Research Square

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High Carbohydrate Intakes May Predict More Inflammatory Status Than High Fat Intakes in Pre-Menopause Women With Overweight or Obesity: A Cross-Sectional Study

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Research note

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Abstract

Objective

Until now, studies on the association between dietary carbohydrate and fat intakes and inflammation have indicated conflicting results. We evaluated the association of fat and carbohydrate intakes with inflammatory markers in pre-menopause women with overweight or obesity.

RESULTS

360 women with BMI ≥ 25 participated in this study. The levels of monocyte chemoattractant protein-1 (MCP-1) indicated a significantly increasing trend across tertiles of total dietary carbohydrate (P=0.048). We found that the levels of galectin-3 were negatively associated with dietary carbohydrate in adjusted model (β= -0.28, P=0.04). In addition, the levels of MCP-1 and transforming growth factor beta (TGF-β) were positively correlated to carbohydrate amount in the diet (β= 0.23, P=0.002 and β= 0.29, P=0.002 for MCP-1 for crude and adjusted models, respectively, β= 0.57, P=0.03 and β= 1.23, P=0.003 for TGF-β for crude and adjusted models, respectively). No significant relationship was observed between inflammatory parameters and total fat intake (P>0.05). However, there was borderline significant negative association between total fat intake and TGF-β level in adjusted model (β= -0.95, P=0.05). Therefore, high carbohydrate diet may increase inflammation in women with obesity. To achieve similar results, it is necessary to perform more observational and clinical trial studies in this issue.

Introduction

The obesity epidemic are continuing at an alarming rate from developed to developing societies, with an exceptionally high incidence rate among women of reproductive age [1]. Women with obesity have a higher probability of developing metabolic disorders including type-2 diabetes mellitus (T2DM), hypertension, heart diseases and other adverse metabolic conditions [2]. In addition, obesity is often associated to elevated serum concentrations of pro-inflammatory mediators such as interleukin-6 (IL-6), transforming growth factor beta (TGF-β), monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP) [3, 4]. In fact, systemic inflammation might have involvement in the pathogenesis of various chronic diseases in obesity [5]. For example, there is substantial document supporting the role of CRP in the worsening and pathogenesis of cardiovascular diseases (CVDs) [6]. Therefore, assessing these biomarkers helps to early detection of metabolic disorders caused by obesity [7]. Diet is a potentially modifiable lifestyle factor which is correlated to obesity-induced inflammation [7]. Studies have indicated conflicting results regarding the association between high-carbohydrate diet (HCD) and high-fat diet (HFD) and chronic inflammation [8–10]. It has been recorded that excessive consumption of dietary fat might lead to obesity as well as chronic inflammation [11]. However, a meta-analysis of 4 clinical trials showed no significant effect of very-low-carbohydrate ketogenic diet versus low-fat diet on serum CRP levels [12]. Conflicting changes have also been observed in changes of pro-inflammatory cytokines during HCD [12–14].

We aimed to determine the association between dietary fat and carbohydrate amounts and inflammatory markers in women in reproductive age with overweight or obesity.

Materials And Methods

Research design and Study population

This observational investigation was a multi-center uncontrolled cross-sectional study that was performed by a multistage cluster random sampling method. 360 women who referred to community health centers of Tehran university of medical science were recruited for this investigation. Inclusion criteria consisted of healthy women aged 18–50 with BMI equal or more than 25. Exclusion criteria were those who had medical history of hypertension, addiction to alcohol, drugs and/or smoking, thyroid diseases, diabetes mellitus, CVDs, malignancies, hepatic or renal diseases, lactation, pregnancy and acute or chronic infections. The recruitment duration of participant in this observational investigation was during June 2017 to January 2018.

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (with ID number: IR.TUMS.VCR.REC.1395.1480) at 2017-1-17.
Written and informed consent requirement was provided by all participants, prior to initiation of any clinical screening procedures.

Assessment of anthropometrics variables, dietary intakes and physical activity

An expert nutritionist measured weight and height of recruited women to the nearest 100 grams and 0.5 cm, respectively, using calibrated, digital scale (SECA, Vogel & Halke, Hamburg, Germany). BMI was calculated as body weight divided by square of the height (m2) and expressed as kg/m2. BMI ≥ 25 and ≥ 30 were interpreted as being overweight and obese, respectively. WC and hip circumference were also measured to the nearest 1.0 cm using an un-stretchable measuring tape. WHR calculation was by dividing WC by hip circumference. Afterwards, general characteristics (age, smoking and alcohol dependency and medical history) were questioned from eligible participants. Usual dietary intake of subjects was obtained using 147-item semi-quantitative food frequency questionnaire (FFQ) [15]. Trained dietitians, asked the participants to report their intake frequency for each food or drink item consumed over the past year in terms of day, week, month and year. The reproducibility and relative validity of the 147-item FFQ were examined previously in the Tehran Lipid and Glucose Study [15]. The reported frequency according to the desired serving size of each food item or household measure was turned into grams per day via Nutritionist IV software (version 7.0; NSquared Computing, Salem, OR, USA). All foods and beverages intakes were assessed for the amount of fat and carbohydrate calculation. Physical activity (PA) evaluation was done through the short form of the International Physical Activity Questionnaire (IPAQ) (Occupational, Transport, Yard/Garden, Household, and Leisure). In IPAQ, physical activity was indicated as metabolic equivalent hours per week (MET-h/wk). The final added scores < 600, 600–3500 and > 3500 (MET-h/wk) were interpreted as low, moderate and strict physical activity, respectively.

Assessment of biochemical factors

Following a 12-h overnight fast, we collected venous blood samples from all study participants.

The blood samples were centrifuged at 1000 x g for 15 min at 4°C. Then, plasma was immediately aliquoted into separate tubes and stored at − 80°C. The extent of CRP was measured by use of an immunoturbidimetric assay (high-sensitivity assay by Hitachi 902). Furthermore, the active form of TGF- β and galectin-3 were measured using enzyme-linked immunosorbent assay (ELISA) by the ELISA-Quantikine kit (R&D Systems, Minneapolis, MN). The analyzer IMMULITE One (Medical System S.p.A., Genova, Italy) and the ELISA-Quantikine kit (Human CCL2/MCP-1 Quantikine R&D Systems kit, USA) were used for measuring IL-1-β and MCP-1 levels, respectively.

Statistical analysis

The minimum samples size (equal to 347) was calculated through following formala, in which r = 0.21, β = 0.95, and α = 0.05.

$N= (([(Z1 - \alpha + Z1 - \beta)\times\sqrt{1 - r^2}]/r)^2+2)$,

However, due to data availability, we conducted study analysis on 360 participants.
All statistical analyses were performed by SPSS software (version 16.0; SPSS Inc, Chicago) and a p-value < 0.05 was considered as statistical significance. Normality testing of study variables was via Kolmogorov-Smirnov's analysis. Unnormal data were normalized following square or logarithmic transformations. Comparison of continues variables for each study member in tertiles of total fat and carbohydrate intakes was performed by one-way analysis of variance (ANOVA). In addition, multiple linear regression models (crude and adjusted for age, BMI, physical activity and energy intake) were used to assess the association of inflammatory variables with fat and carbohydrate consumptions.

Results

Research participants

Table S1shows the general characteristics and laboratory parameters for 360 pre-menopause women with overweight and obesity. The mean age of the subjects was 36.52 years and the mean BMI was 30.33 Kg/m2.

Primary findings

The general characteristics and inflammatory markers in study participants among tertiles of total dietary carbohydrate and fat intakes are shown inTable S2 and S3. As mentioned in Table S2, significant differences were found for age, body weight and height across tertiles of dietary carbohydrate (P = 0.01, P = 0.02 and P = 0.01, respectively). Moreover, the levels of MCP-1 indicated a significantly increasing trend among tertiles of dietary carbohydrate (P = 0.048). There was near to significant difference in subjects' height across dietary fat intake tertiles (P = 0.05).

Additional findings

Table 1and Table 2indicate multiple linear regression analysis between inflammatory variables with dietary carbohydrate and fat, respectively. Based on the Table 1, we found that the levels of galectin-3 were independently and negatively associated with dietary carbohydrate in adjusted model [P = 0.04]. In addition,

the levels of MCP-1 and TGF-β were independently and positively correlated to dietary carbohydrate in crude and adjusted models (P = 0.002 and P = 0.002 for MCP-1 and P = 0.03 and P = 0.003 for TGF-β for crude and adjusted models, respectively). As indicated in Table 2, there was borderline significant relationship between dietary fat intake and TGF-β in adjusted model (P = 0.05). However, no significant relationship was observed between inflammatory parameters and dietary fat (P > 0.05).

Table 1
Multiple linear regression analysis between dietary carbohydrate intake and inflammatory markers

Variable	Model	Beta	CI 95%	$\varvecP - \varvecv\varveca\varvecl\varvecu\varvece$
CRP (mg/L)	Model 1	0.00	-0.37 to 0.37	0.96
	Model 2	0.05	-0.26 to 0.58	0.45
IL-1β (mg/L)	Model 1	-0.09	-0.18 to 0.07	0.40
	Model 2	-0.09	-0.21 to 0.11	0.51
TGF-β (mg/L)	Model 1	0.57	5.63 to 104.45	**0.03**
	Model 2	1.23	52.71 to 184.40	**0.003**
Galectin-3 (mg/L)	Model 1	-0.19	-1.84 to 0.13	0.09
	Model 2	-0.28	-2.43 to -0.01	**0.04**
MCP-1 (mg/L)	Model 1	0.23	2.53 to 11.38	**0.002**
	Model 2	0.29	3.28 to 14.02	**0.002**

Notes: CRP: C-reactive protein; IL1β: Interleukin 1 Beta; TGF-β: Transforming growth factor beta; MCP-1: Monocyte chemoattractant protein-1. Model 1: Crude model. Model 2: Adjusted model for age, BMI, physical activity and calorie intake.

Table 2
Multiple linear regression analysis between dietary fat intake and inflammatory markers.

Variable	Model	Beta	CI 95%	$\varvec{P-\varvec{v}\varvec{a}\varvec{l}\varvec{u}\varvec{e}}$
CRP (mg/L)	Model 1	0.00	-0.26 to 0.29	0.91
	Model 2	0.02	-0.29 to 0.39	0.79
IL-1β (mg/L)	Model 1	0.13	-0.04 to 0.16	0.26
	Model 2	0.14	-0.07 to 0.20	0.35
TGF-β (mg/L)	Model 1	-0.19	-40.25 to 20.85	0.50
	Model 2	-0.95	-95.06 to 0.15	**0.05**
Galectin-3 (mg/L)	Model 1	-0.05	-0.97 to 0.60	0.64
	Model 2	-0.01	-1.18 to 1.11	0.95
MCP-1 (mg/L)	Model 1	-0.06	-4.86 to 2.15	0.44
	Model 2	-0.17	-0.26 to 0.29	0.09

Notes: CRP: C-reactive protein; IL1β: Interleukin 1 Beta; TGF-β: Transforming growth factor beta; MCP-1: Monocyte chemoattractant protein-1. Model 1: Crude model. Model 2: Adjusted model for age, BMI, physical activity and calorie intake.

Discussion

In this paper, we aimed to probe the association between carbohydrate and fat contents of diet with inflammatory markers in women in reproductive age with overweight and obesity. Our findings illustrated that serum MCP-1 levels were positively correlated to total carbohydrate.

Our results suggest that high carbohydrate diets can probably lead to an increase in the levels of MCP-1, a chemokine whose role has been demonstrated in the etiology of obesity-related diseases [16].

The results of this article are in accordance with Forsythe et al.'s study [17] in which a very low carbohydrate diet led to a decrease in inflammatory markers such as TNF-a, MCP-1, IL-6, IL-8, and PAI-1 in comparison with a low fat diet. They expressed that the anti-inflammatory influences of carbohydrate restriction may be mediated through down-regulation of nuclear factor kappa B (NF-κB) pathway [17, 18]. It has also been established that HCD induces the production of the major lipogenic products and increases lipogenesis that it is related to higher levels of adiposity [17] which is associated with elevated levels of MCP-1 [16]. In the current study also, an inverse correlation was observed between MCP-1 and fat content in the diet, however this finding was insignificant, possibly due to small sample size.

However, Hall et al [19] demonstrated that the serum levels of MCP-1 remained constant after reduction of both fat and carbohydrate intakes in 6 weeks in obese subjects. The inconsistency between results of current study and tHall et al's study might be due to various designs of study and different numbers of participants.

The TGF-β levels had positive significant relationship with dietary carbohydrate amount in and borderline significant negative association with dietary fat amount.

TGF-β is a recently recognized cytokine that regulates insulin resistance in obesity. In addition, it has been illustrated to induce macrophages proliferation and deposition in adipose tissue of obese mice [3]. TGF-β over-expression along with high carbohydrate consumption was reported to be related to high blood glucose level that leads to stimulated IKK phosphorylation and secretion of NF-κB-mediated pro-inflammatory such as TGF-β [20, 21]. In line with the current results an experimental study indicated that in fishes with HCDs, TGF-β, TNF-α and IL 1β, NF-κB, and IL-6 increased [21]. A human study also reported that low-carbohydrate diets with high amounts of fat contributed to reduction in serum level of TGF-β [22]. Near to significant negative association between total dietary fat and TGF- β was also observed in our study which might have reached to significant level with a larger study population. Although there is no clear explanation for this negative relationship, it is possible that the insignificant reducing trend of body weight during dietary fat tertiles, mediated the reduction of TGF by higher fat intake [23]. Despite the pro-fibrogenic dark side of TGF-β's function, its healing effects on tissue injuries as well as on the modification of the immune responses have been observed, indicating its paradoxical effects on inflammatory state [24]. In fact, the multi-faceted properties of this cytokine are environmental and cellular context dependent. Contrary to our results, Ohtomo et al. in 2010 investigated the effects of high-carbohydrate/low-fat diet and middle-carbohydrate/middle-fat diet (as normal group) on hypertensive, obese, type 2 diabetic rats for 12 weeks and observed that the TGF-β in the kidney tissue meaningfully reduced in the high- carbohydrate/low-fat diet compared to the control group. Inconsistency between human and animal findings might be a result of bias or unsuitability of animal models in mimicking biochemical functions adequately [25].

We also explored that the galectin-3 level had significant negative relationship with dietary carbohydrate amount in adjusted model. Several investigations have shown that galectins are involved in various diseases including atherosclerosis and diabetes [26, 27]. Galectin-3, a member of this group, plays various and sometimes contradictory roles in pathological and physiological pathways depending on type of involved

organs [28]. In case of kidney and vessels, lack of galectin-3 and its scavenging function in kidney raise the production of advanced lipoxidation and glycation end products (ALEs and AGEs) and contribute to damages to these tissues [29]. Moreover, further studies revealed that galectin-3 correlates with the prevention of the chronic inflammation and associated metabolic illnesses [28].

We did not explore any article investigating the impact of macronutrients proportion on galectins levels. Although, a clinical trial study in mice with progressive hepatopathy indicated that low-carbohydrate and high-fat ketogenic diets (KDs) led to significant expression of galectin-3 gene in comparison to control diet which was probably due to improved mitochondria-related functions [30].

Conclusion

The current investigation indicated that high carbohydrate in diet might predict more inflammatory state compared to high dietary fat in healthy women with obesity. The current results be interpreted with caution. Further investigations are warranted to determine the effects of total fat and carbohydrate intakes on inflammatory factors and inflammatory diseases.

Limitations

The limitations of our article were small sample size and its cross-sectional design with no exact cause-effect and failure to follow the subjects during change in diet.

Declarations

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Authors' contribution.

Elmira Karimi: Conceptualization, Methodology, Investigation, Writing - Original Draft, Habib Yarizadeh: Software, Formal analysis, Leila Setayesh: Writing - Review & Editing, Visualization, Seyyedeh Forough Sajjadi: Resources, Data Curation, Nasim Ghodoosi: Resources, Data Curation, Khadijeh Mirzaei: Validation, Supervision, Project administration, Funding acquisition.

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Availability of data and material

"The datasets supporting the conclusions of this article are included within the article and its additional file."

Ethics approval and consent to participate

The present study was carried out in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. This investigation was also approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (with ID number: Ethics number: R.TUMS.VCR.REC.1395.1593). All of the study participants signed a written consent form related to this study.

Consent for publication

Written consent forms were approved and signed by subjects of this study for publication of this article.

Competing interests

The authors in our study declare no conflict of interests.

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