Fructose Feeding and Hyperuricemia: a Systematic Review and Meta-Analysis

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ABSTRACT

High fructose feeding has been suggested to involve in several features of metabolic syndrome including hyperuricemia (HP). We designed and implemented a study to determine the effect size of fructose intake and the relative risk of HP based on the type of fructose feeding (diet or solution), duration of treatment (2–6, 7–10, and > 10 weeks), and animal race. The required information was accepted from international databases, including PubMed/MEDLINE, Science Direct, Scopus, and etc., from 2009 until 2019 on the basis of predetermined eligibility criteria. The data selection and extraction and quality assessment were performed independently by two researchers. Results were pooled as random effects weighting and reported as standardized mean differences with 95% confidence intervals. Thirty-five studies including 244 rats with fructose consumption were included in the final analysis. The heterogeneity rate of parameters was high (I² = 81.3%, p < 0.001) and estimated based on: 1) type of fructose feeding (diet: I² = 79.3%, solution 10%; I² = 83.4%, solution 20%; I² = 81.3%), 2) duration of treatment (2–6 weeks: I² = 86.8%, 7–10 weeks: I² = 76.3%, and > 10 weeks: I² = 82.8%), 3) the animal race (Wistar: I² = 78.6%, Sprague-Dawley: I² = 83.9%). Overall, the pooled estimate for the all parameters was significant (p < 0.001). The results of this study indicated that a significant relationship between HP and fructose intake regardless of the treatment duration, animal race, fructose concentration and route of consumption.

Keywords: Fructose; Rats; Uric acid; Hyperuricemia; Meta-analysis; Systematic review

INTRODUCTION

Over the past few decades, the mean serum uric acid (UA) level and prevalence of hyperuricemia (HP) appear to have increased in all individuals. The significant increase in sweetened sugary beverages and fructose intake coincides with the secular trend of HP [1]. HP has known as a serious risk factor for metabolic, cardiovascular and renal diseases. It also plays a role in the development of associated disorders with metabolic syndrome including diabetes, coronary artery disease and gout. Furthermore, in some studies it has been linked with premature mortality and its incidence has been rising during the last decades [1,2]. HP or excessive circulating urate concentration (higher or equal to 6.8 mg/dL), the end product
of purine metabolism, is an important risk factor for gout and plays a role in its pathogenesis [3,4]. This abnormality arises by high level formation of UA or reduced its excretion [2].

UA is synthesized in the liver, adipose and muscle tissue and is mostly excreted through the kidney. Several factors, such as high-fructose feeding and the using of xenobiotic and alcohol can be contributed to induction of HP [5].

Fructose is a simple sugar with 6 carbons similar to glucose, which differs in spatial pattern with glucose and is found in many fruits and vegetables [6]. It can cause several adverse effects including insulin resistance, dyslipidemia, oxidative stress, neuronal loss, and HP when used in high concentrations [7,8].

However, a meta-analysis of isocaloric replacement tests does not support the relationship between fructose and serum UA [9]. The role of fructose in all food sources as a risk factor for incidental HP remains unclear. In addition, there is a significant lack of meta-analysis studies evaluating the role of dietary fructose in the occurrence of metabolism disorders. The purpose of this study was to evaluate the systematic review and meta-analysis of the effect size of fructose intake and the relative risk (RR) of HP based on the route of fructose feeding (diet or solution 10% and 20%), duration of fructose consumption (2–6, 7–10, and > 10 weeks), and race of animal (Sprague-Dawley or Wistar rats).

**MATERIALS AND METHODS**

**Study protocol**

Current research is a systematic review and meta-analysis on the relationship between fructose intake and acid uric level by reviewing available studies. This study was conducted according to design of Meta-analysis in Observational Studies in Epidemiology protocol and their results reported according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [10]. To avoid possible bias, search strategy, article selection, quality assessment and data extraction have been independently done by 2 researchers and agreement was reached on the obtained results with the help of a third researcher.

**Search tactic**

The required information was accepted from national databases, including Iranian Journal Database or Magiran (http://www.magiran.com/), Barakat Knowledge Network System (http://health.barakatkn.com), Scientific Information Database (http://www.sid.ir), Iranian National Library (http://www.nlai.ir/), Regional Information Center for Science and Technology (http://en.ricest.ac.ir/), Iranian Research Institute for Information Science and Technology (https://irandoc.ac.ir), and also international databases, including PubMed/ MEDLINE, Science Direct, Embase, Scopus, Cochrane Library, Web of Science as well as the Google Scholar search engine from 2009 until 2019. To maximize the comprehensiveness of the search, Medical Subject Headings keywords such as “fructose feeding”, “fructose consumption”, “fructose intake”, “fructose”, “high fructose corn syrup” “uric acid”, “hyperuricemia”, “rats”, “humans” “mice” and “uricemia” were used. Previous review researches were also studied to identify other relevant articles. Combined search was performed with “and” and “or”.

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Inclusion and exclusion criteria
Inclusion criteria was done according to Population, Intervention, Comparison, and Outcome [11]: 1) Population: rat, mice and human with or without HP; 2) Intervention: consumption of fructose; 3) Comparison: variable aimed for serum UA level, gender, concentration of fructose intake, methods of consumption (solution or diet), duration of fructose intake and etc.; 4) Outcome: estimating the relationship of HP with fructose consumption.

The exclusion criteria were: 1) Fructose feeding with other sweeteners such as sucrose or glucose and in combination with fat; 2) Irrelevance; 3) Fructose feeding with injecting a drug such as alloxan, streptozotocin and etc. and 4) Review articles, case reports, letter to the editor and comments. For articles that the full text was not available, we requested the author for the full text of it.

Selection of articles
All studies that have been assessed the serum uric acid levels following fructose consumption were screened independently by 2 researchers; a list of titles and abstracts was first developed. Full text of articles submitted to researchers after concealing the characteristics of articles, including author(s) and journal name. Multiple publications from a similar research were considered as a one study. If a study was rejected, the reason was stated. A third researcher judged the article if they disagreed. For articles with incomplete information, we contacted the relevant author to provide information by email.

Quality assessment
Next, the selected research was evaluated using the modified Newcastle Ottawa Scale for non-randomized studies [12]. In the checklist, the lowest acceptable score was considered 4 and the studies that reached this score were included in the study.

Data extraction
All final papers in the study process were ready for extraction through a pre-prepared checklist. The checklist for the selected articles included the author’s name, year of publication, location and duration of the study, sample size, concentration of fructose intake, and method of fructose consuming (as solution or diet forms).

Data analysis
The variance of the HP was estimated using binomial distribution. The odds ratio (OR) was used to assess the impact of gender (male to female ratio) on HP. According to Cochran’s Handbook, heterogeneity between studies was assessed using Cochran Q test and I^2 index. However, for I^2 there are 3 categories: (0%-24% may not matter, 25%-75% shows moderate heterogeneity, and more than 75% indicates high heterogeneity) [13]. For combining data in low and high heterogeneity, were used fixed and random effect models, respectively [14]. Sensitivity analysis was performed with the exception of one study at a time to evaluate the combined strength of OR and 95% confidence interval (CI). To find out the reason for the heterogeneity between studies, subgroup analysis was performed based on duration and concentration of fructose intake, and meta-regression was used between concentration and duration of fructose intake with HP. Egger and Begg’s test were used to evaluate the publication bias and was presented in the funnel plot design. Data analysis was done in STATA software version 11.1 and was shown through flowcharts, tables, OR, and funnel plots. A p < 0.05 were considered as the significance level.
RESULTS

Search results
Totally, 1,034 articles were found in the systematic literature assessment. We dismissed 870 articles basis of title and abstract and the rest of studies (n = 164; 153 + 11) due to the following reasons; duplicate papers (n = 7; 164 − 7 = 157 remained), irrelevant records include the review articles, letter to the editor, low quality (n = 103; 157 − 103 = 54 remained), not related to UA measurement (n = 19; 54 − 19 = 35 remained). Figure 1 shows the PRISMA diagram of our study. Finally, 35 studies entered the final review (Figure 1).

The association between the form of fructose intake and HP
The heterogeneity rate was high based on the method of consumed fructose (diet, solution 10% and 20%) (Diet: $I^2 = 79.3\%$, $p < 0.001$; solution 10%: $I^2 = 83.4\%$, $p < 0.001$; solution 20%: $I^2 = 81.3\%$, $p < 0.001$). The overall pooled estimate of the association between fructose feeding and HP was significant (OR, 1.86; 95% CI, 2.38–1.33; $p < 0.001$) (Figure 2).

Sub-category analysis
Also, the heterogeneity rate was estimated based on the duration of fructose intake (2–6, 7–10, and > 10 weeks) (first: $I^2 = 86.8\%$, $p < 0.001$; second: $I^2 = 76.3\%$, $p < 0.001$; last: $I^2 = 82.8\%$, $p < 0.001$). The overall pooled estimate of the association between duration of fructose consumption and HP was significant (OR, 1.86; 95% CI, 2.38–1.33; $p < 0.001$) (Figure 2B).

Finally, the heterogeneity rate was estimated based on the race of animal (Sprague-Dawley or Wistar rats) (Wistar: $I^2 = 78.6\%$, $p < 0.001$; Sprague-Dawley: $I^2 = 83.9\%$, $p < 0.001$).
### A

| Study ID       | SMD (95% CI)               | Weight (%) |
|---------------|---------------------------|------------|
| **Diet**       |                           |            |
| Vasanthi J (2016) | −2.15 (−3.62, −0.68)       | 2.97       |
| Mohamed K (2017)  | −0.95 (−1.93, 0.06)        | 3.45       |
| Parkaj B (2012)   | −0.34 (−1.40, 0.71)        | 3.35       |
| Hee-y (2014)      | −0.61 (−1.62, 0.39)        | 3.39       |
| Raji Padiya (2011) | −1.93 (−2.34, 0.04)       | 0.39       |
| Kanglin Z (2012)  | −0.58 (−1.74, 0.58)        | 3.26       |
| Shafatula M (2016) | −3.30 (−4.96, −1.55)      | 1.91       |
| *Linda T* (2014)  | −7.48 (−10.41, −4.54)      | 1.76       |
| *Sona E* (2012)   | −11.12 (−15.38, −6.90)     | 1.11       |
| *Hee-y* (2018)    | −0.09 (−1.07, 0.89)        | 3.41       |
| *Derek E* (2013)  | 1.59 (−0.73, 4.27)         | 2.91       |
| *Zhang J* (2019)  | −11.55 (−18.23, −4.87)     | 0.54       |
| *Moont J* (2013)  | −1.27 (−2.24, −0.30)       | 3.42       |
| *Arika K* (2012)  | −0.47 (−1.73, 0.79)        | 3.17       |
| *Arika K* (2012)  | −0.45 (−1.81, 0.87)        | 3.12       |
| *Subtotal* (I-squared = 79.3%, p = 0.000) | 1.65 (−2.41, 0.89) | 42.30 |

### B

| Study ID       | SMD (95% CI)               | Weight (%) |
|---------------|---------------------------|------------|
| **7–10 weeks** |                           |            |
| Vasanthi J (2016) | −2.15 (−3.62, −0.68)       | 2.97       |
| Mohamed K (2017)  | −0.95 (−1.93, 0.06)        | 3.45       |
| Parkaj B (2012)   | −0.34 (−1.40, 0.71)        | 3.35       |
| Hee-y (2014)      | −0.61 (−1.62, 0.39)        | 3.39       |
| Raji Padiya (2011) | −1.93 (−2.34, 0.04)       | 0.39       |
| Kanglin Z (2012)  | −0.58 (−1.74, 0.58)        | 3.26       |
| Shafatula M (2016) | −3.30 (−4.96, −1.55)      | 1.91       |
| *Linda T* (2014)  | −7.48 (−10.41, −4.54)      | 1.76       |
| *Sona E* (2012)   | −11.12 (−15.38, −6.90)     | 1.11       |
| *Hee-y* (2018)    | −0.09 (−1.07, 0.89)        | 3.41       |
| *Derek E* (2013)  | 1.59 (−0.73, 4.27)         | 2.91       |
| *Zhang J* (2019)  | −11.55 (−18.23, −4.87)     | 0.54       |
| *Moont J* (2013)  | −1.27 (−2.24, −0.30)       | 3.42       |
| *Arika K* (2012)  | −0.47 (−1.73, 0.79)        | 3.17       |
| *Arika K* (2012)  | −0.45 (−1.81, 0.87)        | 3.12       |
| *Subtotal* (I-squared = 79.3%, p = 0.000) | 1.65 (−2.41, 0.89) | 42.30 |

### C

| Study ID       | SMD (95% CI)               | Weight (%) |
|---------------|---------------------------|------------|
| **Wistar**     |                           |            |
| Vasanthi J (2016) | −2.15 (−3.62, −0.68)       | 2.97       |
| Mohamed K (2017)  | −0.95 (−1.93, 0.06)        | 3.45       |
| Kanglin Z (2012)  | −0.58 (−1.74, 0.58)        | 3.26       |
| Parkaj B (2012)   | −0.34 (−1.40, 0.71)        | 3.35       |
| Hee-y (2014)      | −0.61 (−1.62, 0.39)        | 3.39       |
| Raji Padiya (2011) | −1.93 (−2.34, 0.04)       | 0.39       |
| Kanglin Z (2012)  | −0.58 (−1.74, 0.58)        | 3.26       |
| Parkaj B (2012)   | −0.34 (−1.40, 0.71)        | 3.35       |
| Hee-y (2014)      | −0.61 (−1.62, 0.39)        | 3.39       |
| Raji Padiya (2011) | −1.93 (−2.34, 0.04)       | 0.39       |
| Shafatula M (2016) | −3.30 (−4.96, −1.55)      | 1.91       |
| *Pereina CD* (2014) | 1.00 (−14.23)           | 3.20       |
| *Linda T* (2014)  | −7.48 (−10.41, −4.54)      | 1.76       |
| *Kehinde S* (2018) | −11.13 (−15.38, −6.90)    | 1.11       |
| *Daniel C* (2013) | −0.09 (−1.07, 0.89)        | 3.41       |
| *Blige A* (2015)  | 1.59 (−0.73, 4.27)         | 2.91       |
| *Gang C* (2016)   | −1.71 (−2.75, −0.67)       | 3.36       |
| *Zhang DM* (2012) | −2.79 (−4.31, −1.26)       | 2.92       |
| *Chun-H* (2015)   | −2.62 (−4.74, −1.57)       | 2.00       |
| *Mohamed K* (2009) | −7.01 (−10.66, −3.36)      | 1.36       |
| *Ochuko L* (2019) | −3.38 (−7.59, −2.79)       | 2.92       |
| *Daniel C* (2013) | −1.66 (−4.16, −5.14)       | 1.56       |
| *Mahamed A* (2014) | −0.09 (−1.14, 0.86)        | 3.35       |
| *J. Soutelo* (2018) | 1.89 (−2.67, 1.12)       | 52.25      |
| *Subtotal* (I-squared = 83.9%, p = 0.013) | −3.00 (−6.00, −0.00) | 5.45 |

### Figure 2

Fructose intake and the relative risk of HP base on the form of fructose feeding (diet, solution 10% and 20%) (A), duration of fructose consumption (2–6, 7–10, and > 10 weeks) (B), race of animals (Sprague-Dawley or Wistar rats) (C). Mean point of each part indicates the estimated OR, and the length of each part displays 95% CI in each study; the rhombic sign shows the OR in each study.

HP, hyperuricemia; OR, odds ratio; CI, confidence interval; SMD, standardized mean difference.

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overall pooled estimate of the association between race of animals and HP was significant (OR, 1.86; 95% CI, 2.38–4.33; p < 0.001) (Figure 2C). The cumulative analysis based on the author’s name and year of publication also is shown (Figure 3).

**Relationship between the duration and concentration of fructose treatment with HP using meta-regression**

Between duration (p = 0.495) of fructose consumption with HP was not a significant association, while a significant association was observed between fructose concentration (p = 0.029) with HP (Figure 4).

**Publication bias**

Based on Egger’s assay test, publication bias of the relationship between fructose consumption and HP was estimated. Visual inspection of the produced funnel design was used to interpret any publication bias between studies to evaluate symmetry. The funnel plot shows that an asymmetry under random-effects model representing the tendency to lower the standardized mean differences (Figure 5).

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**Table 1:**

| Study ID       | SMD (95% CI) |
|----------------|--------------|
| Mahalaxmi M (2009) | -1.75 (-2.32, -1.18) |
| Raju Padya (2011)  | -1.01 (-1.43, -0.59) |
| Lyvi C (2011)      | -1.88 (-2.46, -1.30) |
| Panisk B (2012)    | -1.00 (-1.63, -0.37) |
| Kangbin Z (2012)   | -0.96 (-1.35, -0.57) |
| Qing-H (2012)      | -1.03 (-1.40, -0.65) |
| Soha E (2012)      | -1.59 (-2.30, -0.88) |
| Zhang DM (2012)    | -1.51 (-2.06, -0.95) |
| Akira K (2012)     | -1.93 (-2.49, -1.37) |
| Akira K (2012)     | -1.86 (-2.38, -1.33) |
| Pablo A. Scacchi (2013) | -1.15 (-1.55, -0.75) |
| Daniel C (2013)    | -1.48 (-2.11, -0.86) |
| Derek E (2013)     | -1.50 (-2.03, -0.97) |
| Moon J (2013)      | -1.99 (-2.57, -1.42) |
| Cihan Cet (2014)   | -1.22 (-1.86, -0.57) |
| QY Zhang (2014)    | -0.99 (-1.44, -0.53) |
| Pereira CD (2014)  | -1.02 (-1.52, -0.51) |
| Mohamed A (2014)   | -1.21 (-1.80, -0.62) |
| Linda T (2014)     | -1.33 (-2.03, -0.63) |
| AA Mahmoud (2014)  | -2.04 (-2.65, -1.43) |
| Zaid O. Ibrahim (2014) | -1.91 (-2.45, -1.37) |
| RACHEL W (2015)    | -1.07 (-1.68, -0.46) |
| Wang W (2015)      | -1.56 (-2.22, -0.90) |
| Bilge A (2015)     | -1.45 (-2.04, -0.86) |
| Chun-H (2015)      | -1.65 (-2.20, -1.08) |
| Vasanthi J (2016)  | -2.15 (-3.62, -0.68) |
| Shahataa M (2016)  | -1.18 (-1.63, -0.73) |
| Gang C (2016)      | -1.45 (-2.02, -0.88) |
| Mohamed K (2017)   | -1.43 (-2.52, -0.33) |
| Hwee-Y (2018)      | -0.90 (-1.40, -0.40) |
| Kehinde S (2018)   | -1.35 (-1.98, -0.71) |
| Hwee-Y (2018)      | -1.49 (-2.16, -0.81) |
| J. Soutelo (2018)  | -2.04 (-2.64, -1.44) |
| Ochuko L. (2019)   | -1.36 (-2.03, -0.69) |
| Zhang J (2019)     | -2.13 (-2.75, -1.51) |

Figure 3. The cumulative analysis with a 95% CI based on the author’s name and year of research according to the random effects model. The midpoint of each section shows the hyperuricemia incidence following fructose feeding in rats.

CI, confidence interval; SMD, standardized mean difference.
Fructose Intake and Hyperuricemia

Meta-regression
REML estimate of between-study variance
% residual variance due to heterogeneity
Proportion of between-study variance explained
With Knapp-Hartung modification

| ES          | Coef.   | SE     | t      | p > | (95% CI) |
|-------------|---------|--------|--------|------|----------|
| Duration    | 0.4620148 | 0.6697704 | 0.6900 | 0.495 | (−0.9006433, 1.824673) |
| Concentration | −2.954535 | 1.294889 | 0.0290 | 0.029 | (−5.589007, −0.3200632) |

Number of objects = 35
τ = 4.53
I²-res = 81.67%
Adj R-squared = −3.28%

Figure 4. Relationship between the duration and concentration of fructose treatment with HP using meta-regression. It shows that there is no relationship between the duration of fructose feeding and its concentration (A) with HP (p = 0.495, p = 0.029 respectively). The size of the bubbles shows the precision of the studies. CI, confidence interval; SE, standard error; HP, hyperuricemia; SMD, standardized mean difference; Coef, coefficient.

Figure 5. Publication bias in meta-analysis of studies regarding the relationship between hyperuricemia and fructose feeding. Visual inspection of the produced funnel design was used to interpret any publication bias between studies to evaluate symmetry. The funnel plot shows asymmetrical under random-effects model representing the tendency to lower the SMD. SMD, standardized mean difference; SE, standard error.
DISCUSSION

The aim of the present study was to assess the relationship between the effect size of fructose intake and the RR of HP based on several parameters including; the method of fructose feeding, duration of fructose treatment, and animal race (Table 1). After searching the related databases, 35 articles were entered in the final analysis with the overall OR of the relationship between fructose feeding and HP which was estimated 1.86 (95% CI, 1.33–2.38; p < 0.001), representing the higher risk of HP following fructose intake (Figure 2). Rate of heterogeneity in our research was high (I² = 81.3%; p < 0.001), which it may be related to the different duration of treatment and concentration of fructose intake; therefore, subgroup analysis was performed based on duration and concentration of fructose intake. In meta-regression analysis, was estimated the relationship between duration and concentration of fructose treatment with HP. Between duration (p = 0.495) of fructose consumption with HP was not a significant association, while a significant association was observed between fructose concentration (p = 0.029) with HP (Figure 4). It seems that an unknown defect may be the cause of this event.

Table 1. Detailed characteristics of 35 studies included in the systematic review on the fructose feeding and UA level measurement

| Study           | Year | Place      | Concentration of fructose | Method of use | Duration in week | UA₀ | UA₁ | Sample size | Race | Sex |
|-----------------|------|------------|----------------------------|---------------|------------------|-----|-----|-------------|------|-----|
| Zhang et al. [15] | 2019 | China      | 60 Diet                    | 8             | 1.41 ± 0.07      | 2.97 ± 0.06 | 4    | SD          | M    |
| Erukainure et al. [16] | 2019 | South Africa | 10 Solution               | 2             | 2.46 ± 0.1       | 3.48 ± 0.31 | 5    | SD          | M    |
| Ng et al. [17]    | 2018 | Taiwan     | 60 Diet                    | 13            | 0.72 ± 0.43      | 0.81 ± 0.24 | 8    | SD          | M    |
| Ng et al. [17]    | 2018 | Taiwan     | 60 Diet                    | 21            | 0.72 ± 0.43      | 1.72 ± 0.69 | 8    | SD          | M    |
| Olaniyi and Olatunji [18] | 2018 | Nigeria     | 10 Solution               | 8             | 3 ± 0.25         | 3.9 ± 0.3   | 6    | Wis         | F    |
| Soutelo et al. [19] | 2018 | Argentina  | 10 Solution               | 5             | 1.02 ± 0.03      | 1.03 ± 0.05 | 7    | Wis         | F    |
| Jayakumar et al. [20] | 2016 | India      | 60 Diet                    | 8             | 12.05 ± 1.5      | 22.9 ± 2.48 | 6    | Wis         | M    |
| Chen et al. [21]  | 2016 | China      | 10 Solution               | 8             | 2.4 ± 0.16       | 3.35 ± 0.19 | 10   | Wis         | M    |
| Shahata et al. [22] | 2016 | Egypt      | 60 Diet                    | 8             | 1.41 ± 0.12      | 4.2 ± 0.45  | 7    | SD          | M    |
| Ma et al. [23]    | 2015 | China      | 10 Solution               | 4             | 2.98 ± 0.08      | 4.82 ± 0.12 | 8    | SD          | M    |
| Wilson and Islam [24] | 2015 | South Africa | 10 Solution              | 2             | 2.71 ± 0.41      | 1.9 ± 0.34  | 7    | SD          | M    |
| Aygen et al. [25] | 2015 | Turkey     | 10 Solution               | 9             | 1.06 ± 0.1       | 1.64 ± 0.2  | 9    | Wis         | M    |
| Bernasconi et al. [26] | 2015 | Argentina  | 10 Solution               | 5             | 1.2 ± 0.3        | 2.2 ± 0.4   | 8    | Wis         | M    |
| Essawy et al. [27] | 2014 | Egypt      | 60 Diet                    | 4             | 2 ± 0.3          | 8 ± 0.25    | 8    | SD          | M    |
| Citil et al. [28] | 2014 | Turkey     | 10 Solution               | 13            | 6.8 ± 1.25       | 9.9 ± 1.07  | 7    | SD          | M    |
| Ibraheem et al. [29] | 2014 | Malaysia   | 20 Solution               | 8             | 0.19 ± 0.02      | 0.28 ± 0.02 | 7    |SD          | M    |
| Tran et al. [30]  | 2014 | Canada     | 60 Diet                    | 9             | 3.86 ± 0.17      | 9.41 ± 0.33 | 8    | Wis         | M    |
| Jung et al. [31]  | 2013 | Korea      | 65 Diet                    | 8             | 0.55 ± 0.018     | 0.64 ± 0.026 | 10   | Wis         | M    |
| Cardinali et al. [32] | 2013 | Argentina  | 10 Solution               | 8             | 1.7 ± 0.1        | 1.9 ± 0.2   | 8    | Wis         | M    |
| Erion et al. [33] | 2013 | USA        | 67 Diet                    | 4             | 2.18 ± 0.21      | 3.02 ± 0.16 | 8    | SD          | M    |
| Kitagawa et al. [34] | 2012 | Japan      | 60 Diet                    | 4             | 0.19 ± 0.01      | 0.21 ± 0.025 | 5   | Wis         | M    |
| Kitagawa et al. [34] | 2012 | Japan      | 60 Diet                    | 6             | 0.19 ± 0.01      | 0.2 ± 0.01  | 5    | Wis         | M    |
| Padiya et al. [35] | 2011 | India      | 65 Diet                    | 8             | 1.9 ± 0.2        | 3.1 ± 0.5   | 7    | SD          | M    |
| Chen et al. [36]  | 2011 | China      | 10 Solution               | 8             | 2.21 ± 0.07      | 3.63 ± 0.11 | 8    | SD          | M    |
| Hu et al. [37]    | 2012 | China      | 10 Solution               | 8             | 2.33 ± 0.19      | 3.9 ± 0.46  | 7    | SD          | M    |
| Mohan et al. [38] | 2009 | India      | 10 Solution               | 6             | 2.42 ± 0.07      | 3.96 ± 0.12 | 5    | Wis         | M    |
| Bagul et al. [39] | 2012 | India      | 65 Diet                    | 8             | 1.9 ± 0.25       | 2.5 ± 0.9   | 7    | SD          | M    |
| Kelany et al. [40] | 2017 | Egypt      | 65 Diet                    | 8             | 1.81 ± 0.28      | 5.28 ± 1.54 | 10   | Wis         | M    |
| Zhou et al. [41]  | 2012 | Canada     | 60 Diet                    | 13            | 0.2 ± 0.03       | 0.7 ± 0.5   | 6    | Wis         | M    |
| Pereira et al. [42] | 2014 | Portugal   | 10 Solution               | 8             | 6.14 ± 0.66      | 4.72 ± 0.37 | 6    | SD          | M    |
| Ibrahim et al. [43] | 2014 | Egypt      | 20 Solution               | 6             | 3.39 ± 0.27      | 7.43 ± 0.34 | 7    | Wis         | M    |
| Wang et al. [44]  | 2015 | China      | 10 Solution               | 6             | 2.44 ± 0.19      | 4.11 ± 0.23 | 8    | SD          | M    |
| Zhang et al. [45] | 2012 | China      | 10 Solution               | 8             | 1.94 ± 0.04      | 2.85 ± 0.17 | 7    | SD          | M    |
| Zhang et al. [46] | 2014 | China      | 10 Solution               | 6             | 1.85 ± 0.24      | 3.7 ± 0.6   | 7    | SD          | M    |
| Mahmoud and Eshazly [47] | 2014 | Egypt      | 10 Solution               | 12            | 0.37 ± 0.07      | 2.42 ± 0.1  | 8    | Wis         | M    |

Data are shown as mean ± standard error or number (%).

SD, Sprague-Dawley; M, male; F, female; Wis., Wistar; UA₀, uric acid in control group; UA₁, uric acid in fructose treated group.
Based on the egger’s test and funnel plot in our study, was found an asymmetry under random-effects model and a considerable effect for publication bias, suggesting that several studies may not have been published with significant effect yet (Figure 5).

The present data was in consistent with the results of a meta-analysis by Jamnik et al. [3] that had shown the effect of fructose consumption on HP in human. Their report were includes two studies with 125299 participants and 1533 incident gout cases. In that study, the correlation between fructose feeding with gout was evaluated in a 17-year follow-up, showed that an enhancement in the risk of gout (RR, 1.62; 95% CI, 1.28–2.03; p <0.001).

In line with the present study, Ebrahimpour-Koujan et al. [48] also showed the effect of sugar sweetened beverages (SSB) and fructose feeding with the risk of HP in adult humans. It showed that the SSB intake was associated with 35% greater odds of HP (summary effect size, 1.35; 95% CI, 1.19–1.52).

Also, Bomback et al. [49] reported a relationship between sugar-sweetened soda intake and prevalence of HP, but not significant. This inconsistency might be due to the difference in research population, study design and gender of subjects [49].

It is known that fructose feeding could induce UA synthesis through increasing of ATP decomposition as a precursor of UA. ATP depletion can also occur due to the conversion of fructose into fructose mono phosphate and subsequent activation of AMP deaminase, nucleotide turnover and subsequent UA generation. Increased insulin level following fructose intake has also been shown to raise of urate reuptake and reduce the excretion of UA in kidney [1].

Due to hepatic metabolism of fructose, fat accumulation occurs in the liver. Perhaps, this disrupts the beta oxidation of hepatic fatty acids and rises of de novo lipogenesis. Some studies have shown that an increased expression of keto-hexokinase (fructo-kinase C) plays a major role in hepatic fat accumulation through a reduction of ATP, UA generation and nucleotide modification [7,50,51].

We restricted our analysis to reports of animal. As a result, because of the incompatibility between human’s parameters with animal, it may have led to decrease the number of studies that were available for inclusion.

In the present study, the amount of fructose consumption by animals has been neglected. Therefore, the increase of uric acid level may be related to the amount of consumed fructose (fructose entering the body/day), not the concentration and duration of consumption.

CONCLUSION

Results of the current meta-analysis study showed that there is a significant relationship between fructose feeding and HP regardless of the time duration of treatment, animal race, concentration and method of fructose consumption. Further researches are needed to assess the relationship between dietary fructose intake and risk of HP according to the amount of fructose consumption.
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