. Mean differences (MDs) between the intervention and control arms and their standard deviations (SD) were extracted for each eligible study.

Data Synthesis and Analysis

We used Nested Knowledge web-based software for all analyses (6). This included data extraction within the Nested Knowledge interface, exporting the data as a .csv file, and importing it for further analysis.

RESULTS & DISCUSSION

The initial reference search resulted in 1930 documents in the PubMed database. However, after filtering for clinical trial features, particularly fructose interventions in healthy

individuals, 81 documents were obtained. A stepwise review was conducted on the obtained documents, including an initial screening for contextual relevance at the abstract level. At the stage of full-text analysis and reading, 9 documents were found eligible for meta-analysis.

Exclusion was carried out on studies with incomplete data, invisible fructose doses, non-health participants, and non-fructose interventions. All analyzed documents were in English. The workflow process of this study is displayed in the PRISMA flow diagram (Figure 1).

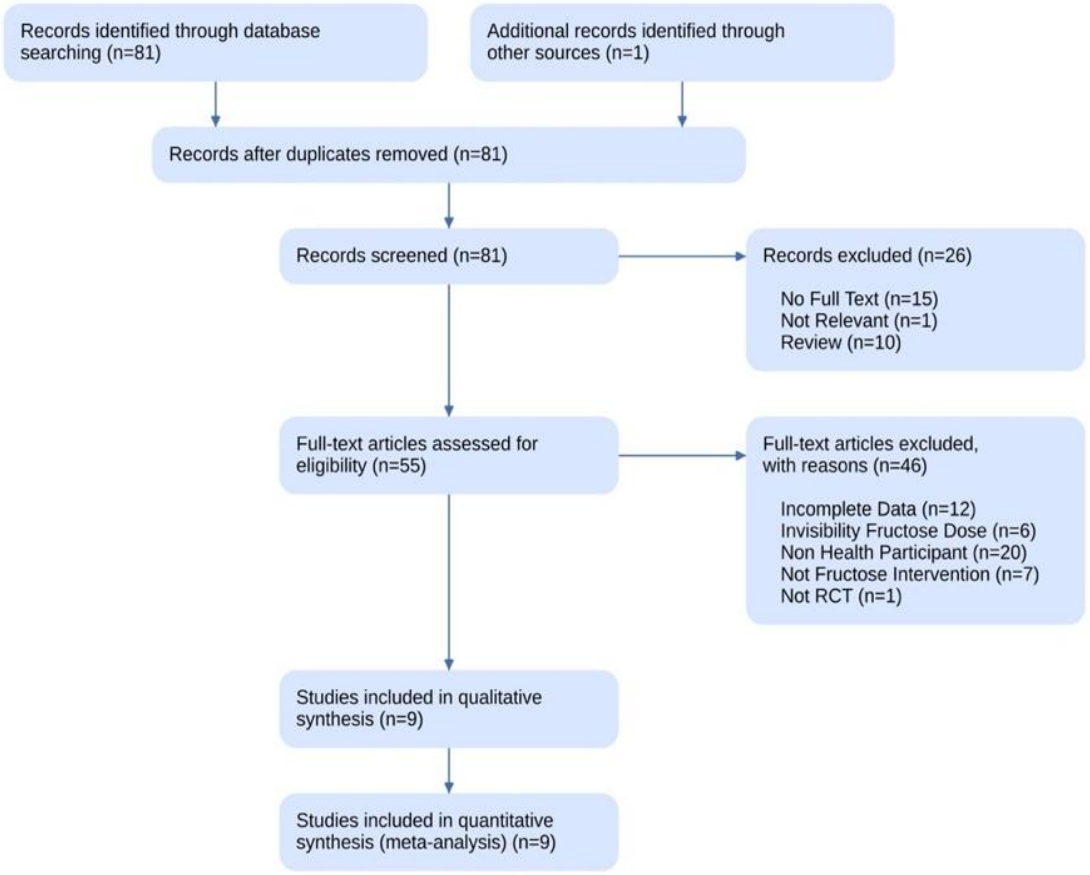

Figure 1. PRISMA flow diagram showing the search, screening, and extraction process of references related to fructose and uric acid in humans.

The Risk of Bias (RoB) was used to perform a critical appraisal of the scientific reporting of each paper. In this case, we used the JBI quantitative critical appraisal tool for the analysis. The results of the RoB analysis showed that the 9 evaluated documents had Low Risk characteristics. The complete RoB results in this study are displayed in the Traffic Light diagram (Figure 2).

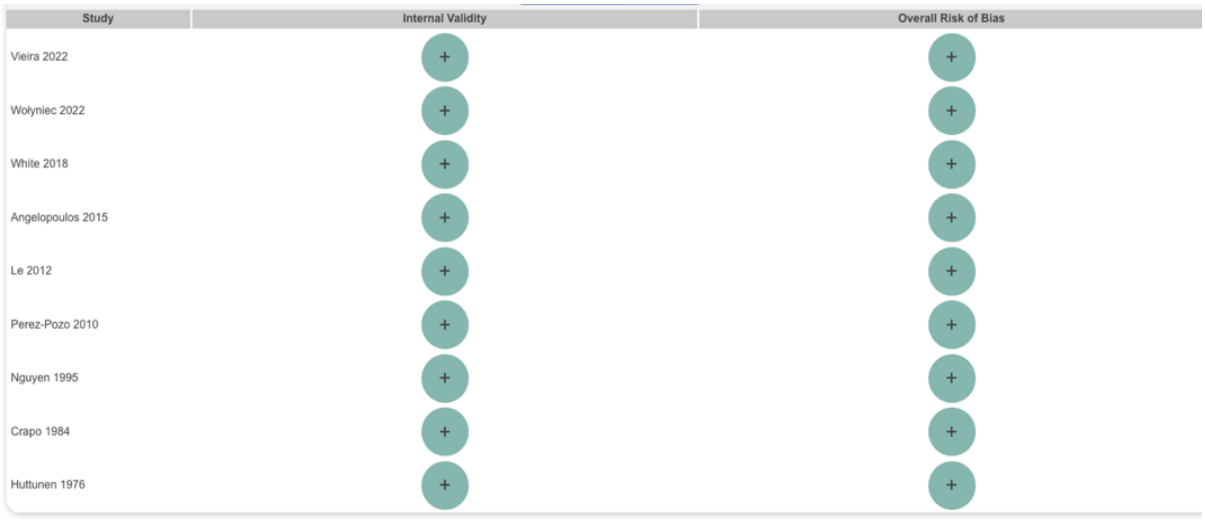

Figure 2. Summary of RoB using the JBI quantitative critical appraisal tool.

From the 9 studies, data extraction was carried out, including baseline and outcome data. This data included information on the intervention or comparator arm, baseline uric acid, outcome uric acid, standard deviation, and the number of participants (N) in each arm of the study. The description table of the eligible documents' baseline characteristics is shown in Table 1.

In the table, it is evident that the fructose and glucose intervention arms have sufficient proportions for comparative analysis between studies (meta-analysis). Similar findings are seen in previous studies by Vieira et al. (7), Angelopoulos et al. (8), and Nguyen et al. (9), which have both fructose and glucose arms. The table also shows variations in mean uric acid levels at both baseline and outcome. Similar observations are seen in the standard deviation (SD) values. The highest mean outcome uric acid values

were observed in the xylitol arm (7.88 mg/dL) and the sucrose arm (6.83 mg/dL). Variations in comparison can be found in studies by Lee and White. The largest sample size (N) was observed in the study by Angelopoulos. The tabulated data also shows various fructose intervention combinations in the studies, such as with fruits, beverages, exercise, and even with medication.

Table 1. Data extraction including baseline and outcome (Mean, SD, N).

Author	Year	Arm	Mean Baseline Uric Acid mg/dl	Baseline SD	N Baseline	Mean Outcome Uric Acid mg/dl	Outcome SD	N Outcome
Vieira	2012	Fructose	4,46	1,11	7	4,74	1,22	7
Vieira	2012	Fructose-Exercise	5,23	0,42	7	5,66	0,66	7
Vieira	2012	Glucose	5,27	1,56	7	5,4	1,32	7
Wolyniec	2022	Fructose-Exercise	5,83	0,99	11	6,51	0,97	11
Wolyniec	2022	Glucose	5,76	1,04	11	6,2	0,98	11
Wolyniec	2022	Xylitol	5,93	1,07	11	7,88	1,34	11
Wolyniec	2022	Sukrose	6,03	0,9	11	6,83	0,95	11
White	2018	Fructose-Fruit	4,69	1,13	23	4,91	0,92	19
White	2018	Fructose-Juice	4,45	0,96	21	4,57	0,79	17
Angelopoulos	2015	Fructose	5,08	1,37	92	5,02	1,33	65
Angelopoulos	2015	Sucrose	5,06	1,48	89	4,94	1,38	64
Angelopoulos	2015	Fructose-HFCS	4,84	1,37	91	4,91	1,39	61
Angelopoulos	2015	Glucose	4,88	1,45	94	4,83	1,25	77
Lee	2012	Fructose-HFCS	4,9	1	22	5	1	22
Lee	2012	Sucrose	4,9	0,9	18	4,8	0,8	18
Perez-Pozo	2010	Fructose	5,2	0,2	36	6,29	0,3	36
Perez-Pozo	2010	Fructose-Allopurinol	6	0,2	38	4,1	0,2	38
Nguyen	1995	Fructose	5,13	0,37	7	6,24	0,44	7
Nguyen	1995	Glucose	5,28	0,39	7	5,06	0,39	7
Crapo	1984	Fructose	5,7	0,3	11	5,7	0,3	11
Huttunen	1976	Fructose	4,71	0,17	35	4,87	0,17	35
Huttunen	1976	Sucrose	4,71	0,34	33	5,21	0,17	33
Huttunen	1976	Xylitol	4,54	0,17	48	4,87	0,17	48

Uric Acid Levels by Fructose Intervention vs. Glucose Intervention

We evaluated the effect of fructose on uric acid levels by analyzing each study based on its weight. The influential factor here is the sample size (N) used for the effect size. Through forest plot visualization, we can observe the cumulative effect mean in Figure 2 (Nested Knowledge) and Figure 3 (R Studio).

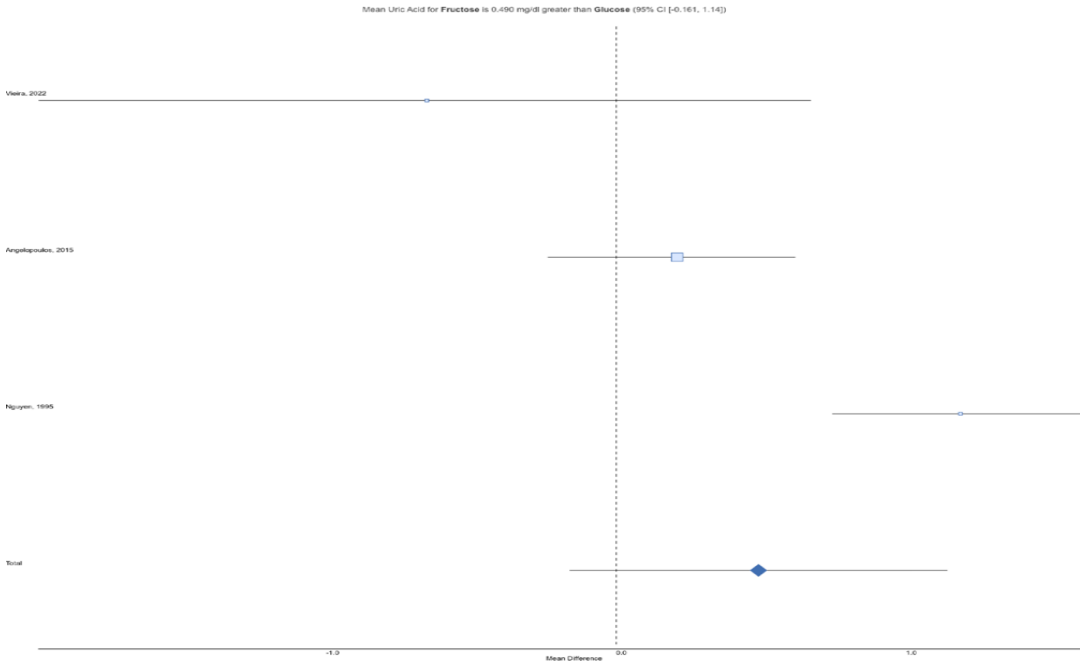

Figure 3. Summary forest plot of the differences in uric acid levels in each study between fructose intervention and glucose intervention using Nested Knowledge software.

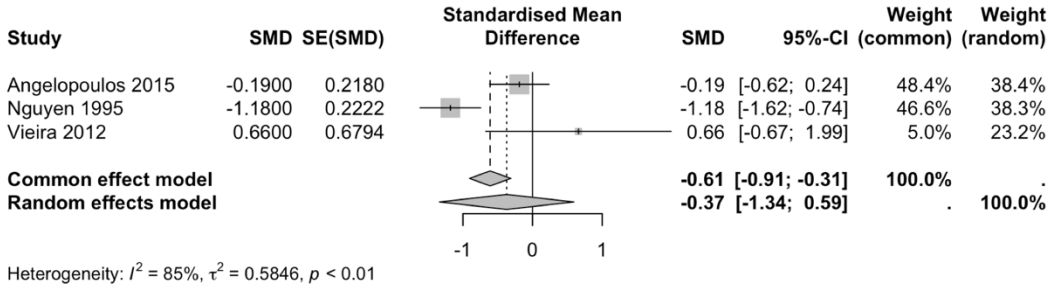

Figure 4. Summary forest plot of the differences in uric acid levels in each study between fructose intervention and glucose intervention using R Studio software.

In the cross-study analysis, it is evident that fructose intervention does not yield significantly different effects compared to glucose intervention based on the uric acid level outcome parameter. Based on the Random Effects model (RE), the SMD value is -0.37 (95% CI; -1.34 to 0.59). The RE value crosses the vertical 0 line. This finding is consistent with the meta-analysis study by Sievenpiper in 2012 (10). The discrepancy in findings between this study and the 2014 study (11) arises from the inclusion of studies involving unhealthy subjects such as those with obesity in the latter. This study also shows considerable variation among studies, as indicated by the large SD values.

Uric Acid Levels by Fructose Intervention vs. Variation in Interventions

In this study, an analysis and evaluation of all intervention variations were also conducted. We compared the variations of fructose intervention with various other interventions in the eligible studies (Figure 5). The fructose intervention ranks 6th out of 9 interventions.

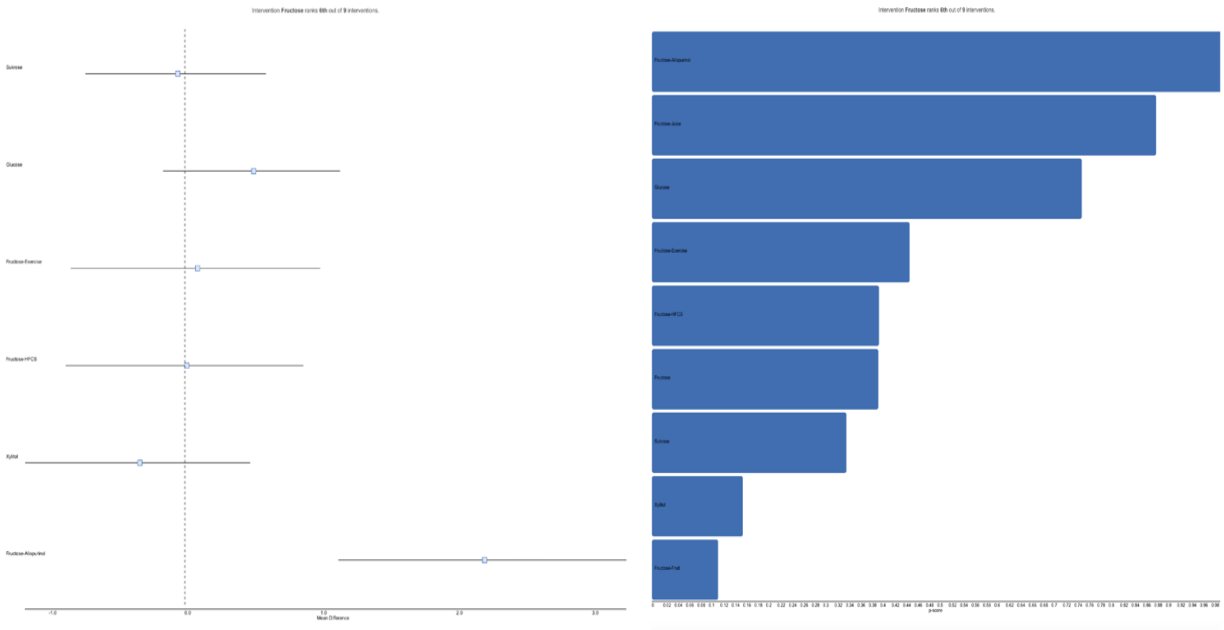

Figure 5. Summary forest plot of the differences in uric acid levels in each study between fructose intervention and other interventions. Analysis of effects using SUCRA.

It can be seen that in the comparative analysis of interventions, significant differences in uric acid levels occur between fructose and allopurinol interventions. Uric acid levels decreased significantly with the fructose-allopurinol intervention. The SUCRA (Surface Under the Cumulative Ranking Curve) analysis shows that the fructose-allopurinol intervention is effective in lowering uric acid levels in humans.

Fructose is a naturally occurring carbohydrate. More precisely, it is a type of monosaccharide (hexose) with the general structure β-D-fructofuranose (12,13). Natural substances high in fructose include honey. The sweetness of honey is due to its fructose content, and although sweet, honey also has numerous benefits such as antioxidant properties. This contrasts with high fructose corn syrup (HFCS), produced industrially, which poses health risks (14). The unique structure of the fructose molecule tends to be irregular, forming a five-atom ring. This molecular structure of fructose differs from the more stable glucose, which forms a six-atom pyranose ring. The hydroxyl group (-OH) in fructose makes it highly hygroscopic, capable of attracting and retaining water from its surroundings. The furanose structure of fructose makes it more flexible and less stable compared to the pyranose form of glucose. The low stability and hygroscopic nature of fructose make the crystallization process difficult. Fructose is highly soluble in water and tends to form hydrogen bonds with water molecules, making it more commonly found in dissolved or liquid form rather than forming solid crystals. Therefore, HFCS is more commonly found in liquid form due to its better stability in this state.

Currently, HFCS is widely used in various food and beverage products. The excessive consumption of this sweetener can have negative health impacts as shown in various studies. One of the main effects is steatosis, which is the formation of fat in the liver (lipogenesis). Excessive consumption of fructose can be converted into fat by the liver, leading to fat accumulation and increasing the risk of non-alcoholic fatty liver disease (NAFLD). Therefore, it is important to control the intake of HFCS and other sweeteners to maintain long-term health.

Studies have indicated that diets high in refined carbohydrates, including fructose from HFCS, are linked to the onset of various metabolic disorders. These disorders include

metabolic syndrome, obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), specific cancers (notably liver, pancreatic, and colon cancers), as well as cardiac and renal diseases, and hyperuricemia (15,16).

Variations in baseline subject values can occur due to factors such as gender, age, and metabolic rate. However, these determinants are not clearly observed in this study due to insufficient data. Variations in outcomes can occur due to factors such as dose, duration of intervention, activity, and intervention combinations. The combination with exercise is interesting because fructose-exercise ranges from 5.66-6.51 mg/dL. As we know, increased exercise increases metabolic rates, including catalytic substrate and end product production. High fructose consumption can lead to an increase in serum uric acid levels. Hyperuricemia negatively affects atherosclerosis and inflammation and is commonly seen in patients with arterial hypertension. Some antihypertensive medications, like diuretics, can elevate serum uric acid. Conversely, the angiotensin II receptor blocker (ARB) losartan has been shown to decrease serum uric acid levels, likely by promoting renal excretion, whereas other ARBs generally do not affect uric acid levels (17).

Consumption of fructose elevates plasma uric acid (UA) levels by enhancing purine biosynthesis and reduces renal clearance of UA by raising plasma lactate concentrations (18). Akhavan T, Anderson GH demonstrated a clear difference in the body's response to the presence of fructose and glucose. The administration of glucose triggers insulin secretion, as seen from differences in the insulin graph. In contrast, when fructose is given, insulin secretion is much lower. The initial insulin increase (at 30 minutes) in the fructose graph is a response to the sweet taste on the tongue, which activates the brain's response to insulin production. However, after this initial response, the body adjusts as it processes the large amount of fructose ingested. Additionally, the presence of glucose in the experiment also plays a role.

The reason for using the specific “PubMed” database in this study is to evaluate the quality of PubMed's metadata. This study shows that PubMed still has shortcomings in language filtering, as non-English languages still appear within English language groups.

We also observe that the PubMed database does not cover all important references in RCT research, which can lead to a lack of representative data.

CONCLUSION

In various clinical studies, fructose does not show a significantly negative effect. Although some studies show dynamic changes, they remain within the normal range. However, this conclusion cannot be generalized directly as the long-term effects of fructose are still very limited. Additionally, aspects such as dose, duration, type of fructose, anthropometry, and subject characteristics need to be further analyzed in each study related to fructose as they can be major factors contributing to differences in study results.

Limitations

This study has limitations as it focuses on data exploration from PubMed. Therefore, future studies are expected to incorporate references from other databases.

Ethics Approval

Not required.

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Conflict of Interests

The authors have no relevant financial or non-financial interests to disclose.

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Underlying Data

Derived data supporting the findings of this study are available as part of the study.

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