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The association between dietary acid load and indices of insulin resistance

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The role of diet-induced acid-base imbalance in insulin resistance (IR) and related cardiometabolic abnormalities has attracted considerable attention. This study sought to investigate the association between dietary acid load and IR indices among Iranian adults. The study included 6,531 participants, with dietary acid load estimated using a validated questionnaire which comprised 65 food frequency items. The IR indices assessed included: Triglyceride to high-density lipoprotein (TG: HDL), Metabolic score for insulin resistance (METS-IR), Triglyceride Glucose-Body mass index (TyG-BMI), Triglyceride glucose (TyG), and Triglyceride glucose-waist circumference (TyG-WC). The results revealed that all IR indices were significantly higher in participants positioned in the top tertiles of dietary acid load as opposed to those in the lowest, with a notable increasing trend ($p < 0.001$). Using a crude model, there was a significant positive association between TG: HDL, TyG, TyG-WC, TyG-BMI, and METS-IR with dietary acid load ($p < 0.001$). However, in the fully adjusted model, only TyG and TyG-WC remained significant (OR=1.16, 95% CI: 1.04-1.30, and OR=1.69, 95% CI: 1.51-1.90, respectively). In summary dietary acid load is significantly associated with IR indices, with TyG-WC showing the strongest relationship.

Keywords Dietary acid load, Insulin resistance, TyG Index, Glycemic control

Abbreviations

DAL	Dietary acid load
PRAL	Potential renal acid load
NEAP	Net endogenous acid production
FFQ	Food frequency questionnaire
FBG	Fasting blood glucose
IR	Insulin resistance
TG/HDL-C	Triglyceride-to-high-density-lipoprotein-cholesterol
METS-IR	Metabolic score for insulin resistance
TyG	Triglyceride glucose
TyG-WC	Triglyceride glucose-waist circumference
TyG-BMI	Triglyceride glucose- Body mass index
HC	Hip circumference
ANOVA	One-way analysis of variance
PAL	Physical activity level
BMR	Basal metabolic rate
TEE	Total energy expenditure
IEI	Integrated energy index
QUICKI	Quantitative insulin sensitivity check index

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HOMA-IR Homeostatic model assessment of insulin Resistance

Background

Insulin resistance (IR) contributes to the development of chronic diseases, that include: metabolic syndrome (MetS), diabetes mellitus and cardiovascular diseases (CVDs). These conditions account for over 41 million deaths each year, representing 71% of global mortality[1]. Lifestyle choices are considered significant modifiable risk factors for IR. These include decreased physical activity, tobacco use, and dietary habits. Notably, diet has an especially significant role in IR[2,3]. The body's acid-base balance has been related to the progression of IR and related metabolic disorders[4].

The buffering system in healthy human bodies maintains acid-base balance with the assistance of organs such as the lungs and kidneys[5]. Previous research has highlighted diet as a major factor influencing body acidity[6]. Specifically, western-style diets, characterized by low fruit consumption and vegetable intake (alkalizing foods) and high consumption of acidogenic foods like products of processed wheat and meat[7,8]. The common indices applied in the estimation of dietary acid load include Potential Renal Acid Load (PRAL), Dietary Acid Load (DAL), and Net Endogenous Acid Production (NEAP). NEAP only considers protein and potassium intake, while DAL and PRAL consider additional nutrients like calcium, phosphorus, and magnesium, offering a more comprehensive assessment[9]. Increasing in the dietary acid load suggest a tendency toward acid-forming potential of diet[10].

Previous research has shown higher dietary acid load is associated with adverse metabolic conditions such as central obesity[11], high blood pressure[12], and disordered lipid profiles[13]. Recent studies have further highlighted an association between DAL and IR, suggesting that a higher DAL may increase the risk of IR[4,14].

To assess IR, different methods are available. While the euglycemic clamp method is considered the gold standard, its invasive nature, cost, and complexity limit its use for large scale studies[15]. Alternative insulin-based measures, such as the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) are routinely used. Nevertheless, these methods are unsuitable for diagnosing individuals already undergoing insulin treatment, and circulating insulin concentrations are not routinely measured by laboratories[15]. As a result, simpler, non-insulin-based indices have become popular in epidemiological research for assessing IR. Several studies have demonstrated that these indices are not only reliable for evaluating IR, but also show strong correlations with the euglycemic clamp method, having been validated across various populations[15–17]. Furthermore, by incorporating both biochemical and anthropometric factors, they are well-suited for large-scale epidemiological studies[18].

In the last few years, interest has grown into how disturbances in acid-base homeostasis resulting from diet, affect health[19]. Although previous research has examined the association between DAL and IR, especially in Western and East Asian populations[6,20], there is a lack of data on how these relationships appear in Middle Eastern populations, which follow distinct dietary habits. This study aims to fill that gap by exploring the relationship between DAL and IR indices within a large cohort of Iranian adults.

Methods

Study design and population

This cross-sectional study included 6531 participants from the MASHAD cohort, which has a total sample size of 9704. The cohort was chosen for its large and diverse population. Participants aged 35 to 65, were recruited between 2010 and 2016 through a stratified cluster random sampling method. The details have been previously explained[21]. We excluded pregnant and lactating women, individuals without dietary intake data, those who over-reported energy intake (> 4,200 kcal), and those who under-reported energy intake (< 800 kcal). All participants gave informed consent. The Ethics Committee of Mashhad University of Medical Sciences (MUMS) approved the study.

Dietary assessment and definition of DAL

Dietary intake was evaluated by means of a reliable and validated food frequency questionnaire (FFQ) that included 65 food items[22]. Details of dietary assessment is previously described[23,24]. To evaluate dietary acid load, the DAL score was calculated based on nutrient intake equations, as outlined below:

- DAL (mEq/day) = [(body surface area [m2] × 41 [mEq/day]/ 1.73 m2 + PRAL][25],
- PRAL (mEq/day) = (0.4888 × protein [g/day]) + (0.0366 × phosphorus [mg/day]) − (0.0205 × potassium [mg/day]) − (0.0263 × magnesium [mg/day]) − (0.0125 × calcium [mg/day])[26],
- Body surface area = 0.007184 × height$^{0.725}$ × weight$^{0.425}$[27,28].

Insulin resistance criteria

Non-insulin-based IR indices, including TG/HDL-C ratio, TyG index, TyG-BMI, TyG-WC, and METS-IR were used to determine IR as follows[29]:

- TG: HDL = triglycerides (mg/dL) / HDL (mg/dL)
- TyG = Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]
- TyG-WC = TyG index × WC
- TyG-BMI = TyG index × BMI
- METS-IR= (ln ((2 × FPG) + TG) × BMI)/ (ln (HDL))

Biochemical measurements

Blood samples of all the participants were collected in 2010 and analyzed for fasting plasma glucose (FPG), triglycerides (TG), and high-density lipoprotein (HDL) after fasting for 14-hrs overnight. Details of biochemical measurements are previously published[21,23]. All samples were stored at -80 °C until analysis, which was carried out simultaneously for all specimens.

Anthropometric assessments

For all participants, weight (kg), height (cm), body mass index (BMI), waist circumference (WC) (cm), hip circumference (HC) (cm), and waist-to-hip ratio (WHR) were measured according to standardized protocols as previously described[21].

Assessment of physical activity level (PAL)

To assess the activity levels of participants in the study, a selection of questions from the Scottish Heart Health Study (SHHS)/MONICA questionnaire was used[30]. The questions were divided into three distinct categories: activities during work, leisure time, and time spent in bed. Detailed description of PAL assessment is previously reported[31].

Statistical analysis

Data were analyzed using SPSS version 20 (SPSS Inc., IL, USA). Continuous variables are presented as the mean ± standard deviation (SD), while categorical variables were shown as numbers and percentages. Participants' characteristics were assessed according to DAL tertiles using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test for categorical variables. All analyses were two-sided, with statistical significance defined as a P-value < 0.05. Multivariable ordinal logistic regression was employed to examine the association between DAL and IR indices. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for both the crude model and multivariable-adjusted models. Model 1 was adjusted for age (continuous) and sex (male/female). The fully adjusted model further accounted for BMI (continuous), energy intake (continuous), education level (university graduate), smoking status (current/ex-/non-smoker), PAL (continuous), chronic diseases (such as diabetes, hypertension, or dyslipidemia), and marital status (single, married). The tertiles of each outcome variable were treated as ordinal variables.

Results

The study involved 6,531 participants (39.69% male) with an average age of 48.44 ± 8.20 years. The mean DAL score was 36.19 ± 14.24, and the mean BMI was 27.98 ± 4.73. Table 1 presents the baseline characteristics of participants and their IR indices across tertiles of DAL. Compared to those in the lowest tertile of DAL, individuals with higher DAL scores were more likely to be male, younger, and had higher BMI and WHR, as well as lower levels of physical activity. Additionally, all IR indices were significantly higher in the highest tertile of DAL compared to the lowest, with a significant increasing trend ($P < 0.001$).

Table 2 shows the average dietary intakes of participants by the tertiles of DAL. Those in the highest tertile of DAL had higher intakes of energy, protein, fat, phosphate, and calcium, and lower intakes of carbohydrates, fiber, and magnesium compared to the ones in the lowest three category (all $P < 0.01$). Diets linked to a high acid load featured increased intake of grains and meats, and reduced intake of vegetables, fruits, and dairy products (all $P < 0.001$).

The association between DAL and IR indices is shown in Table 3. Higher DAL levels were associated with an increased risk of IR, as indicated by TG: HDL, TyG, TyG-WC, TyG-BMI, and METS. After adjusting for age and sex, this association remained significant in Model 1(OR (95% CI) = 1.31 (1.18–1.47), 1.37 (1.23–1.53), 2.17 (1.94–2.42), and 1.49 (1.34–1.66), respectively). In the model which was fully adjusted, however, higher DAL levels were only associated with an increase in TyG and TyG-WC (OR = 1.16, 95% CI: 1.04–1.30, and OR = 1.69, 95% CI: 1.51–1.90, respectively).

The Ptrend values for TG: HDL, TyG, TyG-WC, TyG-BMI, and METS-IR were significant in both the crude and Model 1 analyses (all P-trend < 0.001). In the fully adjusted model, TyG (Ptrend = 0.01) and TyG-WC (Ptrend < 0.001) also showed significant results. This suggests a consistent and statistically significant trend, where higher DAL is linked to worsening IR as measured by these indices.

Discussion

In this population-based study, we investigate the relationship between DAL and IR indices among an Iranian population. We assessed the acid load of participants' diets using the DAL score. This index measures the intake of acid-forming and base-forming nutrients, including potassium, magnesium, phosphorus, calcium, and protein[25]. The study's results indicated that people in the highest tertiles of DAL scores had TyG and TyG-WC levels that were 1.16 and 1.69 times higher, respectively, as opposed to those in the lowest tertile. Additionally, the study came to the conclusion that participants eating more alkaline diets consumed greater amounts of vegetables, fruits, dietary fiber, and milk-based items than those with more acidic diets. This finding supports previous research showing that a higher intake of fruits and vegetables, known to be more alkalizing, is associated with a lower risk[32].

Our results align with previous studies reporting a significant link between DAL scores and increased IR risk. An Iranian prospective cohort study found that a higher DAL might be a contributing factor to the development of IR[14]. Similarly, other studies carried out in Japan[4] and Denmark[33] showed an association between DAL and HOMA-IR scores, a widely used marker of IR. However, contrary to our results, a study carried out in Sweden

Variables	T1 (*n* = 2177)	T2 (*n* = 2177)	T3 (*n* = 2177)	*p*-value	*p*-trend
DAL, mEq/day	21.13 ± 10.53	36.95 ± 2.99	50.37 ± 7.73	< 0.001	< 0.001
Age, year	49.04 ± 8.24	48.41 ± 8.25	47.90 ± 8.06	< 0.001	< 0.001
Gender, n (%)				< 0.001	-
Male	650 (29.86)	810 (37.21)	1132 (52)		
Female	1527(70.14)	1367(62.80)	1045(48.41)		
BMI, kg/m^2	27.43 ± 4.65	27.81 ± 4.67	28.70 ± 4.77	< 0.001	< 0.001
Waist to Hip ratio	0.91 ± 0.09	0.91 ± 0.08	0.92 ± 0.08	< 0.001	< 0.001
Marital status, n (%)				< 0.001	-
Single	21(00.96)	6(00.27)	15(00.68)		
Married	2012(92.42)	2008(92.23)	2053(94.30)		
Divorced	23(1.5)	43(1.97)	24(1.10)		
Widow	121(5.55)	120(5.51)	85(3.90)		
Education level, n (%)				0.93	-
University	142(6.66)	140(6.56)	148(6.84)		
Graduated	1990(93.33)	1994(93.43)	2014(93.15)		
Smoking status, n (%)				< 0.001	-
Current smoker	418(19.20)	438(20.12)	509(23.38)		
Ex-smoker	196(9.00)	190(8.73)	259(11.90)		
None smoker	1563(71.80)	1549(71.52)	1409(64.72)		
PAL	1.68 ± 0.28	1.61 ± 0.28	1.52 ± 0.29	< 0.001	< 0.001
Chronic disease, n (%)				0.270	-
Yes	221(10.22)	211(9.73)	190(8.80)		
No	1941(89.77)	1957(90.27)	1970(91.20)		
TG_HDL	3.44 ± 2.73	3.61 ± 2.83	3.76 ± 2.77	< 0.001	< 0.001
TyG	8.57 ± 0.67	8.60 ± 0.64	8.64 ± 0.63	< 0.001	< 0.001
TyG-WC	795.52 ± 135.75	814.47 ± 134.58	845.17 ± 131.63	< 0.001	< 0.001
TyG-BMI	235.88 ± 47.61	240.27 ± 47.89	248.65 ± 48.52	< 0.001	< 0.001
METS-IR	42.06 ± 8.64	43.01 ± 8.80	44.71 ± 8.80	< 0.001	< 0.001

Table 1. Baseline characteristics of study participants by DAL categories. Variables are presented as mean ± SD. ANOVA used to compare means that significance is determined by P-values < 0.05. BMI, body mass index; DAL, dietary acid load; PAL, physical activity level; TyG, triglyceride glucose; TyG-WC, triglyceride glucose-waist circumference; TG/HDL-C, triglyceride-to-high-density-lipoprotein-cholesterol; METS-IR, metabolic score for insulin resistance.

found no association between PRAL and NEAP scores on one hand and β-cell function or insulin sensitivity on the other[34]. These inconsistencies could be attributed to variations in participant characteristic features.

Our study contributes to the literature by highlighting the utility of non-insulin-based indices in assessing IR in relation to DAL. One of the key advantages of using these indices over traditional methods like HOMA-IR is their simplicity and cost-effectiveness, making them more suitable for large-scale epidemiological studies[15]. Additionally, some of these indices incorporate both anthropometric features (e.g., WC, BMI) and biochemical factors (e.g., TG, HDL, and FBG), providing a more comprehensive assessment of IR. Non-insulin-based measures also show a more robust correlation with the gold standard method for the evaluation of IR[16].

A study by Akter revealed no association between dietary acid load indices and FBS[20]. Various studies found that individuals in the top PRAL or NEAP classifications tend to have lower HDL levels and higher concentrations of TG and LDL cholesterol[13,35–38]. In another study the highest levels of PRAL score were associated with greater TG and an increased presence of obesity. Other studies, however, showed no significant difference between serum lipid levels across PRAL or NEAP categories[10,35,38,39]. The proposed mechanism for higher TG levels in study participants with higher dietary acid loads could be increased secretion of cortisol and reduction in the secretion and sensitivity of insulin[38].

A study on women in Iran found a direct relationship between DAL and higher WC and WHR[40]. Another study exploring Iranian adults reported a significant association between PRAL and increased weight and WC[39]. In contrast, a Japanese investigation of younger females ranging in age from 18 to 22 found no significant link between WC, obesity, and PRAL score[41]. While the precise mechanism by which dietary acid load affects body composition remains unclear, some studies suggested that higher acidity may increase proteolysis through an increase in mRNA expression[42]. Further justification offered for this mechanism was a positive relationship between IR high lactate, low bicarbonate, and high anion gap[43,44]. Furthermore, protein and micronutrients such as magnesium and potassium could have affected anthropometric indices[45].

	Dietary Acid Load				
	T1	T2	T3	*p*-value	*p*-trend
Nutrient intake					
Energy, kcal/d	1984.07 ± 583.80	1916.41 ± 538.33	2203.20 ± 616.11	< 0.001	< 0.001
% Energy from carbohydrate	58.15 ± 7.76	57.44 ± 7.54	55.91 ± 8.98	< 0.001	< 0.001
% Energy from fat	29.56 ± 6.42	29.87 ± 6.22	30.29 ± 6.97	0.001	< 0.001
% Energy from protein	14.93 ± 2.36	15.19 ± 2.13	15.74 ± 2.39	< 0.001	< 0.001
Dietary fiber, g/d	27.43 ± 9.85	24.00 ± 8.92	26.33 ± 10.45	< 0.001	< 0.001
Phosphorous, mg/d	1294.59 ± 383.03	1226.84 ± 357.48	1406.67 ± 402.00	< 0.001	< 0.001
Potassium, mg/d	3837.78 ± 1102.27	3074.52 ± 831.75	3090.88 ± 869.99	< 0.001	< 0.001
Calcium, mg/d	955.50 ± 346.66	885.30 ± 323.72	960.81 ± 329.40	< 0.001	< 0.001
Magnesium, mg/d	332.19 ± 99.43	302.46 ± 93.01	337.34 ± 109.09	< 0.001	< 0.001
Food group consumption, g/d					
Grains, g/d	304.72 ± 129.94	344.92 ± 138.77	428.22 ± 176.13	< 0.001	< 0.001
Vegetables, g/d	362.41 ± 169.90	251.63 ± 107.27	216.08 ± 102.39	< 0.001	< 0.001
Fruits, g/d	346.75 ± 264.14	199.70 ± 147.61	157.27 ± 123.07	< 0.001	< 0.001
Meat, g/d	97.07 ± 43.01	99.73 ± 42.66	131.37 ± 72.51	< 0.001	< 0.001
Dairy products, g/d	382.71 ± 233.75	345.22 ± 217.60	345.05 ± 201.89	< 0.001	0.003

Table 2. Nutrient and food group intakes by tertile of DAL. Variables are presented as mean ± SD. ANOVA used to compare means that significance is determined by *P*-values < 0.05.

Variable		DAL			
		T1	T2	T3	p-trend
TG: HDL	Crude	1	1.17(1.05–1.30)	1.38(1.24–1.53)	< 0.001
	Model 1	1	1.16(1.04–1.29)	1.31(1.18–1.47)	< 0.001
	Model2	1	1.06(0.95–1.18)	1.07(0.96–1.20)	0.20
TyG	Crude	1	1.1(0.99–1.22)	1.30(1.17–1.45)	< 0.001
	Model 1	1	1.14(1.02–1.26)	1.37(1.23–1.53)	< 0.001
	Model2	1	1.04(0.93–1.16)	1.16(1.04–1.30)	0.01
TyG-WC	Crude	1	1.25(1.12–1.40)	1.85(1.66–2.06)	< 0.001
	Model 1	1	1.34(1.20–1.50)	2.17(1.94–2.42)	< 0.001
	Model2	1	1.13(1.01–1.27)	1.69(1.51–1.90)	< 0.001
TyG_BMI	Crude	1	1.15(1.03–1.28)	1.49(1.34–1.66)	< 0.001
	Model 1	1	1.27(1.14–1.42)	1.91(1.71–2.14)	< 0.001
	Model2	1	0.95(0.84–1.06)	1.01(0.89–1.14)	0.87
METS	Crude	1	1.18(1.06–1.31)	1.61(1.45–1.79)	< 0.001
	Model 1	1	1.26(1.13–1.41)	1.92(1.72–2.15)	< 0.001
	Model2	1	0.96(0.84–1.10)	0.97(0.84–1.11)	0.86

Table 3. Ordinal logistic regression for the association between DAL and IR indices. Crude: unadjusted, Model1: adjusted for age and sex Model2: Model1 + BMI, energy intake, education level, smoking status, physical activity level, chronic diseases including diabetes, hypertension, or dyslipidemia, and marriage status. DAL: dietary acid load.

Several mechanisms have been suggested for the associations between DAL and IR indices. Metabolic acidosis has been reported to cause a higher degree of IR by increasing cortisol and glucocorticoid secretion[46] as well as suppression of blood levels of adiponectin, which acts as an insulin sensitizer[47]. Potassium and magnesium, found in plant-based foods, are essential for maintaining acid-base balance. Thus, a reduction in consuming fruit and vegetable pushes the body's pH balance toward acidosis suppressing the beta-cell function. This, in turn, results in IR[43]. Also, a higher intake of dietary fiber, lowers the risk of IR through enhancing glucose metabolism[48]. Defective functioning of renal ammonia synthesis or abnormal levels of hydrogen, sodium, and potassium transport in the kidney tubules can lead to decreased urine citrate excretion, highly associated with IR[45]. Moreover, an acidotic condition might also influence insulin-like growth factor I (IGF-I). This can trigger sensitivity to insulin as well as other disorders[46].

The present study has several strengths. First, the participants completed the FFQ with the help of a trained dietitian to improve completeness. Next, although the association between DAL and IR has previously been investigated, but to our best understanding, the current study is most likely the first on the association between

DAL (DAL score) and non-insulin-based IR indices in the case of Iranian adults. These IR indices are by no means complicated. On the contrary, they are simple to apply, more reliable and useful clinically and make a more precise alternative marker for detecting IR at earlier stages[17] However, there are some limitations, too. First, as an observational study, like many other studies of the type, the current study is definitely subject to the same methodological restraints. As a result, establishing a causal link between IR and DAL is impossible. Second, acid-base levels of the participants were determined as per calculations obtained from FFQ questioner. If measurements of serum and urine pH had also been used, the results would have certainly been more accurate. It should also be noted that medications, a potential confounder on the association between DAL and IR, were not adjusted for in the analysis because reliable data was not readily available.

Conclusions

Our findings suggest that a diet high in acid load may increase the risk of IR in Iranian adults. While certain food groups, such as vegetables, fruits, and milk-based products, are associated with lower acid load, further research is needed to understand the acid-forming capacity of specific foods, before making specific dietary recommendations. Future studies need to take into account regional dietary patterns when reproducing this research in other geographic areas. Modifications to the calculation of dietary scores and the design of questionnaires should reflect local food habits and cultural differences in diet.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to university data ownership policies, but are available from the corresponding author on reasonable request.

Received: 22 March 2024; Accepted: 21 October 2024
Published online: 19 March 2025

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Acknowledgements
The support provided by Mashhad University of Medical Sciences (MUMS) to conduct this study is highly acknowledged.

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Study concept and design: N. S. and M.Gh.; Data collection: A.A.A.A., N.S.S.S., H.K., and A.F.; data analysis and interpretation of data: N.S. and H.E.; drafting of the manuscript: N.A. and N.S.; funding acquisition and supervision: H.E. and M.Gh.; editing and critical revision: G. A.F. and M.Gh. All authors contributed to the article and approved the submitted version.

Funding
This study was supported by Mashhad University of Medical Sciences (MUMS). The funders had no involvement in study design; collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declarations

Ethics approval and consent to participate
All experiments were performed in accordance with the declaration of Helsinki and Mashhad University of Medical Sciences ethical guidelines and regulations. The research protocol was approved by the School of Medicine, Mashhad University of Medical Sciences, Biomedical Research Ethics Committee (IR.MUMS.MEDICAL.REC.1398.228). All participants signed a written inform consent before participating in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-77262-4.

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