Dietary glycemic index and dietary glycemic load is associated with apelin gene expression in visceral and subcutaneous adipose tissues of adults

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Abstract

Background: Apelin, as an adipokine, plays an important role in the pathogenesis of insulin resistance and type 2 diabetes. This study aimed to determine whether the quality and quantity of dietary carbohydrates were associated with apelin gene expression in subcutaneous and visceral adipose tissues.

Methods: In this cross-sectional study, 102 adults who underwent minor abdominal surgery were selected. Approximately 100 mg of subcutaneous and visceral adipose tissues were collected during the surgery to measure apelin gene expression. Anthropometric measurement, blood samples, and dietary intakes were collected before surgery. The dietary carbohydrate intake, glycemic index (GI), and glycemic load (GL) were determined.

Results: The average apelin concentration was 269.6 ± 98.5(pg/mL), and 16.3% of participants were insulin resistant. There was a correlation between insulin (p-value = 0.043), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)(p-value = 0.045) and apelin gene expression in visceral adipose tissue. There was a positive association of apelin gene expression with dietary GI and GL after adjustment for age, sex, and waist circumference in visceral and subcutaneous adipose tissues(p < 0.05). Apelin gene expression in visceral(p = 0.002) and subcutaneous(p = 0.003) adipose tissues was directly associated with foods with a higher GI. There was no association between total carbohydrate intake and apelin gene expression in both visceral and subcutaneous adipose tissues.

Conclusions: Dietary GI and GL, not total carbohydrate intake, were positively associated with apelin gene expression in both visceral and subcutaneous adipose tissues. Future studies are warranted to illustrate the chronic and acute effect of carbohydrate quality on apelin homeostasis.

Keywords: Glycemic index, Glycemic load, Carbohydrate, gene expression, Visceral and subcutaneous adipose tissue

Background

More attention has been paid to the role of adipocytes in the body homeostasis in the recent decade. Adipose tissue acts as an endocrine organ which has an important effect on insulin sensitivity and regulates energy homeostasis through adipocyte-derived regulatory hormones termed adipokines [1, 2]. Apelin, as an adipokine, is a 36 amino-acid bioactive peptide that in humans is encoded by the apelin gene and located on chromosome Xq25–26.1. It is a key regulator in glucose and lipid metabolism [3] and plays an important role in the pathogenesis of insulin resistance and type 2 diabetes [4, 5]. Apelin regulates glucose homeostasis by increasing glucose uptake, enhancing insulin sensitivity in adipocytes [3] and inhibiting adipocyte lipolysis [6, 7].

Carbohydrates are the primary source of energy in the human diet. Glycemic index (GI) and glycemic load (GL),
as measurements of carbohydrate quality, provide an additional benefit compared to carbohydrate counting alone [8]. Dietary glycemic measures may affect body homeostasis [9] and contribute to the adipose-related pathways [10].

In our previous systematic review, we concluded that diet could alter apelin gene expression and concentration by mediating on plasma insulin levels [11]. It is well-established that insulin concentration is the important stimulator of apelin gene expression in adipose tissue [12]. Thus, we hypothesized that habitual dietary intake of carbohydrates, including quality and quantity, might have a distinguishing role in the prediction of apelin gene expression in adipose tissue by chronic manipulating of insulin concentration.

According to recent studies, apelin concentration may be affected by dietary intake in both human and animals [13, 14]. However, these studies mostly focused on dietary fatty acid, and data regarding dietary carbohydrate was rare. Thus, this study aimed to determine whether quality and quantity of dietary carbohydrates were associated with apelin gene expression of in subcutaneous and visceral adipose tissues.

Materials and methods

Participants

In this cross-sectional study, 102 participants aged more than 20-years, who had been admitted for elective abdominal surgery including appendectomy and hernia repair, were selected from Mostafa Khomeini and Khatam Al-Anbia Hospitals, Tehran, Iran. All participants were hospitalized for less than three days. Individuals were eligible for inclusion if they had no known medical illnesses such as diabetes mellitus or cancer, did not take lipid-lowering or anti-obesity medications, were not pregnant or lactating woman, and not on special diets. Approximately 100 mg of subcutaneous and visceral adipose tissues were collected during the surgery. All information and questionnaires were completed before surgery.

The ethics committee of the Research Institute for Endocrine Sciences (RIES) of Shahid Beheshti University of Medical Sciences approved the study (NO: IR.SB-MU.ENDORCINE.REC.1395.372), and the study was conducted in accordance with the Declaration of Helsinki, as well as our institutional guidelines. Written informed consent was obtained from all participants.

Dietary measurement

Using a valid and reliable semi-quantitative food frequency questionnaire (FFQ), expert interviewers gathered regular dietary intakes of each participant during the past year, on a daily, weekly, or monthly basis, and according to household measures. Then, portion sizes of consumed foods were converted to grams. Energy and nutrient contents were obtained from the US Department of Agriculture (USDA) food composition tables (FCT) because the Iranian FCTs were incomplete; although, the Iranian FCTs were used for traditional food items (like Kashk). The reliability and validity of the FFQ was evaluated in a previous study and indicated that the FFQ provides reasonably valid measures of the long-term average [15].

In the current study, we considered total carbohydrate intake and dietary GI and GL. Then, the food types were categorized based on their GI and GL into three different groups including high (≥70), medium (56–69) and low (≤55) GI foods (Additional file 1: Table S1) [16]. Dietary GI and GL were derived from the FFQ as follow [16]:

\[
\text{Dietary GI} = \frac{\text{carbohydrate content of each food item} \times (\text{number of servings/d}) \times (\text{GI})}{\text{total daily carbohydrate intake}}
\]

\[
\text{Dietary GL} = \frac{\text{carbohydrate content of each food item} \times (\text{number of servings/d}) \times (\text{GI})}{\text{total daily carbohydrate intake}}
\]

Quantitative real-time polymerase chain reaction analysis of gene expression

We extracted total RNA from visceral and subcutaneous fat tissues according to the manufacturer’s protocol by using RNX-plus solution (Cinnagen, Iran). The quality of the extracted RNA was assessed by NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, USA) and the ratio of absorption (260/280 nm) of all preparations were in an acceptable range.

In order to remove traces of genomic DNA before complementary DNA (cDNA) synthesis, total RNA was treated with DNase I. The cDNA synthesis kit (Thermo Scientific, USA) was used according to the manufacturer’s recommendations. The product was stored at –20°C for further investigations.

Primers based on the sequences of the National Center for Biotechnology Information (NCBI) GenBank database were checked by Genrunner Software (version 3.05). The glycerinaldehyde-3-phosphate dehydrogenase GAPDH gene was used as the reference gene for normalization across samples. Primer sequences of apelin were as follows:

apelin Forward: 5’- TCT GAC CCC CAA AGA TGA TG-3’;
apelin Reverse: 5’- TCT GAC CCC CAA AGA TGA TG-3’;

The Real-Time quantitative PCR (qPCR), carried out using a Real-Time PCR instrument (Rotor-Gene 6000, Sydney, Australia), was performed in 25 μL volumes
containing 12.5 μL 2X SYBR Green Master mix (Thermo Scientific, USA), 0.3 μL forward primers, 0.3 μL reverse primers, 8.9 μL RNase- free water, and 3 μL of the cDNA. For each gene, samples were run in duplicate for inter assay control along with GAPDH (housekeeping) and the non-template control (NTC); qPCR amplification was performed with the following thermal cycling conditions: 5 min at 95 °C for denaturation, followed by 45 cycles at 95 °C for 30 s, 60 °C for 30 s and 72 °C for 30 s for annealing, amplification, and quantification. The relative expression of apelin in each sample was calculated based on its threshold cycle (Ct), normalized to the Ct of the reference gene. All qPCR laboratory procedures were performed according to the MIQE guidelines [17].

Anthropometric and laboratory measurements

Weight was measured in minimum clothing to the precision of 0.1 kg on a SECA digital weighing scale (Seca 707; Seca Corporation, Hanover, Maryland; range 0.1–200 kg), and height was measured to the nearest 0.1 cm while barefoot. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m²). Waist circumference (WC) was measured to the nearest 0.5 cm, using a measuring tape while in standing position and after a gentle respiration, at the level of the umbilicus.

Physical activity was assessed during interviews, using the long forms of the reliable and validated Persian version of the International Physical Activity Questionnaire (IPAQ) [18]. The concept of metabolic equivalents (MET) was used to measure energy expenditure. Low level of physical activity was considered as equivalent metabolic task < 600 min/wk.

Arterial blood pressure (BP) was measured for each participant using a mercury sphygmomanometer. Systolic blood pressure (SBP) was determined by the onset of the tapping Korotkoff sound and diastolic blood pressure (DBP) as the disappearance of this sound. Blood pressure was measured twice, and the average was considered as the participant’s BP.

Blood samples were drawn from all study participants between 7:00 and 9:00 AM after 12–14 h of overnight fasting. All the blood analyses were done at the TLGS research laboratory on the day of blood collection. Fasting plasma glucose (FPG) was measured by the enzymatic colorimetric method using glucose oxidase. Inter- and intra-assay coefficients of variation (CV) were both 1.0% for FPG. Serum triglycerides (TGs) were assayed using an enzymatic colorimetric method with glycerol phosphate oxidase. Inter- and intra-assay CV for TGs were 0.4 and 2.1%, respectively. These analyses were performed using commercial kits (Pars Azmoon, Tehran, Iran) and a Selectra 2 autoanalyzer (Vital Scientific, Spankereen, The Netherlands). Insulin was measured using the enzyme-linked immunosorbent assay (ELISA) with Mercodia kits (Uppsala, Sweden). Inter- and intra-assay CVs of insulin were 1.7 and 2.3, respectively.

Statistical analysis

Normality of variables was tested by the histogram and Kolmogorov-Smirnov test. Because plasma TGs and insulin were skewed, log transformation was used. Quantitative variables were described as mean ± standard deviation (SD) or median with interquartile range, and qualitative variables were reported as percentage. Relative mRNA expression levels were determined for each sample separately using internal reference genes GAPDH with the formula 2^-ΔΔCt, where ΔCt is Ct (target gene) - mean of Ct (reference genes) [19] . In order to adjust energy, we used the residual method for all dietary exposures including total carbohydrate, GI, GL, and food groups. Then, these variables were used for all statistical analysis [20].

The association of apelin gene expression according to tertiles of energy-adjusted dietary GI in visceral and subcutaneous adipose tissues was determined using LSD. The correlation of apelin gene expression in visceral and subcutaneous adipose tissues with energy-adjusted dietary carbohydrate was performed by bivariate correlation. To investigate the trend of variables according to tertiles of GI, the linear regression and chi-square test was used for continuous and categorical variables, respectively. Adjusted linear regression tests were performed in two models (model 1 adjusted for age and sex, and model 2 additionally adjusted for WC) to evaluate possible associations of dietary carbohydrates, GI, GL, and high, medium and low glycemic foods with apelin gene expression. Both unstandardized (95% confidence interval) and standardized β (STZ β) were reported. Before running multivariable linear models, the interaction terms between age, sex and WC, and dietary exposures were examined. No interaction was observed between considered covariates and dietary carbohydrates, GI, GL, and high, medium and low glycemic foods. All data were analyzed using the Statistical Package for Social Sciences program (SPSS) (version 15.0; SPSS Inc., Chicago IL) and P-values < 0.05 were considered statistically significant.

Results

The current study consisted of 102 non-diabetic participants characterized by a mean age of 41.7 ± 14.6 years, and mean BMI of 35.2 ± 10.7 kg/m². The average apelin concentration was 269.6 ± 98.5 (pg/mL). Among participants, 16.3% presented insulin resistance.

The biochemical, anthropometric, and dietary characteristics of participants according to tertiles of dietary GI are summarized in Table 1. Insulin concentration, HOMA-IR, and prevalence of insulin resistance were significantly increased in subjects across the tertiles of dietary GI.
Participants in the highest tertile of dietary GI had more apelin gene expression in visceral and subcutaneous adipose tissue (Fig. 1). No significant differences were observed in mean BMI across dietary GI groups. There was a significant correlation of insulin ($r = 0.201$, $p$-value = 0.043) and HOMA-IR ($r = 0.210$, $P$ value = 0.045) with apelin gene expression only in visceral adipose tissue (data not shown).

Energy-adjusted dietary GI was positively correlated with apelin gene expression in visceral ($r = 0.495$, $P < 0.001$) and subcutaneous ($r = 0.437$, $P < 0.001$) adipose tissues. Furthermore, dietary GI had a significant direct correlation with both visceral ($r = 0.421$, $P < 0.001$) and subcutaneous ($r = 0.262$, $P = 0.008$) apelin gene expression. A positive correlation was also observed between intake of high GI foods and apelin gene expression in both visceral and subcutaneous adipose tissues (Fig. 2).

The association between dietary GI and apelin gene expression remained significant upon adjustment for age, sex and WC in the visceral (STZ $\beta = 0.402$, $P < 0.001$) and subcutaneous (STZ $\beta = 0.477$, $P < 0.001$) adipose tissues. Furthermore, there was a significant positive association between dietary GL and apelin gene expression in both visceral (STZ $\beta = 0.224$, $P = 0.005$) and subcutaneous (STZ $\beta = 0.350$, $P = 0.029$) adipose tissue. After adjusting for confounders, each standard deviation higher intake of foods with higher GI, was directly associated with apelin gene expression in visceral (STZ $\beta = 0.253$, $P = 0.002$) and subcutaneous (STZ $\beta = 0.255$, $P = 0.003$) adipose tissue (Table 2). Foods which were mainly contributed to high GI category including date and Lavash were directly associated with apelin gene expression in both adipose tissues (Additional file 1: Table S2).

### Table 1: Demographic, anthropometric, dietary intake and serum biochemical parameters according to the tertiles of dietary glycemic index

| Dietary glycemic index tertiles | T1 | T2 | T3 | $P$ value$^b$ |
|--------------------------------|----|----|----|--------------|
| Age (years)                    | 43.3 ± 14.4 | 43.4 ± 14.2 | 38.3 ± 14.2 | 0.252        |
| Female (%)                     | 85.3 | 70.6 | 78.8 | 0.514        |
| Low physical activity (%)      | 47.1 | 44.1 | 42.4 | 0.882        |
| Body mass index (kg/m$^2$)     | 33.8 ± 10.7 | 36.6 ± 10.8 | 35.3 ± 10.6 | 0.561        |
| Waist Circumference            | 107.1 ± 22.5 | 113.2 ± 22.0 | 107.6 ± 24.3 | 0.491        |
| Fasting plasma glucose (mg/dl) | 86.7 ± 12.1 | 86.7 ± 10.9 | 87.6 ± 8.3 | 0.925        |
| Insulin (μU/mL)                | 6.0 (4.4–9.8) | 5.8 (3.1–8.1) | 9.4 (5.6–19.6) | 0.007        |
| HOMA-IR                        | 1.74 ± 1.5 | 1.47 ± 1.1 | 3.3 ± 4.3 | 0.012        |
| Insulin resistant (%)           | 11.8 | 5.9 | 22.3 | 0.020        |
| Triglycerides (mg/dl)          | 68.0 (61.7–90.2) | 66.5 (60.2–83.7) | 72.5(65.0–87.5) | 0.463        |
| Apelin (pg/mL)                 | 263.2 ± 68.9 | 244.4 ± 82.6 | 302.6 ± 120.6 | 0.048        |
| Total energy intake (kcal)     | 2778 ± 628 | 2951 ± 849 | 2896 ± 1027 | 0.694        |
| Total carbohydrate (% of energy) | 54.6 ± 6.1 | 57.8 ± 8.2 | 57.7 ± 6.7 | 0.121        |
| Total carbohydrate (g/d)       | 397.9 ± 53.1 | 403.4 ± 53.2 | 421.4 ± 54.9 | 0.181        |
| Dietary glycemic index         | 48.1 ± 5.5 | 56.5 ± 1.7 | 65.7 ± 6.8 | < 0.001      |
| Dietary glycemic load          | 188.8 ± 33.4 | 232.3 ± 40.8 | 275.8 ± 47.5 | < 0.001      |
| High glycemic foods (serv/d)   | 6.9 ± 2.2 | 8.8 ± 3.6 | 11.7 ± 4.1 | < 0.001      |
| Medium glycemic foods (serv/d) | 1.3 ± 0.6 | 0.9 ± 1.9 | 1.1 ± 1.5 | 0.258        |
| Low glycemic foods (serv/d)    | 11.3 ± 4.6 | 11.3 ± 6.0 | 8.4 ± 11.0 | 0.006        |
| Protein (% of energy)           | 14.7 ± 2.8 | 14.2 ± 2.5 | 13.7 ± 2.7 | 0.328        |
| Fat (% of energy)               | 33.6 ± 5.9 | 30.8 ± 6.7 | 30.7 ± 5.1 | 0.090        |

$^a$Data are represented as mean ± standard deviation or median (interquartile range) for continuous variables and percent for categorically distributed variables

$^b$linear regression was used for continuous variables and chi-square test for categorical variables

The residual model was used to adjust total energy intake for dietary exposures

**Discussion**

In the present study, dietary GI and dietary GL were directly associated with the apelin gene expression in both visceral and subcutaneous adipose tissue after controlling for age, sex, and WC. Moreover, habitual intake of high GI food had a positive association with subcutaneous and visceral apelin gene expression; per 3.9 serv/d increase in intake of high GI foods, apelin gene expression in subcutaneous and visceral adipose tissues increased 0.253 and 0.255 unit, respectively.
To the best of our knowledge, this was the first study which focused on the association of dietary quality and quantity of carbohydrate with apelin gene expression in human fat depots. However, a number of studies have investigated the relationship between different feeding patterns and apelin concentration and gene expression in both human and animals [13, 21–23]. In interventional studies, a caloric-restricted diet could decrease both the apelin concentration and gene expression in human [13, 21]. Castan laurel et al., have found that 12 weeks hypocaloric weight-reducing diet in 20 obese women was associated with increased plasma and adipose tissue expression of apelin gene [21]. Nevertheless, Celik et al., found that Ramadan fasting did not affect the apelin concentration in healthy men [22]. Moreover, apelin gene expression increased in the subcutaneous adipose tissue in response to a high-fat diet in rats [23]. It seems that the results of these studies are inconsistent and most of them had focused on the restricted calorie intakes and dietary fatty acids, and none of them had considered the dietary carbohydrate content as a probable factor which affects apelin concentration and gene expression.

Carbohydrates are the primary nutrient contributing to the supply of energy requirements; constituting 45–65% of the energy intake in a regular diet. It should be noted that dietary GI and GL imply some other aspects of dietary quality, which can partly reflect dietary characteristics. It is possible that higher carbohydrate intake may be substituted with dietary fat or protein while maintaining a constant energy intake [24]. Therefore, dietary composition might be a factor which can influence adiposities. An interesting point of our study was that carbohydrate quality, not total carbohydrate intake, was significantly associated with apelin gene expression, and emphasizing the importance of food quality instead of quantity.

The GI and GL represent different aspects of this macronutrient and are used to characterize the capability of food increasing serum glucose concentrations [25]. Foods with a relatively high GI can potentially affect body composition [26], and impact on specific metabolic processes, (such as lipolysis and lipogenesis) by increasing insulin to a greater extent or for a longer time [27, 28]. In the current study, we observed that high dietary GI foods had a positive relationship with apelin gene expression in both adipose tissues. Physiological alteration in response to low GI against high GI dietary intervention indicated that white adipose tissue gene expression was altered in pathways involving insulin sensitivity and fatty acid metabolism [28]. Furthermore, it was revealed that peroxisome proliferator-activated receptor-gamma (PPAR-γ), an important transcription factor in the regulation of apelin [29], showed an increase with high GI diet [28].

Although none of the participants in the current study had diabetes, by increasing the tertiles of dietary GI, insulin resistance significantly increased in the study population. Evidence showed that insulin resistance induced by a high-fat diet caused an increase in both apelin concentration and gene expression in adipose tissues [14, 30]. Moreover, apelin concentration and gene expression in mice...
Fig. 2 Correlation between apelin gene expression in visceral and subcutaneous adipose tissues and energy-adjusted dietary carbohydrate intake throughout the study participants.
has been reported to be regulated according to the severity of insulin resistance, suggesting a link between apelin and glucose homeostasis [31]. Dray et al. have shown that exogenous glucose promotes the luminal secretion of apelin, when administered to mice by gavage [32]. Regular consumption of meals with high GI increased 24-h blood glucose and insulin levels [33]. Since apelin concentration might be regulated by insulin concentration, dietary factors which influence glucose homeostasis can up-regulate apelin gene expression.

Our study has some limitations. Because of the cross-sectional design of the study, we could not assess the causality of the study. However, as it is less likely that apelin gene expression in fat depots influences the quality and quantity of carbohydrate intakes, we consider our inference that carbohydrate intakes may have primary effects on apelin gene expression plausible. Secondly, since there was no complete Iranian FCT, we had to use the USDA FCT. Third, another limitation of this study was the non-random selection of participants. Therefore, the results may not be representative of the population. The nature of the non-random sample in our study may also lead to a selection bias which warrants caution in interpreting the results. Presence of convenience sampling can prevent generalization of the findings to the broader population and become less representative of the intended population as time goes on. In order to be comparable and generalizable, the findings in future studies must consider recruitment of samples. Fourth, despite controlling critical potential confounders, several other confounders may still affect the association between dietary carbohydrate intake and apelin gene expression. This study also has its strength; it was the first study to provide data on dietary GI and its association with apelin gene expression. Also, the observational design of the current study reflected long-term habitual high GI food on apelin gene expression.

**Conclusion**

In conclusion, dietary GI and GL, not total carbohydrate intake, was associated with apelin gene expression in both visceral and subcutaneous adipose tissues. Future studies are warranted to illustrate the chronic and accurate effect of carbohydrate quality on apelin homeostasis.

**Additional file**

Additional file 1: Table S1. Foods contributed to making up different glycemic categories. Table S2. Foods substantially contributed to each GI category and apelin gene expression in adipose tissues. (DOCX 17 kb)
Abbreviations
BMI: body mass index; BP: blood pressure; CV: coefficients of variation; DBP: diastolic blood pressure; ELISA: enzyme-linked immunosorbent assay; FCT: food composition tables; FFQ: food frequency questionnaire; FPG: Fasting plasma glucose; GI: glycemic index; GL: glycemic load; IPAC: International Physical Activity Questionnaire; MET: metabolic equivalents task; SBP: Systolic blood pressure; SD: standard deviation; SPSS: Statistical Package for the Social Sciences program; STZ: β standardized; TGS: triglycerides; USDA: US Department of Agriculture; WC: waist circumference

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Authors’ contributions
E.Y. conceptualized and designed the study, gathered adipose tissue, performed RNA extraction and Real-time PCR, analyzed and interpreted the data, prepared the manuscript and approved the final manuscript as submitted. A.G. entered data, drafted the initial manuscript, and approved the final manuscript as submitted. M.A. analyzed and interpreted the data, prepared the manuscript and approved the final manuscript as submitted. M.H. supervised the project, consulted lab protocol, and approved the final manuscript as submitted. M.Z. prepared the lab materials; cDNA synthesized, prepared the manuscript and approved the final manuscript as submitted. P.M. drafted the initial manuscript and approved the final manuscript as submitted. A.Rh. biopsied the patients during the abdominal surgery and approved the final manuscript as submitted.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
The design of this study was approved by the institutional ethics committee of the Research Institute for Endocrine Sciences, affiliated to the Shahid Beheshti University of Medical Sciences, and a written informed consent was obtained from participants.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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