Higher phenolic acid intake independently associates with lower prevalence of insulin resistance and non-alcoholic fatty liver disease

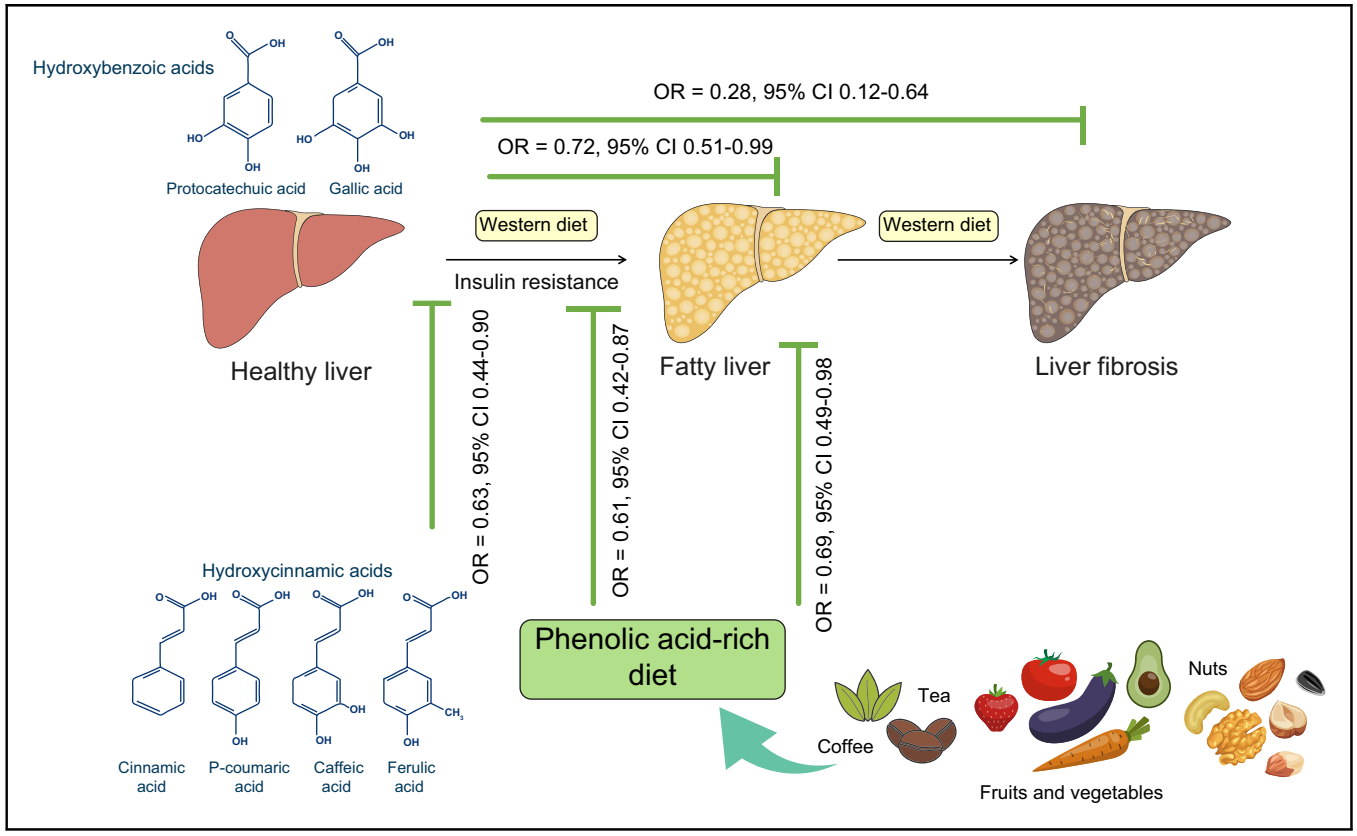
Authors

Federico Salomone, Dana Ivancovsky-Wajcman, Naomi Fliss-Isakov, Muriel Webb, Giuseppe Grosso, Justyna Godos, Fabio Galvano, Oren Shibolet, Revital Kariv, Shira Zelber-Sagi

Correspondence

federicosalomone@rocketmail.com (F. Salomone).

Graphical abstract



Highlights

- High intake of total phenolic acids is associated with a lower prevalence of NAFLD and insulin resistance.
- High intake of hydroxybenzoic acids is associated with a lower prevalence of steatosis and fibrosis.
- High intake of hydroxycinnamic acids is associated with lower prevalence of insulin resistance.

Lay summary

High dietary intake of total phenolic acids is associated with a lower prevalence of non-alcoholic fatty liver disease and insulin resistance. A high intake of hydroxybenzoic acids, a class of phenolic acids, is associated with a lower prevalence of steatosis and clinically significant fibrosis, while a high intake of hydroxycinnamic acids, another class of phenolic acids, is associated with a lower prevalence of insulin resistance.

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Research article

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Higher phenolic acid intake independently associates with lower prevalence of insulin resistance and non-alcoholic fatty liver disease

Federico Salomone,[1,*,†] Dana Ivancovsky-Wajcman,[2,†] Naomi Fliss-Isakov,[3] Muriel Webb,[3,4] Giuseppe Grosso,[5] Justyna Godos,[6] Fabio Galvano,[5] Oren Shibolet,[3,4] Revital Kariv,[3,4] Shira Zelber-Sagi[2,3]

[1]*Division of Gastroenterology, Ospedale di Acireale, Azienda Sanitaria Provinciale di Catania, Catania, Italy;* [2]*School of Public Health, University of Haifa, Haifa, Israel;* [3]*Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel;* [4]*The Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel;* [5]*Department of Biomedical and Biotechnological Sciences, University of Catania, Catania;* [6]*Oasi Research Institute, Troina, Italy*

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Background & Aims: The inverse association between non-alcoholic fatty liver disease (NAFLD) and diets rich in fruit and vegetables has been demonstrated, but the specific compounds that may be responsible for this association need to be elucidated. The aim of this study was to test the association between phenolic acid consumption, NAFLD, and insulin resistance (IR).
Methods: A cross-sectional cohort of individuals included in a metabolic screening program was studied. Liver steatosis was evaluated by ultrasonography and quantified by the hepatorenal index (HRI); fibrosis was assessed by FibroTest; IR by the sample upper quartile of the homeostatic model assessment score. Dietary intake was measured by a food frequency questionnaire. The phenolic acid content of food was calculated according to Phenol-Explorer.
Results: A total of 789 individuals were included (52.6% men, age 58.83 ± 6.58 years). Higher (above the upper median) phenolic acid intake was inversely associated with the presence of NAFLD (odds ratio [OR] 0.69; 95% CI 0.49–0.98; $p = 0.036$), higher HRI (OR 0.64; 95% CI 0.45–0.91; $p = 0.013$) and higher IR (OR 0.61; 95% CI 0.42–0.87; $p = 0.007$), when adjusted for age, gender, body mass index, and lifestyle factors. Considering specific classes of phenolic acids, higher hydroxybenzoic acid intake was independently associated with lower odds of NAFLD, higher HRI and fibrosis. Higher hydroxycinnamic acid intake was independently associated with lower odds of IR.
Conclusion: A higher intake of phenolic acids is associated with a lower prevalence of liver steatosis and IR in a cross-sectional study, suggesting a possible protective effect that requires confirmation in prospective studies.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries and has become a public health concern worldwide because it is associated with increased liver- and cardiovascular-related mortality.[1] The increasing prevalence of NAFLD is a result of the epidemic of obesity caused by unhealthy dietary habits and sedentary lifestyles.[2] There is evidence that adherence to plant-based dietary patterns leads to a lower risk of several non-communicable diseases.[3] In particular, a diet rich in fruits and vegetables confers a lower risk of cardiometabolic disorders including insulin resistance (IR)[4–8] and NAFLD.[9,10]

The health-promoting effects of dietary patterns with a high content of fruits and vegetables have been attributed to fibers, vitamins and non-vitamin antioxidants.[11] Among non-vitamin antioxidants, recent studies have underlined the importance of phenolic compounds in contributing to the health-promoting effects of plant-based dietary patterns. Phenolic acids are compounds containing a phenolic ring and an organic carboxylic acid function (C6-C1 skeleton) that are abundantly present in foods such as berries, nuts, coffee, tea and whole grains.[12–17] Phenolic acids can be classified as hydroxybenzoic acids or hydroxycinnamic acids.[18] Hydroxybenzoic acids include gallic, vanillic, protocatechuic, syringic and salicylic acid.[19] Hydroxycinnamic acids include cinnamic, p-coumaric, ferulic, rosmarinic, caffeic and chlorogenic acid.[20]

There is epidemiological evidence that phenolic acid intake is inversely associated with occurrence of diabetes,[21] hypertension[22,23] and the metabolic syndrome.[24] Furthermore, preclinical data in experimental models have shown that even a single phenolic acid may exert protective effects against NAFLD.[25] However, it is unknown whether dietary intake of phenolic acids may be associated with human NAFLD.

In this study, we aimed to assess the association of dietary intake of phenolic acids with the prevalence and features of NAFLD in a general population cohort of individuals participating in a metabolic screening study.

Keywords: NAFLD; insulin resistance; fibrosis; diet; phenolic acids; metabolic syndrome.
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† Equal contribution
* Corresponding author. Address: Azienda Sanitaria Provinciale di Catania, Via Santa Maria La Grande, 5 95124 Catania, Italy. Tel.: +393206990366.
E-mail address: federicosalomone@rocketmail.com (F. Salomone).

Patients and methods

Study design and population

This is a cross-sectional study among 40–70-year-old individuals who underwent screening colonoscopy at the Department of Gastroenterology and Hepatology in the Tel-Aviv Medical Center, and agreed to participate in a metabolic and hepatic screening study between the years 2010 and 2015 (previously described in detail[26]). Exclusion criteria included: presence of HBsAg or anti-HCV antibodies, fatty liver suspected to be secondary to hepatotoxic drugs and excessive alcohol consumption (≥30 g/day in men or ≥20 g/day in women).[27] In addition, individuals who reported an unreasonable caloric intake were excluded; below or above the acceptable range for men 800–4,000 Kcal/day and for women 500-3,500 Kcal/day.[28]

The study was approved by the Tel-Aviv medical center IRB committee and consent was obtained from all participants.

Data collection and definition of hepatic and metabolic variables

Study participants were invited for a single day visit, in which they underwent fasting blood tests, liver ultrasound and a face-to face interview using a structured questionnaire, assembled by the Israeli Ministry of Health, including demographic details, health status, alcohol consumption, smoking and exercise habits. In addition, they completed a food frequency questionnaire (FFQ). To avoid reporting bias, the participants were informed of their abdominal ultrasonography (AUS) and blood test results only after completing the questionnaires. Fatty liver was diagnosed by AUS using standardized criteria, and was performed in all individuals with the same equipment (EUB-8500 scanner Hitachi Medical Corporation, Tokyo, Japan) and by the same experienced radiologist (Webb M) as previously described.[29] The ratio between the brightness level of the liver and the right kidney was calculated to determine the hepatorenal index (HRI), which has previously been validated against liver biopsy.[30] High HRI defined as levels above the sample median, corresponding to HRI ≥1.2.

IR was evaluated by high homeostatic model assessment (HOMA) score, defined as a value above the upper quartile (Q4) of the study sample (HOMA >3.31). Type 2 diabetes was defined as fasting glucose ≥126 mg/dl and/or HbA1c ≥6.5% and/or use of diabetic medications.[31] Since insulin concentrations may start to decline in advanced diabetes,[31] the patients with diabetes who had no IR according to the upper quartile of HOMA levels (n = 44) were considered as having IR.

Presumed fibrosis was evaluated non-invasively by FibroTest, (BioPredictive, Paris, France), which has been validated extensively.[32] The FibroTest includes serum α2-macroglobulin, apolipoprotein-A1, haptoglobin, total bilirubin, and gamma-glutamyltransferase adjusted for age and gender. The procedures were those recommended by BioPredictive, including exclusion of non-reliable results.[33] The presence of fibrosis was defined as ≥F2, corresponding to ≥0.48, indicating significant fibrosis.[32]

Lifestyle variables – evaluation and definitions

The semi-quantitative FFQ, which was assembled by the Food and Nutrition Administration, Ministry of Health and tailored to the Israeli population, is composed of 117 food items with specified serving sizes, previously described in detail.[26] Individuals were asked to describe their eating habits during the past year.

Estimation of phenolic acid intake was performed through a process previously published elsewhere.[34] Data on the polyphenol content in foods was obtained from the Phenol-Explorer database (www.phenol-explorer.eu). Among the foods available from the FFQ, those containing no phenolic acids were excluded from the calculation, leaving a total of 27 food groups included for the estimation. For every food item in the FFQ, the exact amount (in g or ml) that was consumed per day was calculated. Then, a search was carried out in the Phenol-Explorer database to retrieve the mean content values for phenolic acids contained in the foods obtained and phenolic compound intake from each food was calculated by multiplying the content of each phenolic acid by the daily consumption of each food. In the Phenol-Explorer database, data on reverse phase high-performance liquid chromatography (HPLC) was used to calculate the content of all phenolic compounds. For food groups from which phenolic acid content cannot be released with normal extraction conditions, data corresponding to HPLC after hydrolysis were used. Besides the total phenolic acid intake, additional subclasses and selected individual phenolic acids were also estimated.[34] High intake of total phenolic acids, hydroxybenzoic acids and hydroxycinnamic acids was defined as consumption above the sample median corresponding to >221 mg/day, 8.14 mg/day, and 159 mg/day, respectively.

Tobacco consumption was defined as pack-years that equals to daily cigarettes × years of smoking / 20 (1 pack contains 20 cigarettes). One pack year equals 20 manufactured cigarettes smoked per day for 1 year.

Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM-SPSS Armonk, NY) (see CTAT Table). Continuous variables are presented as means (SD). To test differences in continuous variables between 2 groups, the independent-samples *t* test was performed. Associations between nominal variables were performed with the Pearson's Chi-Square test. A multivariate logistic regression analysis was performed to test the adjusted association between phenolic acid consumption and NAFLD, HRI, IR or fibrosis, adjusting for potential confounders including relevant variables found to be different between the groups. Odds ratios (ORs) and 95% CIs are presented. *P* values of <0.05 were considered statistically significant for all analyses. Sample size was calculated using WINPEPI proportion comparison and mean comparison, with $\alpha = 0.05\%$ and $\beta = 90\%$.

Results

Description of the study population and comparison between individuals with high *vs.* low phenolic acid intake

Out of 970 individuals who participated in the study, 789 were eligible as previously described (124 were excluded because of unreasonable caloric intake which may indicate an unreliable dietary report).[26] NAFLD was diagnosed in 38.7% (n = 305) and IR in 30.5% (n = 240). Reliable FibroMax test was obtained from 714 individuals (7 had an unreliable test and 68 had no serum sample). In this subsample, 51.7% were men, mean age was 58.80 ± 6.59 years and mean body mass index (BMI) was 28.55 ± 5.40 Kg/m^2. Significant fibrosis (≥F2) was observed in 5.3% (n = 38) of participants.

Individuals at the upper median of phenolic acid consumption had lower blood triglycerides and higher HDL (Table 1). In addition, they tended to consume more fiber, coffee, fruits and vegetables, which are the main sources of phenolic acids

Table 1. Comparison between individuals with low or high phenolic acid intake (mean ± SD, unless otherwise stated).

Variable (units)	Total phenolic acid intake ≤221 mg/day (n = 394)	Total phenolic acid intake >221 mg/day (n = 395)	*p* value
Age (years)	58.71 ± 6.69	58.95 ± 6.47	0.614
Gender (men %)	59.10	46.10	**<0.001**
BMI (kg/m^2) (20-25)	28.71 ± 5.75	28.38 ± 5.09	0.391
HRI (score)	1.45 ± 0.47	1.40 ± 0.46	0.105
HOMA-IR (score)	3.20 ± 4.75	2.77 ± 2.39	0.111
Fibrotest score	0.21 ± 0.15	0.20 ± 0.16	0.712
Glucose (mg/dl)	91.16 ± 22.03	89.69 ± 21.53	0.346
HbA1c (%)	5.87 ± 0.71	5.89 ± 0.82	0.724
Insulin (μU/ml)	13.24 ± 11.46	11.94 ± 6.74	0.053
Diabetes* (%)	16.00	13.70	0.359
Antidiabetic drugs (%)	11.90	11.60	0.902
Triglycerides (mg/dl)	123.31 ± 77.03	108.68 ± 54.00	**0.002**
Total cholesterol (mg/dl)	180.62 ± 37.74	182.58 ± 33.27	0.439
ALT (U/L) (8-39 for men or 8-35 for women)	26.52 ± 16.80	25.46 ± 11.00	0.292
Elevated ALT (%)	12.50	11.70	0.733
AST (U/L) (7-40)	24.42 ± 8.93	25.24 ± 8.08	0.181
Elevated AST (%) (>40 U/L)	3.60	3.90	0.822
HDL (mg/dl)	51.56 ± 15.68	55.57 ± 15.83	**<0.001**
CRP (mg/l) n = 766	4.08 ± 6.44	3.37 ± 4.76	0.085
Dietary intake and lifestyle habits			
Energy (Kcal/day)	1,951.14 ± 684.13	2,100.73 ± 707.73	**0.003**
Carbohydrates (% daily Kcal)	42.42 ± 9.21	40.92 ± 8.52	**0.017**
Protein (% daily Kcal)	18.41 ± 4.92	18.66 ± 4.33	0.447
Fat (% daily Kcal)	35.85 ± 6.92	36.78 ± 6.33	0.051
Saturated fat (% daily Kcal)	11.95 ± 3.73	12.80 ± 3.59	**0.001**
Cholesterol (mg/day)	327.34 ± 194.11	342.82 ± 192.55	0.261
Fiber (g/day)	21.46 ± 10.45	24.98 ± 12.63	**<0.001**
Coffee (cups/day)	1.11 ± 1.25	5.04 ± 3.40	**<0.001**
Fruits and vegetables (portions/day)	3.80 ± 2.96	4.33 ± 3.12	**0.013**
Sugared sweetened beverages (cups/day)	2.72 ± 3.87	1.30 ± 2.45	**<0.001**
Red and processed meat intake (portions/day)	0.63 ± 1.00	0.64 ± 0.91	0.920
Alcohol consumption (portions/ week)	1.78 ± 3.16	1.68 ± 2.82	0.643
Pack-years†	15.87 ± 22.57	12.09 ± 21.13	**0.015**
Exercise (h/week)	2.05 ± 2.82	2.29 ± 3.39	0.278
Sedentary time (h/day)	4.20 ± 2.62	4.44 ± 3.22	0.270

Statistical test: independent-samples *t* test, *p* value <0.05.
Coffee includes: coffee with milk, black coffee, espresso. Red and/or processed meat includes: beef steak or roast, beef internal organs, fried beef patties, lamb and pork, hamburger, salami, pastrami, sausages, processed schnitzel and canned meat.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; Hb1Ac, glycated hemoglobin; HRI, hepatorenal index; HOMA-IR, homeostatic model assessment of insulin resistance.
* Diabetes was defined as fasting glucose ≥126 mg/dl and/or HbA1c ≥6.5% and/or use of antidiabetic medications.
† Pack-years calculated among ever smokers, never smokers were considered as zero.

(Table 1). The higher phenolic acid eaters tended to consume less saturated fatty acids (SFAs), carbohydrate (% total calories), sugared sweetened beverages and had fewer pack-years. Since high phenolic acid eaters consumed more calories, we also compared total phenolic acid intake per 1,000 Kcal, and similar results were shown (data is not shown).

Univariate analysis of the association between phenolic acid intake and NAFLD

The prevalence of NAFLD, high HRI and significant fibrosis was higher among individuals who consumed less hydroxybenzoic acids (Fig. 1A-C) whereas the prevalence of IR was significantly lower in those who consumed more hydroxycinnamic acids (Fig. 1D). There was no association between hydroxycinnamic acids and other outcomes. Overall, the prevalence of high HRI and IR was higher among individuals who consumed less phenolic acids (Fig. 1B,D).

Multivariate analysis of the association between phenolic acid intake and NAFLD

In a multivariate analysis, the upper median of phenolic acid intake was associated with lower odds of NAFLD (OR 0.69; 95% CI 0.49–0.98; p = 0.036), higher HRI (OR 0.64; 95% CI 0.45–0.91; p = 0.013) and higher IR (OR 0.61; 95% CI 0.42–0.87; p = 0.007), when adjusted for age, gender, total energy intake, BMI, pack-years, SFA intake, carbohydrate intake (% total Kcal) and sugared sweetened beverage consumption (Table 2, fully adjusted model B). There was no association between phenolic acid intake and significant fibrosis. However, we found significant associations between the consumption of specific phenolic acids and fibrosis. In a multivariate analysis, the upper median of hydroxybenzoic acid intake was associated with lower odds of NAFLD (OR 0.72; 95% CI 0.51–0.99; p = 0.049), high HRI (OR 0.63; 95% CI 0.45–0.89; p = 0.008) and significant fibrosis (OR 0.28; 95% CI 0.12–0.64; p = 0.003, respectively) (Table 2, fully adjusted model B). There was no association between hydroxybenzoic acid intake and IR.

In addition, the upper median of hydroxycinnamic acid consumption was significantly associated with lower odds of IR (OR 0.63, 95% CI 0.44-0.90, p = 0.012), when adjusting for all confounders (Table 2, fully adjusted model B). There was no association between hydroxycinnamic acid intake and other outcomes.

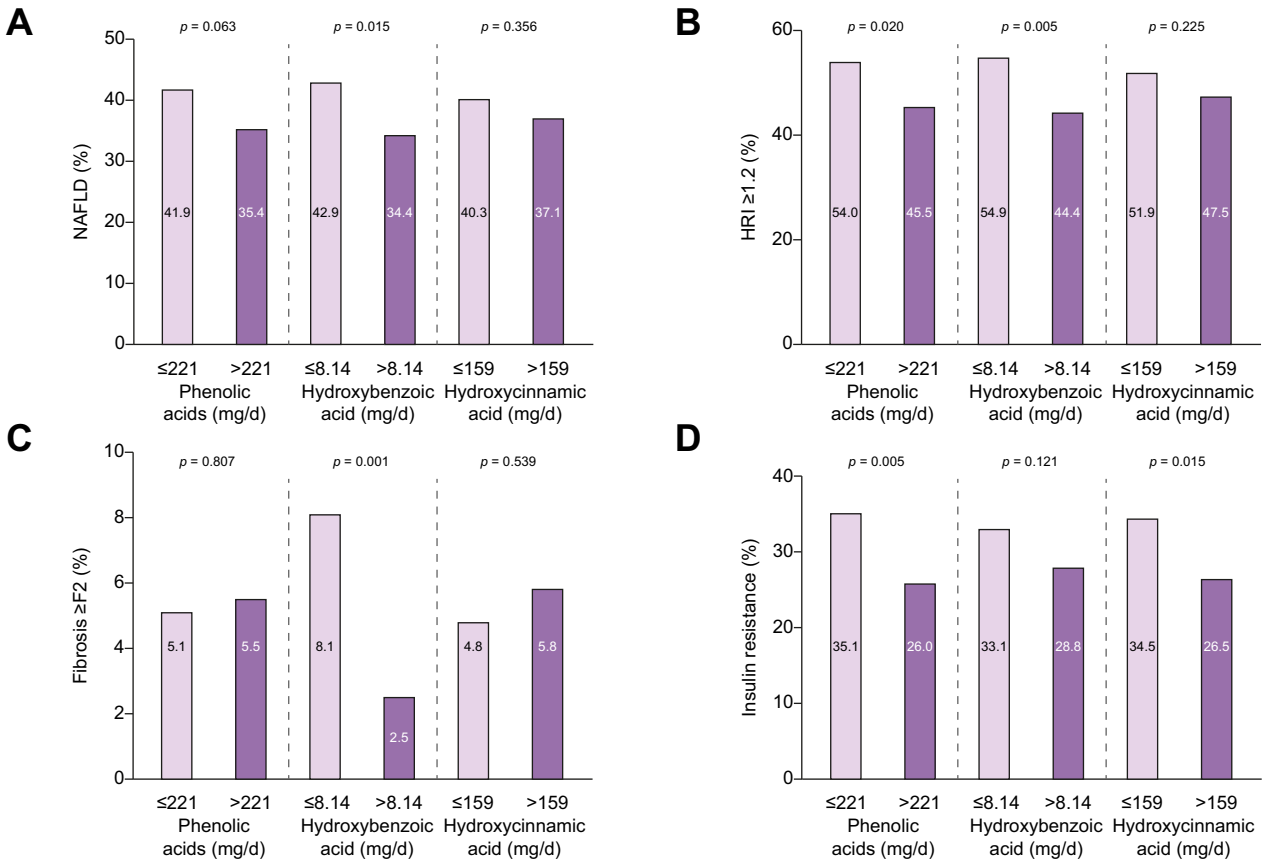

Fig. 1. Univariate association between classes of phenolic acids and NAFLD, high HRI, fibrosis or IR. (Statistical test: Pearson's chi-square, *p* value <0.05). HRI, hepatorenal index; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease.

Discussion

In this study, we assessed the relationship between phenolic acid intake and NAFLD in a cohort of adults participating in a hepatic and metabolic screening program in Israel. Our study demonstrated that the intake of phenolic acids is associated with a lower prevalence of liver steatosis and IR, independently of other lifestyle factors. We also showed that the consumption of hydroxybezoic acids is inversely associated with the prevalence of clinically significant fibrosis and consumption of hydroxycinnamic acids is inversely associated with IR. Our data provides the first epidemiological evidence supporting the evidence obtained in preclinical models of metabolic syndrome and NAFLD that demonstrated the hepatoprotective effects of phenolic acids.[25]

Among hydroxybenzoic acids, there is evidence of a hepatoprotective effect for gallic, vanillic, protocatechuic and syringic acid. Gallic acid, mainly present in tea leaves, grapes, berries and wine, protects against hepatic steatosis in mice with high-fat diet-induced NAFLD.[35] Vanillic acid enhances glucose uptake in insulin resistant mouse hepatocytes and mitigates IR and liver steatosis in rats fed a high-fat diet.[36] Protocatechuic acid, the main metabolite derived from anthocyanin degradation, suppresses triglyceride accumulation and oxidative stress in HepG2 treated with oleate[37] and inhibits hepatic lipogenic enzymes in mice.[38] Consistently, syringic acid reverses liver steatosis in mice fed an obesogenic diet by stimulating liver fatty acid oxidation.[39]

Cinnamic acids and its derivatives have shown pleiotropic effects including stimulation of insulin secretion, improvement of pancreatic β-cell functionality, inhibition of hepatic gluconeogenesis, enhanced glucose uptake, increased insulin signaling, delay of carbohydrate digestion and glucose absorption, thus leading to marked antidiabetic activity.[40] Among hydroxycinammic acid derivatives, ferulic acid, present in eggplants, peanuts, tomatoes and spinach, prevents IR and liver steatosis in mice fed a high-fat diet by suppressing glucogenic and lipogenic enzymes.[41] Ellagic acid attenuates IR, liver steatosis and cardiovascular dysfunction in rats fed a western diet by stimulating antioxidant Nrf2-mediated responses.[42] Evidences support the hepatoprotective effects of caffeic acid and its ester chlorogenic acid, two main components of the polyphenolic fraction of coffee.[43] Chlorogenic acid, which is also abundant in eggplants, peaches and prunes, alleviates hepatic steatosis and IR in mice fed a high-fat diet.[44] Furthermore, chlorogenic acid exerts hepatoprotective effects in mouse models of liver fibrosis.[45,46]

Among dietary patterns with a high content of phenolic compounds, the Mediterranean diet has a well-established protective role against non-communicable diseases and large prospective observational studies also support its inverse association with NAFLD.[47] For this reason, the Mediterranean diet has been recommended for the treatment of NAFLD by the European Association for the Study of the Liver (EASL)/ Diabetes (EASD)/ Obesity (EASO) Clinical Practice Guidelines[27] and recently by the European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines.[48] However, we have demonstrated an independent protective association with phenolic acid intake, after adjusting for other nutritional and lifestyle

Table 2. Multivariate association between phenolic acid intake and NAFLD, fibrosis or IR.

	NAFLD (n = 305)	HRI ≥1.2‡ (n = 366)	Fibrosis ≥F2 (n = 38)	Insulin resistance (n = 240)
	OR (95% CI); *p* value			
Median phenolic acid intake (mg/day)				
Model[a]				
≤221	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>221	0.74 (0.53-1.03); 0.073	0.65 (0.47-0.91); **0.012**	1.37 (0.68-2.75); 0.374	0.66 (0.47-0.93); **0.019**
Model[b]				
≤221	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>221	0.69 (0.49-0.98); **0.036**	0.64 (0.45-0.91); **0.013**	1.79 (0.83-3.84); 0.137	0.61 (0.42-0.87); **0.007**
Median hydroxybenzoic acid intake (mg/day)				
Model[a]				
≤8.14	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>8.14	0.74 (0.54-1.03); 0.072	0.67 (0.48-0.93); **0.018**	0.32 (0.14-0.70); **0.005**	0.89 (0.63-1.23); 0.451
Model[b]				
≤8.14	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>8.14	0.72 (0.51-0.99); **0.049**	0.63 (0.45-0.89); **0.008**	0.28 (0.12-0.64); **0.003**	0.86 (0.61-1.22); 0.410
Median hydroxycinnamic acid intake (mg/day)				
Model[a]				
≤159	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>159	0.86 (0.62-1.19); 0.358	0.78 (0.56-1.09); 0.145	1.55 (0.77-3.12); 0.218	0.69 (0.49-0.96); **0.030**
Model[b]				
≤159	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>159	0.81 (0.57-1.14); 0.228	0.78 (0.55-1.10); 0.155	1.96 (0.92-4.18); 0.081	0.63 (0.44-0.90); **0.012**

Statistical test: logistic regression, *p* value <0.05.
Model[a] adjusted for: age, gender, energy intake and BMI; Model[b] additionally adjusted for: pack-years (calculated among ever smokers, never smokers were considered as zero), SFA intake (% total Kcal), carbohydrate intake (% total Kcal) and sugared sweetened beverages consumption. BMI, body mass index; HRI, hepatorenal index; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; SFA, saturated fatty acids.
‡ By median.

factors. In the last years, small clinical trials assessing the effects of polyphenol-rich diets have shown beneficial effects in improving the components of the metabolic syndrome,[49,50] although such evidence is currently lacking for NAFLD.

This study has some limitations that should be considered. First, the cross-sectional design of the study does not allow for causal inference. Second, food consumption was self-reported and thus prone to a reporting bias. However, since the participants and the research team were blinded to the AUS and blood test results, it is a non-differential reporting bias and therefore it may have only weakened the observed associations. The diagnosis of steatosis and fibrosis were determined by AUS and FibroTest, respectively, and not by liver histology, which cannot be performed in a sample of apparently healthy volunteers. However, AUS is the most widely accepted and common screening method for NAFLD in a general population. The validity of FibroTest has been demonstrated in several studies and biomarkers of fibrosis are considered as reasonably acceptable non-invasive procedures.[27] Finally, residual confounding may occur in every observational study, and therefore our results need to be further confirmed.

In conclusion, this is the first epidemiological evidence showing that higher phenolic acid consumption is associated with lower liver steatosis and IR in a cross-sectional study, suggesting that phenolic acid consumption may contribute to the preventive effects of plant-based dietary patterns against NAFLD. Prospective studies are needed to firmly establish a causal relationship. Clinical trials are required to test if phenolic acid-rich diets can also display therapeutic effects in patients with NAFLD.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUS, abdominal ultrasonography; BMI, body mass index; CRP, C-reactive protein; FFQ, food frequency questionnaire; Hb1Ac, glycated hemoglobin; HRI, hepatorenal index; HOMA, homeostatic model assessment; IR, Insulin resistance; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; SFAs, saturated fatty acids.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

FS conceived and designed the study, contributed to data analysis and wrote the manuscript; DIW performed data collection and analysis and contributed to manuscript drafting; NFI contributed to data collection; MW performed the ultrasonography; GG contributed to study design, provided phenolic acid estimation and critically reviewed the manuscript; JG provided phenolic acid estimation; FG supervised on phenolic acid estimation; OS critically reviewed the manuscript; RK contributed to study design, supervised on data collection and critically reviewed the manuscript; SZS designed the study, supervised on data collection and analysis, contributed to manuscript drafting and is the submission's guarantor.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100069.

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