Association between Healthy Eating Index-2010 and Fetuin-A Levels in Patients with Type 2 Diabetes: a Case-Control Study

Farzad Roshanzamir, Maryam Miraghajani, Marjan Mansourian, Reza Ghiasvand, Seyyed Morteza Safavi

1Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan 81746-73461, Iran
2Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3Department of Biostatistics and Epidemiology, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

The Healthy Eating Index-2010 (HEI-2010) assesses compliance with the 2010 Dietary Guidelines for Americans. Studies suggest that adherence to the HEI-2010 is related to lower the risk of type 2 diabetes (T2D). Fetuin-A, a novel biomarker for T2D, may play a linking role in the inverse association between HEI-2010 and T2D. Thus, a case-control analysis involving 107 patients with T2D and 107 healthy subjects was conducted to determine the association between HEI-2010 and serum fetuin-A levels. The results of simple regression analysis showed that fetuin-A levels were positively associated with full name of body mass index (BMI) (p < 0.001), waist circumference (WC) (p < 0.001), fasting blood glucose (FBG) (p < 0.001), triglycerides (TG) (p = 0.003), gamma-glutamyl transferase (GGT) (p < 0.001), and homeostasis model assessment of insulin resistance (HOMA-IR) (p = 0.001) and negatively associated with physical activity (PA) (p < 0.001), high-density lipoprotein (HDL) (p = 0.022), and HEI-2010 (p < 0.001) in all subjects. After controlling for confounders, the inverse association between fetuin-A and HEI-2010 remained significant in the subjects with T2D (β = −0.386; p < 0.001), 107 healthy controls (β = −0.237; p = 0.028), and all subjects (β = −0.298; p < 0.001). In conclusion, the present results suggested that higher quality diet assessed by HEI-2010 associates with lower serum fetuin-A levels in people with and without T2D. More studies are needed to confirm these findings.

Keywords: Healthy eating index-2010; Fetuin-A; Type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D), characterized by insulin resistance and pancreatic beta-cell dysfunction, is one of the most common chronic diseases globally [1]. Impaired insulin secretion and/or action in T2D lead to multiple metabolic abnormalities such as hyperglycemia and dyslipidemia, which can further insulin resistance and cause tissue damage [2]. Although, the pathogenesis underlying T2D development is complex, the commonly known factors for T2D include genetic background, obesity, advanced age, physical inactivity, and unhealthy diet [3].
Healthy dietary patterns characterized by high intake of whole grains, fruits and vegetables, nuts and a moderate consumption of alcohol and low intake of refined grains, processed and unprocessed red meats, and sugar-sweetened beverages are associated with the reduced risk of T2D [4]. Diet quality scores developed on the bases of dietary recommendations and available evidence of the diseases are design to evaluate compliance to healthy dietary guidelines. In epidemiology studies, adherence to high-quality diets is associated with a lower incidence of T2D [5]. Evidence suggests that higher dietary quality may reduce risk of T2D through increasing insulin sensitivity by modulating some circulating biomarkers involved in the insulin secretion and/or action [4,5].

Fetuin-A, as a novel biomarker for T2D, is synthesized predominantly by hepatocytes and secreted into blood [6,7]. Fetuin-A induces insulin resistance through several mechanisms such as inhibition of insulin receptor tyrosine kinase activity, reduction of adiponectin expression, and increase of inflammatory cytokines in the liver and muscle [8-10]. Cross-sectional studies have reported that higher fetuin-A level is associated with some chronic disorders including obesity, metabolic syndrome, cardiovascular disease, fatty liver disease, and T2D [11]. Also, previous studies demonstrated that dietary factors may influence circulating fetuin-A levels [12]. In the Nurses’ Health Study, alcohol consumption was associated with lower plasma fetuin-A, and fetuin-A partly explained the association between alcohol consumption and the incidence of T2D [13].

To our knowledge, there is no study to investigate the association of dietary quality scores and fetuin-A levels in T2D patients. Therefore, in the present case-control study, we evaluated the association between diet quality score as measured by Healthy Eating Index-2010 (HEI-2010) and circulating fetuin-A levels among patients with T2D and healthy subjects.

**MATERIALS AND METHODS**

**Participants**

This case-control study was conducted in the Diabetic Clinic at Shariati Hospital in Fasa, Iran in 2017. The study was approved by the Research Council (research project number: 1395.226) and Ethical Committee of the School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran (research ethics number: IR.MUI.REC IR.MUI.REC1395.3.226). The written informed consent was obtained from all participants prior to participation in the study.

Subjects including 107 patients with T2D and 107 healthy controls were selected by the convenience non-random sampling method. Patients were eligible if they were diagnosed with T2D according to the American Diabetic Association criteria [14] with a fasting glucose level ≥ 126 mg/dL or a 2-hour postchallenge glucose level ≥ 200 mg/dL. People with fasting glucose level < 100 mg/dL, 2-hour postchallenge glucose level < 140 mg/dL, and normal control subjects were included according to the homeostasis model assessment of insulin resistance (HOMA-IR) < 2.

Major exclusion criteria were age < 45 or > 60 years, use of insulin or sulfonylureas, pregnancy or lactation, alcohol consumption, smoking, total daily energy intake outside the range of 800–4,200 kcal, changes in diet within past 6 months and any medical condition such as other types of diabetes, macrovascular or microvascular complications, thyroid dysfunction, malignant tumor, acute infection, and immune suppression.
Assessment of dietary intake

A validated food frequency questionnaire (FFQ) [15] was used to assess the usual intake of 168 commonly consumed food items and beverages over the previous year. These food items in FFQ had been categorized into 7 food groups and 9 different frequency categories for each item ranging from “less than once per month” to “6 or more times per day”. The standardized portion-size pictures were used to ask about the amount of food consumption. Portion sizes of consumed foods were converted to grams using household measures [16].

The daily energy and nutrient intake were calculated by summing up the energy and nutrient content of each food item using Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA) whose nutrient database was based on the United States Department of Agriculture food composition table modified for Iranian foods. All FFQs were administered by a trained dietitian.

Assessment of dietary quality

All served nutrients were assessed based on the HEI-2010. This index was designed based on the original HEI score which assesses compliance with the 2010 Dietary Guidelines for Americans [16]. The HEI-2010 has 12 food components, 9 adequacy components with higher scores indicating higher consumption and 3 moderation components with higher scores indicating lower consumption. The adequacy components include: total fruit (5 points); whole fruit (5 points); total vegetables (5 points); greens and beans (5 points); whole grains (10 points); dairy (10 points); total protein foods (5 points); seafood and plant proteins (5 points); and fatty acids ([polyunsaturated fatty acids + monounsaturated fatty acids]:saturated fatty acids) (10 points). The moderation components that should be served in moderation include: refined grains (10 points); sodium (10 points); and empty calories (solid fats, alcoholic beverages, and added sugars) (20 points). The mentioned scores were adjusted for energy (per 1,000 kcal or as a percentage of energy) except for the fatty acids ratio. The total HEI-2010 score which has a maximum value of 100 is a sum of all components, with higher total scores reflecting better diet quality [16].

Assessment of biomarkers

Blood samples were taken from fasting participants and collected into a vacuum tube without an anticoagulant with gel (Vacutest Kima, Arzergande, Italy). To separate serum, tubes were immediately centrifuged at 3,000 rpm for 10 minutes after clotting at room temperature. Routine biochemical parameters were measured at the same day. To later determination of fetuin-A and insulin levels, serum was frozen in aliquots at −70°C.

Glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and aspartate aminotransferase (AST) were measured according to the standard commercial methods (Pars Azmoon, Tehran, Iran) and the Hitachi 717 analyzer (Boehringer Mannheim, Mannheim, Germany). The intra- and inter-assay coefficient of variation (CV) of all assays was < 5%. Furthermore, the levels of serum fetuin-A (ZellBio GmbH, Ulm, Germany; intra-assay CV < 10%, inter-assay CV < 12%, sensitivity 5 mg/L) and insulin (Monobind, Lake Forest, CA, USA; intra-assay CV < 8%, inter-assay CV < 9.8%, sensitivity 0.75 µIU/ml) were assessed by commercial enzyme-linked immunosorbent assay (ELISA) method. Ten percent of samples were analyzed in duplicate. All biochemical parameters were measured in one laboratory and laboratory staff was unaware of the case and control groups.
The Friedewald’s formula; low-density lipoprotein (LDL) = (TC − HDL) − TG/5 was used to determine LDL level [17]. HOMA-IR was estimated by the following equation: HOMA-IR = fasting insulin (µU/mL) × fasting glucose (mg/dL)/405 [18].

**Assessment of other variables**

Required information on sex, age, medical history, and physical activity (PA) was collected by the use of questionnaires. PA was also assessed with the short version of the international physical activity questionnaire (IPAQ) and expressed as metabolic equivalent (MET)-h/wk [19]. In addition, anthropometric measurements including height, body weight, and waist circumference (WC) were gathered following an overnight fasting by a trained dietician, while participants were wearing light indoor clothing without shoes. Height was recorded to the nearest 0.1 cm with a stadiometer (Seca, Hamburg, Germany). Weight was measured to the nearest 0.1 kg with Tanita BC 418 MA (Tanita Corporation, Tokyo, Japan). Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²) [20]. WC was measured at the superior border of iliac crest [21].

**Statistical methods**

Quantitative data were expressed as mean ± standard deviation and categorical variable were summarized as percentage. Normality of the variables was checked by Kolmogorov-Smirnov test. Logarithmic transformation was used to improve normality in non-normally distributed continuous variables. Independent sample t-test and chi-square were variables applied to compare continuous and categorical variables, respectively. When data was not normally distributed, Mann-Whitney U-test for continuous variables and fisher's exact test for categorical variables were used to assess differences between the 2 groups. To explore association between fetuin-A and HEI-2010 linear regression analysis was performed. Estimates were presented in 4 models; the first model was adjusted for age and gender. Further adjustment for PA and energy intake was included in the model 2. We also applied additional adjustment for BMI and WC (model 3) and for HOMA-IR, TG, TC, HDL, LDL, AST, ALT, and GGT (model 4). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL, USA). All p-values were two-tailed and values of < 0.05 were considered to be statistically significant.

**RESULTS**

Table 1 shows the general characteristics of participants including 76 (30.8%) male and 148 (69.2%) female, whose average age was 53.3 years. The majority of the participants were overweight and obese (BMI ≥ 25 kg/m²) with an average BMI of 28.4 kg/m². The mean levels of serum fetuin-A in the whole participants were 370.37 µg/mL. The levels of feruin-A in patients with T2D and in control groups were 386.45 and 355.08 µg/mL, respectively. The mean HEI-2010 of the subjects was 67.76.

There were no significant differences in age, gender, BMI, WC, PA, HDL, GGT, AST, and HEI-2010 between the 2 groups. The participants with T2D had higher fasting blood glucose (FBG) (p < 0.001), HOMA-IR (p < 0.001), TG (p = 0.018), TC (p = 0.006), LDL (p = 0.038), and fetuin-A (p = 0.013) than the control subjects.
The results of simple regression analysis showed that fetuin-A levels is positively associated with BMI ($\beta = 0.264$; $p < 0.001$), WC ($\beta = 0.297$; $p < 0.001$), FBG ($\beta = 0.306$; $p < 0.001$), TG ($\beta = 0.210$; $p = 0.003$), GGT ($\beta = 0.270$; $p < 0.001$), and HOMA-IR ($\beta = 0.240$; $p = 0.001$) but negatively associated with PA ($\beta = -0.297$; $p < 0.001$), HDL ($\beta = -0.162$; $p = 0.022$), and HEI-2010 ($\beta = -0.282$; $p < 0.001$) in the whole subjects (Table 2).

The results of multiple regression analysis are shown in Table 3. After controlling for confounders, the inverse association between fetuin-A and HEI-2010 remained significant in the subjects with T2D ($\beta = -0.386$; $p < 0.001$), 107 healthy controls ($\beta = -0.237$; $p = 0.028$), and whole subjects ($\beta = -0.298$; $p < 0.001$).
In this study, we found that fetuin-A level was significantly higher in T2D patients than healthy controls. Furthermore, higher HEI-2010 scores were associated with lower serum fetuin-A level. Our study also showed a significant positive association between fetuin-A and insulin resistance, as assessed by HOMA-IR. Previous research has reported that fetuin-A is involved in insulin resistance, a primary abnormality leading to the development of T2D [22,23]. Fetuin-A impaired insulin signaling and reduced insulin sensitivity by inhibiting insulin receptor tyrosine kinase activity through blocking the autophosphorylation of tyrosine kinase and insulin receptor substrate-1 (IRS-1) [23]. Although, some epidemiological studies have shown that fetuin-A is associated with insulin resistance and incidence of T2D [24,25], a meta-analysis of observational studies reported that mean levels of fetuin-A in patients with T2D were prominently higher than those in healthy subjects [7]. The findings of the present study also demonstrated that diabetic patients had a significantly high level of fetuin-A. However, our results are inconsistent with Axelsson’s study, which showed that fetuin-A levels were significantly lower in T2D as compared to non-diabetic subjects [26]. Similarly, studies by Kim et al. [27] and Scialla et al. [28] also reported that subjects with T2D had significantly lower fetuin-A level than normal subjects. The reasons for the discrepancies may be due to all patients in these studies suffer from chronic kidney disease (CKD). Since fetuin-A inhibits ectopic calcification that associates with vascular disorders, the levels of fetuin-A were low in patients with CKD [29]. In line with several studies, in this study there was a significant association between fetuin-A and several components of metabolic disorders including BMI, WC, FBG, HDL, and TG [30]. Fetuin-A may contribute to the metabolic disorders through promotion insulin resistance and inflammation, which have a central role in the pathophysiology of metabolic disorders [31]. Fetuin-A reduces production of adiponectin, an anti-inflammatory adipokine acting as an insulin sensitizer [32]. Moreover, the genes encoding fetuin-A and adiponectin are located on chromosome 3q27 which is a metabolic syndrome and T2D-susceptibility locus [33]. Fetuin-A was positively correlated with the expression several key enzymes in glucose and lipid metabolism such as phosphoenolpyruvate carboxykinase 1 (PKC1) and sterol regulatory element-binding protein 1c (SREBP-1c) [34]. In vitro studies have shown high levels of glucose and fructose increase fetuin-A expression through activation of the extracellular signal-

### Table 3. Multiple linear regression models for the relationships between fetuin-A and HEI-2010

| HEI-2010 | All (n = 214) Fetuin-A | Cases (n = 107) Fetuin-A | Controls (n = 107) Fetuin-A |
|----------|------------------------|--------------------------|-----------------------------|
| Model 1* | β = -0.296 p < 0.001   | β = -0.355 p < 0.001    | β = -0.275 p = 0.006        |
| Model 2† | β = -0.276 p < 0.001   | β = -0.355 p < 0.001    | β = -0.221 p = 0.025        |
| Model 3‡ | β = -0.286 p < 0.001   | β = -0.385 p < 0.001    | β = -0.192 p = 0.044        |
| Model 4§ | β = -0.298 p < 0.001   | β = -0.386 p < 0.001    | β = -0.237 p = 0.028        |

Dependent variable: serum fetuin-A levels, independent variable: HEI-2010. HEI-2010, Healthy Eating Index-2010; PA, physical activity; BMI, body mass index; WC, waist circumference; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase.

*Model 1, adjusted for age and gender; †Model 2, further adjusted for PA and energy intake; ‡Model 3, further adjusted for BMI and WC; §Model 4, further adjusted for HOMA-IR, TG, TC, HDL, LDL, ALT, and GGT.
regulated kinase 1/2 (ERK1/2) [35] as well as saturated free fatty acids [9]. These conditions related to insulin resistance, diabetes, and metabolic syndrome [34].

In present study, we observed that higher HEI-2010 score was associated with lower fetuin-A level. There is only little data about the relation between dietary factors and level of fetuin-A [12]. In a cross-sectional analysis among 2,198 individuals from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, red meat or whole-grain bread consumption was not associated with plasma levels of fetuin-A [36]. In another cross-sectional study, fetuin-A was not associated with total energy or specific macronutrient intake [12].

Among diabetes-free women from the Nurses’ Health Study, alcohol consumption was associated with lower plasma fetuin-A, and fetuin-A partly explained the association between alcohol consumption and incidence of T2D [13]. In a long-term dietary weight loss intervention, despite the partial regain in mean body weight, mediterranean-style diet was effective in reducing fetuin-A levels in both people with T2D and nondiabetics [37]. To the best of our knowledge, the current study is the first report to demonstrate an association of diet quality assessed by the HEI-2010 and fetuin-A levels.

There are some limitations in this study. First, as this is a cross-sectional study, the causal relationship cannot be established. Second, we were not examined the effects of important adipokines and cytokines (eg, adiponectin and C-reactive protein) on fetuin-A and T2D. Third, the subjects were recruited from one ethnic group and the sample size was small, thus making it difficult to generalize the findings of this study. Forth, we cannot adjust for all confounding factors.

Despite these limitations, our study has strengths. This study may be the first study to investigate the associations between HEI-2010 and fetuin-A levels. We also used a validated-FFQ to investigate dietary intakes. Furthermore, there was no significant difference in age, gender, PA, and BMI between the participants with T2D and the control group.

In conclusion, the present results showed that higher quality diet assessed by HEI-2010 associates with lower serum fetuin-A levels in people with and without T2D. More studies are needed to confirm these finding.

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