Foods Glycemic Index (GI) Affects the Important Inflammatory Biomarkers with Considerations: A Systematic Review

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Abstract

Introduction: The glycemic index (GI) and inflammations both were introduced as essential factors affecting the diseases, but the relation between GI and inflammation is still unclear. In this systematic review, the authors hypothesized GI has effects on inflammatory biomarkers but can be highly disturbed by statical unrecognized confounders.

Method: A comprehensive search was made in Science Direct, PubMed, Cochrane, UpToDate, and Google Scholar from 2010 to March 2021 using MESH and un-MESH keywords. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) was used for the review of articles.

Result: From seven hundred and ninety-one articles, a total of 13 studies including one master thesis enrolled in this review, six studies were conducted on people with diabetes, cardiovascular diseases (CVD), and polycystic ovary syndrome (PCOS). Six studies were on healthy or obese people without any illnesses and one study was on pregnant women. IL-6 was in 8 studies, TNF-a was in 5 studies, TNF was in 2 studies, CRP was in 6 studies, and hs-CRP was in 2 studies. Seven studies including all well-designed studies confirmed GI can affect inflammation while 5 rejected the association. Several unconsidered confounders and limitations had been found in previous studies.

Conclusion: There is some strong evidence that supports a slight effect of GI on inflammatory biomarkers. However, bias risk in different studies according to diet patterns and the impact of various food components on GI remains. In this review, the authors provide some essential considerations for further studies.

Introduction:

Inflammation is a protective biological response through the immunological system, tissues, and organs to different damaging situations, including pathogens, cell damage, and surgery [1-3]. As a whole, inflammation is a driving factor of many diseases [1, 2]. There are many different tools to assess the severity of inflammation. However, the essential factors are inflammatory blood biomarkers [1, 2, 4].

During recent studies, it is well established that nutritional intake and diet can significantly impact the pro-inflammatory and severity of chronic diseases [3, 5-8]. In the previous studies, a significant relationship between carbohydrate and sugar consumption, the insulin level, and the risk of inflammation and chronic diseases founded [9-11].

Glycemic index (GI), one of the most important factors to detect the quality of carbohydrates during the last four decades, was introduced as an efficient factor by Jenkins et al. [12] in the 1980s for the first time. In general, it is known as the degree and duration to which blood glucose is elevated following 12-hours of fasting in response to a specific carbohydrate consumption ratio to standard carbohydrate, which generally is glucose or white bread [12, 13]. It is scaled between 0 to 100 and separated into three categories: Low GI (<56), Medium GI 56-69, and High GI (<69) [12-14].

During the last years, many studies have shown the impact of GI on some chronic diseases, especially diabetes, cardiovascular diseases, and breast cancer [9, 10, 15-21]. Obesity is one of the other factors that elevate the risk of inflammation in individuals, and some studies also showed a significant effect of GI on weight management [22-25]. Also, a weak inflammatory effect of GI in a systematic and meta-analyses was reported [10]. Nevertheless, a meta-analysis in 2018, showed no significant relation between GI and inflammatory cytokines counting CRP, Leptin, IL-6, and TNF-a [26].

Despite the same finding that shows the pro-inflammatory effect of the GL [9, 10, 26], the effect of GI on inflammation is still unclear. In another word, scientists still do not know whether the quality of carbohydrates can lead to inflammation or only the quantity plays a role. Additionally, by considering the effect of carbohydrate quantity and weight on the inflammation that was established several times before [3, 5, 6, 27] and its importance in the calculation of GL [13], the authors believe GL cannot be an excellent factor to assess the quality of carbohydrates independently from the weight of carbohydrate consumption [13]. This is while GI is entirely independent of the carbohydrate's weight [12-14].

According to the unclear overall effect of GI on inflammation as well as the great range of differences in the studies; this systematic review aims to evaluate the impact of the Glycemic Index on inflammatory biomarkers, especially IL-6, IL-1, TNF-a, TNF, CRP, and HS-CRP, independently from GL to understand the association of carbohydrates quality with inflammation, presenting biases that need to be considered, and offer some recommendations for further studies. The authors hypothesis suggested GI effect inflammatory biomarkers but several confounders in previous studies were not considered that required to be addressed.

Methods:

Search strategy: For this study, Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) were used as the guideline. Three independent researchers (MRSh, PZSh, AV) investigated through scientific databases including, Science Direct, PubMed, Cochrane, and UpToDate from 2010 to March 2021 (Table.1). The search timeline of the study was limited based on two factors: 1—the change that was made within the GI table in 2008 [28] and 2—A comprehensive discussion by Galland et al. [9] followed by Milajerdi et al. [26] study in 2010. Also, a comprehensive search was made in Google Scholar from 2010 to July 2021, and all articles in this database were considered in this study.

Search keywords: Search keywords of this study were MESH (Medical Subject Heading) and un-MESH keywords, including ("Glycemic index" OR "Glycemic indices" OR "Glycemic index number" OR "Glycaemic index" OR "Glycaemic indices" OR "GI") AND ("inflammation" OR "inflammatory biomarkers" OR "IL" or "TNF" OR "inflammation biomarkers" OR "inflammation markers" OR "inflammatory markers" OR "inflammatory indices" OR "Interleukin-10" OR "Interleukin" OR "Interleukin-8" OR "Interleukin-6" OR "Inflammation mediator" OR "Tumor necrosis factor" OR "C- reactive protein" OR "Transforming growth factor" OR "Cytokine" OR "Systematic Inflammation") AND ("RCT" OR "clinical trial" OR "Cohort" OR "cross-sectional" OR "cross-sectional" OR "original" OR "case-control" or "case" OR "control" OR "case-control"

(table 1). Moreover, the related and systematic reviews were reviewed to ensure no study would be missed. As a judge of findings, a secondary search was made with a pretty simple search: "glycemic index" and "inflammatory biomarkers" by a fourth researcher (MR), and the findings were compared with the previous search method's conclusions. All the founded papers in each database were merged and duplicated articles were removed. Finally, documents of all databases are merged into one file.

Inclusion criteria: All human studies (paper and theses), including clinical trials, case-control, cohort, and cross-sectional studies included. All the studies that considered the effect of GI, Low GI, and High GI on inflammatory biomarkers or inflammation published during the last ten years were considered.

Exclusion criteria: All duplicated studies were excluded. Reviews, systematic reviews, meta-analyses, editorial letters, and short communications were excluded. Other exclusion criteria of the study were 1. studies conducted in children or animal studies because of biological and physiological differences. 2. Not considering GI as a separate factor from GL. 3. Not to report inflammatory biomarkers in value. 4. Any other intervention besides dietary pattern intervention includes medical, physical activity, and exercise or supplementary interventions. And, 5. Studies in languages that authors were not able to read. The main reason for excluding GL was the effect of carbohydrate intake on inflammation as a possible confounder of GI. All in all, only studies that directly evaluate GI on inflammatory biomarkers were enrolled for review.

Study selection: During the study selection process, researchers reviewed all papers separated, and the final findings were merged. From 892 articles, 381 articles were duplicated and removed. Two researchers (SJ and AV) read each article's title and general information for indicating animal studies, children's studies, and review articles. Meta-analyses, Reviews, letters, systematic reviews, animal studies, and studies conducted on children were removed. Abstract of 244 papers thoroughly reviewed by reviewers (MRSh, PZSh, and FK). Two hundred and three articles met the exclusion criteria, and 41 articles were eligible for full-body review, which was reviewed by three reviewers (PZSh, MR, and MRSh). The final number of relevant articles suitable for this systematic review was thirteen. In all the review processes, two-judge (FK and RR) was presented. Reviewing process was repeated one more time, and there was no significant difference between the process. For full detail of this process is reported in figure 1.

Results:

From the total of 13 studies [27, 29-40] including one MSc. full theses [39] that enrolled in this review; six studies [29-31, 33, 38, 40] were conducted on people with diabetes mellitus, cardiovascular diseases (CVD), and polycystic ovary syndrome (PCOS). Six studies [27, 32, 35-37, 39] investigated within healthy or obese people without any diseases and one study [34] was at pregnant women, which were reviewed. Nine of the studies [27, 31, 33-40] assessed GI, and 3 Studies [27, 29, 30, 38] assessed both GI and GL. IL-6 was in 8 studies [27, 29, 30, 32-34, 37, 39], TNF-a was in 5 studies [27, 31-34], TNF was in 2 studies [29, 39], CRP was in 6 studies [27, 35-39] and HS-CRP was in 2 studies [30, 40]. The full detailed description of findings can be reached in the table 2.

From studies that addressed the relevance of GI to inflammatory biomarkers; a total of 7 Studies [29, 30, 32, 33, 36, 39, 40] with overall and mean sample sizes of 933 and 133 respectively, found a significant relationship between GI with at least one of the inflammatory biomarkers. There were also 5 Studies [31, 34, 35, 37, 38] with an overall sample size of 1409 and a mean sample size of 281 that did not find any relation between GI and inflammation. Nevertheless, one study [27] did not perform any statistical analyses for the GI and biomarkers. The effect of dietary patterns on the inflammatory effect of GI, the importance of study design, and the sensitivity of GI are some considerations derived out from studies. However, the evidence supporting the slight effect of GI on inflammation was more than the evidence that rejected this effect.

Discussion:

The reviewed studies confirmed the hypothesis of the authors. The findings of the reviewed studies showed GI can have a slight effect on inflammation. However, the complication of GI and the lack of sufficient studies with the same findings prevent us from providing a firm answer to this question. In this review, as any study had its own considerations, the authors provided a possible link between GI and inflammation as well as described the main limitations that are better to be considered during GI studies.

In 2010, findings from a multicenter diet intervention reported no significant differences between groups for CRP before and after adjustment in this study [35]. However, more investigations within the study showed two completely different effects of GI on CRP, one positive and one negative, with two different diet patterns. The findings of this study made this hypothesis that diet patterns, especially fat values, can affect the effect of GI [35].

The impact of diet patterns on GI and inflammation was repeated several times in other studies. According to the reports of a cohort study, diet patterns with higher GI scores had a slightly higher reported level of TNF-a and CRP than lower GI groups [27]. Another finding that could drive out from this study was that GI might significantly change in different diet patterns. In this study, diet patterns with sweets and desserts group had a lower GI than refined grains and breakfast cereal group which were believed to have a higher GI [27]. This can be a significant limitation for GI and GL studies. According to the current study, considering the populations' diet pattern and the consumption of unhealthy foods with higher inflammatory index and lower GI as a confounder is recommended.

However, the main limitation of GI and inflammatory studies can be related to their small sample size along with short follow-up. The majority of studies fell in this category [31, 38]. Nevertheless, all three studies that had a well-controlled low biased risk protocol showed a significant direct relation between GI and inflammation despite a small sample size [33, 36, 39]. In all of these studies, all the participants followed a close diet pattern during the assessment that showed the priority of confounders over the sample size [33, 36, 39]. However, another study shown providing linear graphs for these small sample-sized studies can provide good information [32].

In another Study with a considerable population, a 137-item Food Frequency Questionnaire (FFQ) was used to determine the dietary intake and GI [29]. In this study, which was based on the Brand-Miller GI table [28], a significant relation was found between IL-6 (P-ANOVA = 0.050) and TNF (P-ANOVA = 0.046) with GI at the baseline [29]. However, after the one-year intervention, no significant differences between GI with both IL-6 and TNF resulted [29]. The main reason for this difference can be explained by the method of this study which used low inflammatory diet patterns in the groups [41–43]. In this study, two possible anti-inflammatory patterns were compared to each other that could impact the finding.

However one of the most surprising findings was in the Bahado-Singh et al. study [40]. This study has shown a 38.24% decrease in HS-CRP level in the low-intermediate GI group in comparison with a 15.18% decrease in the low-intermediate GI group [40]. Despite the decrease in both groups, the decrease in the low-intermediate GI group was significantly lower than in the high GI group ($p < 0.05$), but there was no description of the reason for the anti-inflammatory effect of both high and low-intermediate GI diets in this study. However, despite both groups having the same diet during the assessment, this decrease can be affected by other anti-inflammatory components of both diets. Nevertheless, low GI had a higher anti-inflammatory impact.

Despite supporting data on the effect of GI on different diseases [7, 9, 10, 15–21, 44, 45], findings on inflammatory biomarkers are vastly ranged. A meta-analyzed study shows a significant difference between low and high GI groups in CRP for both models in obese people with and without diabetes [46]. A meta-analysis study by Milajerdi et al. rejected any inflammatory effect for GI that supported the Buyken et.al study [26, 47]. This is while another study showed GI is associated with oxidative stress [48].

Nevertheless, the most important finding regarding this relation was reported in Yeon-soo et al. study in 2018 [49]. In this study, an association had been found between GI and Dietary inflammatory Index (DII), which was developed by Dr. Shivapa and Dr. Hebert [50–53] to determine the dietary inflammatory potentials. This study and the effect of GI on CRP, which was reported by Schwingshackl et al. [46], suggests a reconsideration of the effect of GI on inflammation which was reported by Milajerdi et al. [26] recently.

Overall, the main weakness of GI is related to its nature which increases the bias risk (Fig. 2). Food processing, sugar-containing, other nutrients, food PH, speed of eating, blood glucose level, and insulin level are some factors that can affect the GI response of the body [12–14, 54–56]. The other critical weakness of GI is related to its pattern in food classification [12–14]. In this pattern, some pro-inflammatory foods like pizza (GI = 39), fructose (GI = 15), chocolate (GI = 40), ice cream (GI = 51), Soft drink/soda (GI = 59), potato crisps (GI = 56) have been classified as low-moderate GI foods while some fruits like pineapple (GI = 59), mango (51), watermelon (GI = 76) have higher GI [12–14]. Considering these issues, it may be possible that an unhealthy diet pattern has a lower GI than a healthy one; but research is needed to confirm this hypothesis.

Finally, by considering limitations, running a well-designed GI study has several complications that must be addressed first. Of all food components, it seems lipids have the most cofounding bias but still require

more investigation. Continued follow-ups as a controlled clinical trial can be helpful too. In addition, a study to understand the association of diet patterns with GI is recommended. To understand the effect of GI on inflammation, using more homogenized populations as well as removing the effect of differences in diet patterns that can make biases has extra benefits. However, all in all, a dietary pattern high in fruit, vegetables, fish, poultry and legumes, whole grains, and low in red and processed meat, sweetened beverages, sweets, refined grains, and fried potatoes has been linked to a lower level of inflammatory biomarkers [3, 5, 6, 27].

The strength of this study is related to the point of view of the reviewers. In all steps, at least two researchers with two different opinions made the review of studies which provides a new point of view and hypotheses for further studies. Nevertheless, the main weaknesses of this study were related to the nature of GI and the lack of sufficient studies. The other limitation of this review is its close time to previous systematic studies, which is uncommon. The other limitation was the lack of any statistical analysis. Nevertheless, the authors understood current findings in GI are not suitable and homogenized for this purpose. As the effect of dietary patterns in the reviewed studies is unclear, any analysis can lead to a wrong but maybe statically specific answer on this subject.

Conclusion:

Unfortunately, despite research in this field, the findings of studies are not homogenized and unexpected confounders that can affect the result of studies are too many. There is some strong evidence that supports a slight effect of GI on inflammatory biomarkers. Based on the evidence, the dietary lipid quality can significantly affect GI's relation to inflammation. However, for deciding on the link between GI and inflammation, first more research with a homogenized population with near the same diet pattern, and second continuous monitoring follow-up studies are suggested. Concerning the previous meta-analysis on this subject, the finding may have diet-related biases that statically are not recognized.

Abbreviations:

Interleukins-1: IL-1

Interleukins-6: IL-6

Interleukins-10: IL-10

Tumor Necrosis Factor: TNF

Tumor Necrosis Factor-α: TNF-α

C-Reactive Protein: CRP

High Sensitive C-Reactive Protein: HS-CRP

Glycemic Index: GI

Glycemic Load: GL

Food Frequency Questionnaire: FFQ

Preferred Reporting Items for Systematic Review and Meta-analysis: PRISMA

Declarations:

Ethics approval and consent to participate: not applicable.

Consent for publication: not applicable

Availability of data and materials: Data is available upon reasonable request.

Competing interests: Authors of this paper declare no conflict of interest.

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Tables

Table 2 is available in the Supplementary Files section

TABLE 1. PICOS criteria for inclusion of studies in the systematic review

PICOS component	Description
Population	people of above 18 years, in any country
Intervention	With low GI or high GI diet pattern or report the GI score of diet (GL studies excluded)
Comparators	N/A
Outcomes	Reported any changes in IL-6, IL-1, TNF-a, TNF, CRP, and HS-CRP related to GI food consumption
Study design	Case-Control Studies, Intervention Studies, Cross-sectional studies, cohort studies
Language	English, Farsi

GI: Glycemic Index, GL: Glycemic Load, IL-6: Interleukin-6, IL-1: Interleukin-1, TNF-a: Tumor Necrosis Factor Alfa, TNF: Tumor Necrosis Factor, CRP: C-Reactive Protein, HS-CRP: High Sensitive C-Reactive Protein, N/A: Not applied

Figures

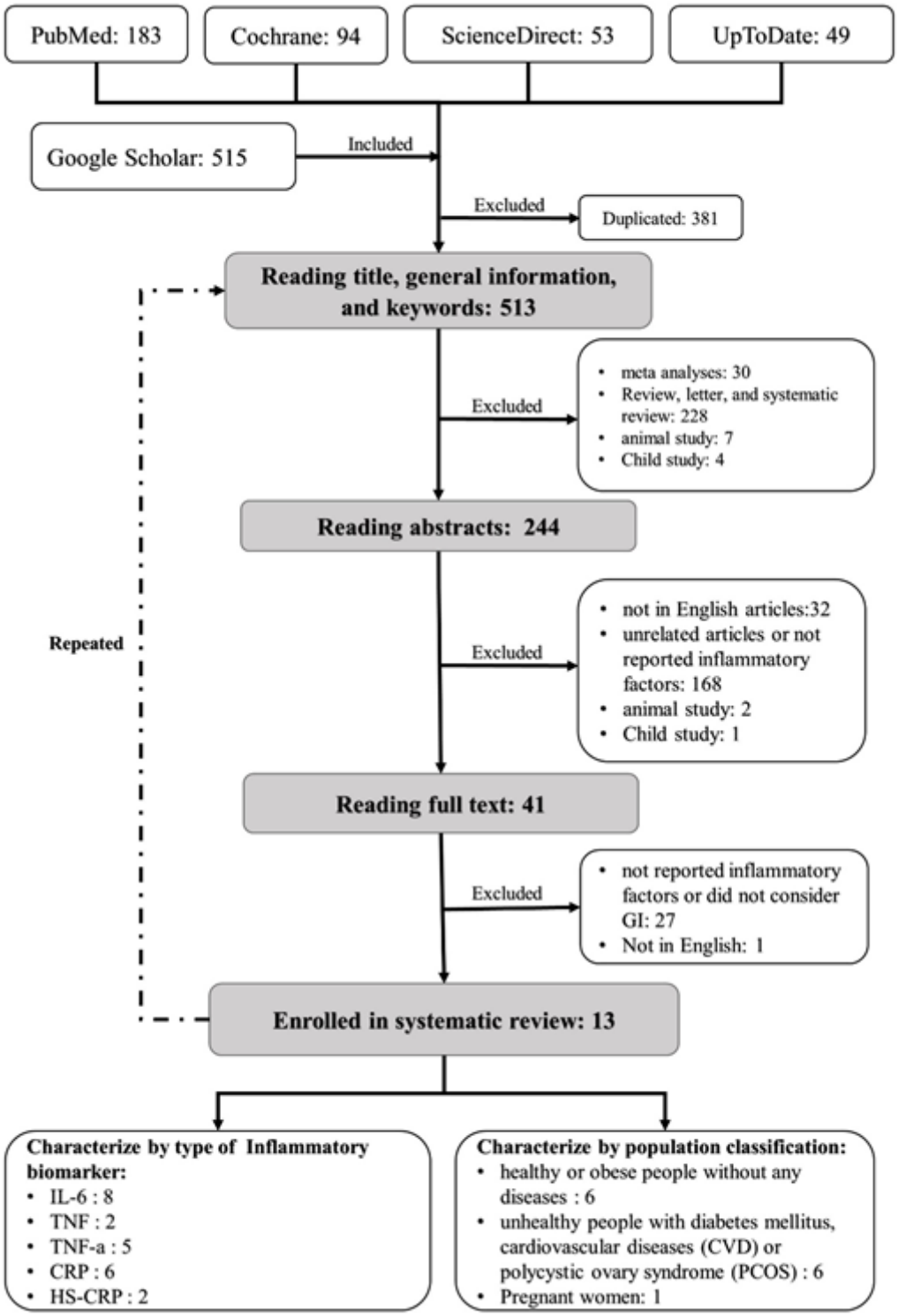

Figure 1

Flow diagram of study selection. GI: Glycemic Index, GL: Glycemic Load, IL-6: Interleukin-6, IL-1: Interleukin-1, TNF-a: Tumor Necrosis Factor Alfa, TNF: Tumor Necrosis Factor, CRP: C-Reactive Protein, HS-CRP: High Sensitive C-Reactive Protein, N/A: Not applied

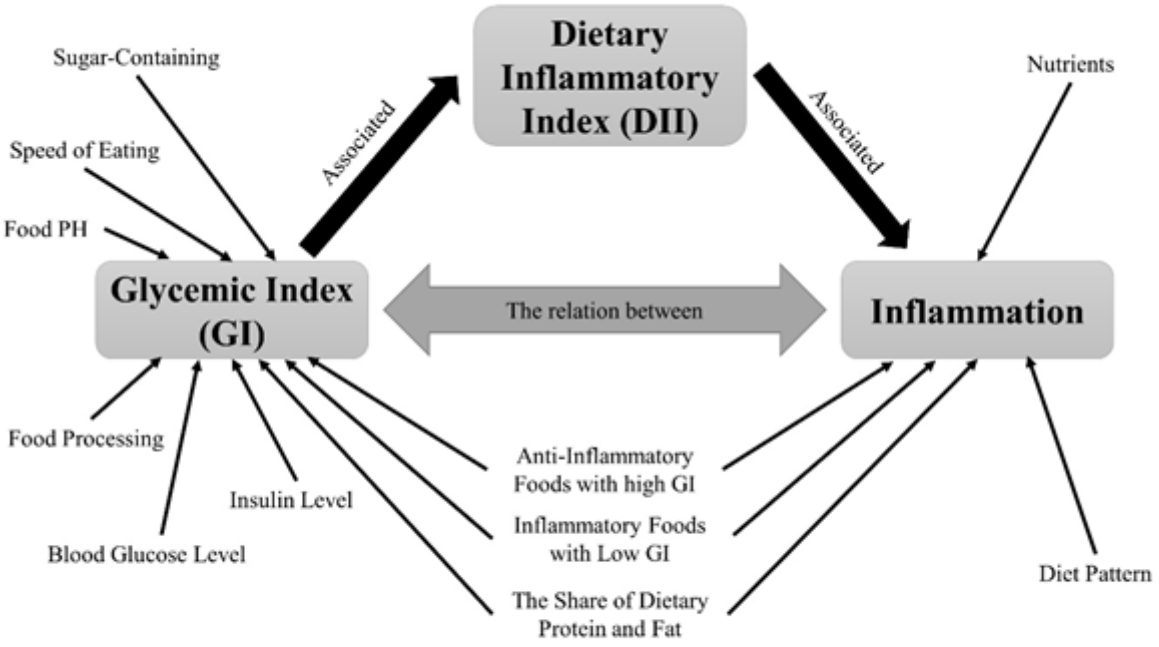

Figure 2

the possible direct and indirect confounders of the effect of GI on inflammatory biomarkers.

Supplementary Files

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- TABLE2.docx