


## RESEARCH ARTICLE

## Dietary parameters in patients with drug allergy: Assessing dietary inflammatory index

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**Abbreviations:** DII, dietary inflammatory index; ADR, adverse drug reaction; ENDA, European Network of Drug Allergy; IPAQ, Intensity Physical Activity Questionnaire; DPT, drug provocation test;

## Abstract

## Background

Research on the increasing incidence of allergic diseases evidenced the role of diet as a potential key factor. Diet can modulate the low-grade systemic inflammation related to obesity and several diseases. There are no published data on drug allergy.

## Aim

To investigate a potential association between diet, including dietary inflammatory index (DII), and drug allergy. Also, to evaluate correlations between diet and obesity, inflammatory and metabolic parameters in patients with drug allergy.

## Methods

Ninety consecutive patients studied for suspected drug allergy were evaluated in terms of dietary parameters, anthropometric measurements, bioimpedance and biochemical analysis. DII was calculated based on information collected from a food frequency questionnaire.

## Results

After diagnostic work-up, 39 patients had confirmed drug allergy and 45 excluded, representing the study group and the control group, respectively. The majority (79%) were female, with mean age of 39.58±13.3 years. The 84 subjects revealed an anti-inflammatory diet pattern. No significative difference was found in DII scores between drug allergic patients and controls (-3.37±0.95 vs -3.39±0.86, p = 0.985). However, the patients with drug allergy revealed higher obesity and inflammatory parameters. A significative negative correlation was found between DII and adiponectin levels, in the control group (r = -0.311, p = 0.040). In the patient group, a significative positive correlation was observed between DII and triglycerides (r = 0.359, p = 0.032). No other correlations were found between DII and

FFQ, food frequency questionnaire; BMI, body mass index; WC, waist circumference; IDF, International Diabetes Federation; HP, hip circumference; WHR, waist-hip ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BFP, body fat percentage; MUFA, mono-unsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty-acid; SD, standard deviation; IQR, interquartile range; BP, blood pressure.

the assessed parameters. Patients with drug allergy presented a significant higher intake of mono-unsaturated fatty-acids comparing to controls ( $19.8 \pm 3.7$  vs  $17.8 \pm 4.0$ ,  $p = 0.021$ ). No other statistically significant differences were achieved in dietary parameters, between patients and controls.

## Conclusion

The population assessed in this study revealed an anti-inflammatory diet profile. Although we have found in a previous work that the same patients with drug allergy revealed higher obesity and inflammatory parameters, the DII did not allow to distinguish between patients with drug allergy or controls. The DII scores correlated with triglycerides levels in the drug allergy patients and inversely with adiponectin levels in the control group. Larger studies are needed to clarify the potential role of the diet in drug allergy and its outcomes.

## 1 –Introduction

Drug allergic reactions are unpredictable adverse drug reactions (ADR) that are mediated by an immunological mechanism [1, 2]. These reactions are usually classified according to the underlying mechanism [2, 3], but also based on the time of the onset [2]. Several manifestations with different degrees of severity can occur [2–4]. Although it is estimated that drug allergy accounts for less than 10% of all ADR [5], its incidence increased in line with the overall increase in the incidence of allergic diseases [1]. This is especially reported in developed countries and some factors of a westernized lifestyle have emerged as potential contributors, including obesity and changes in dietary pattern [5]. In fact, obesity has become epidemic [6] and a major public health problem in the developed world [7, 8]. Much of the disease risk is related to the associated low-grade systemic inflammation [6–10], that has been linked with several chronic conditions and that can be modulated by diet [11–14].

While polyunsaturated fatty acids and antioxidant vitamins have shown a protective role [11, 13, 15, 16], total fat and saturate fat acids revealed pro-inflammatory properties [11, 13, 16].

A dietary pattern approach has been considered advantageous since it considers the combined and interacting effects of nutrients and other food components [12, 17].

The dietary inflammatory index (DII) is a tool, developed by Cavicchia [11], and updated by Shivappa [12], that measures the inflammatory potential of the diet, from maximally anti-inflammatory to maximally pro-inflammatory. The purpose was to be used across diverse population in order to predict inflammatory levels and related health outcomes [13]. It has been used in several studies and chronic diseases [18–24] like metabolic [13] and cardiovascular diseases [19, 20], but also in asthma [22–24].

Research on the increasing incidence of asthma and other allergic diseases evidenced the role of diet as a potential key factor influencing immune homeostasis through a complex interplay between nutrients, their metabolites and immune cell populations [5]. There are no published studies involving patients with drug allergy.

In a previous study [25], we investigated and reported, for the first time, a potential link between obesity and drug allergy. The group of patients with drug allergy revealed significantly higher parameters associated with both global and central obesity and also higher levels of systemic inflammatory markers, than controls. Moreover, body fat percentage (BFP) emerged as a predictor of drug allergy.

The aim of this study was to investigate a potential association between diet, including dietary inflammatory index, and drug allergy.

It was also our objective to evaluate correlations between dietary parameters and obesity, inflammatory and metabolic parameters, in drug allergic patients.

## 2 –Material and methods

To pursue the proposed aims we developed a prospective, observational, cross-sectional and case-control study.

### Study population

Ninety consecutive adult patients with a suggestive history of drug allergy were prospectively studied in our Department, from September 2017 to October 2018. A complete history based on a validated questionnaire (the drug hypersensitivity questionnaire developed by European Network of Drug Allergy- ENDA) [26] was obtained in the outpatient clinic, during the first clinical assessment. Patients with a suggestive history of drug allergy were referred to a day hospital for diagnostic procedures, as routine in our clinical practice. One hundred of patients that met the inclusion criteria were invited to participate by phone the day before their first visit to the day hospital. If they agreed to participate, an overnight fasting was recommended. The inclusion criteria were: age  $\geq 18$  years; history suggestive of drug allergy in the previous 5 years and any suspected drug involved. Patients that did not complete the drug allergy diagnostic protocol or that did not have a conclusive diagnosis at the end of the study, were excluded. The same population were used in our previous work [25] to assess obesity parameters in patients with drug allergy, where the algorithm for patients' inclusion is outlined.

Social-demographic data were collected.

Leisure-time physical activity was evaluated through two questions about the type of exercise and the time spend on it in a week (number of hours) and classified in intensity categories (sedentary, irregularly active, active and intensely active), considering the 4 categories of the Intensity Physical Activity Questionnaire (IPAQ) classification [27].

The protocol was approved by the Hospital Ethics Committee (CE-66-2016) and written informed consent was obtained from all participants included in the study.

### Drug allergy diagnostic work-up

The diagnostic work-up was performed considering clinical history and according to international guidelines [2], as usual in our clinical practice. The characteristics of the reaction, namely the type (immediate versus non-immediate), clinical manifestations (anaphylaxis, urticaria/angioedema, or maculopapular exanthema, for example) and severity of reaction, are relevant factors to guide diagnostic procedures. These included skin tests, prick and intradermal [28, 29], specific IgE and drug provocation tests (DPT) [30].

The diagnosis of drug allergy was confirmed when skin tests were positive for validated concentrations or when specific provocation test with the suspected drug was positive (group of patients with drug allergy). If all diagnostic procedures were negative, including DPT with the suspected drug, drug allergy was excluded (control group). So, the study randomization was done according to the result of the drug allergy diagnostic work-up.

### Dietary inflammatory index (DII)

The Dietary inflammatory Index (DII) score is a calculated parameter that provides an estimate of the inflammatory potential of the diet. An individual's diet is considered more pro-

inflammatory when the DII score is more positive, while the diet is considered more anti-inflammatory when the DII score is more negative. The DII score was calculated according to Shivappa *et al* [13] and categorizes a list with 45 possible food items, which range from maximally anti-inflammatory to maximally pro-inflammatory potential.

Dietary data were obtained from a 91-item self-administered and semi-quantitative food-frequency questionnaire validated (FFQ) for Portuguese population [31]. This questionnaire was applied indirectly by a nutritionist to all participants allowing to assess the eating habits related to the previous 12 months. Dietary intake estimation was made multiplying the portion size in grams by the multiple fraction of daily frequency intake and by a seasonality variation factor. The conversion, from food to energy and nutrients intake, was performed using The Food Processor Plus program version SQL (ESHA Research, Salem, OR, USA). This database was supplemented with the Portuguese food composition database [32].

The DII score was calculated considering 28 of 45 possible food parameters. Data on  $\beta$ -carotene, eugenol, garlic, ginger, onion, saffron, turmeric, pepper, green/black tea, thyme/oregano, rosemary, flavan-3-ol, flavones, flavonols, flavonones, isoflavones and anthocyanidins, were not included since no information was available for these components in the Food Processor nutritional database.

To derive the individual DII scores, the global average intake (taken from Shivappa *et al* [13]) was subtracted from the reported daily intake of each nutrient in the FFQ and divided by the standard deviation of the global daily intake, rendering a z-score which was converted into a centered percentile score. This score was then multiplied with an overall inflammatory effect score. All 28 parameters included individually calculated nutrient-specific effect scores were then summed to obtain the global DII score.

### Anthropometric measurements and body composition

Height (to the nearest 0.5 cm) and body weight (to the nearest 0.1 kg) were measured with patients wearing light clothing and no shoes.

Body mass index (BMI) was calculated by dividing weight by squared height. According to the BMI categories defined by World Health Organization guidelines, patients were classified as normal weight ( $\geq 18.5$  and  $< 25$  kg/m<sup>2</sup>); overweight ( $\geq 25.0$  and  $< 30$  kg/m<sup>2</sup>) and obese ( $\geq 30.0$  kg/m<sup>2</sup>) [33].

Waist circumference (WC) was measured at the level midway between the lowest rib and the iliac crest. Based on International Diabetes Federation (IDF) criteria, central obesity was defined as WC  $\geq 0.80$  m in women and  $\geq 0.94$  m in men [34, 35]. Hip circumference (HC) was measured at the level of the widest circumference over the great trochanters. Both circumferences were measured with a flexible tap with subjects standing at the end of gentle expiration. The waist-hip ratio (WHR) was calculated [33].

Body composition, including fat mass (Kg and percentage), was assessed by bioimpedance (*Inbody 230*, Body Composition Analyzer; tetra polar 8-point tactile electrodes, BIOSPACE).

### Biochemical analysis

Serum leptin and serum adiponectin concentration were measured with the double antibody sandwich ELISA assay by using an antibody specific for human leptin and for human adiponectin, respectively (Mercodia Leptin ELISA/Mercodia Adiponectin, Mercodia AB, Uppsala, Sweden). Blood samples were obtained after overnight fasting, between 8 and 9 am. After clotting at 4°C, serum was separated by centrifugation and stored at -70°C until assay.

Blood samples for glucose, total cholesterol, high-density lipoprotein (HDL) and triglycerides in serum were obtained, at the same time using anticoagulant-treated tubes and their

concentrations determined by standard techniques. The low-density lipoprotein (LDL) levels were calculated according to the manufacturer's instructions (Roche, Rotkreuz, Switzerland).

### Statistical analysis

The statistical Package for Social Sciences® version 25 was used to analyze data and statistical significance was defined as  $p < 0.05$ .

For continuous quantitative variables, the existence of normal distribution was tested through histogram observation, kurtosis and skewness analysis and using the Kolmogorov-Smirnov test. To describe these variables, central tendency measures (mean and median) and dispersion measures (standard-deviation and percentiles 25–75) were used. To compare continuous variables with normal and non-normal distribution between two groups, an Independent Samples t Test and a Mann Whitney test were used, respectively. To compare continuous variables with normal and non-normal distribution between more than two groups, an ANOVA with Bonferroni correction and a Kruskal-Wallis test were used, respectively. For qualitative variables we used absolute numbers and percentages. To analyze differences between groups in categorical variables, the chi-square test and the Fisher exact test were used. Correlations were evaluated using the Pearson and the Spearman correlation tests for continuous symmetrical and asymmetrical variables, respectively.

## 3 –Results

### Study population

Eighty-four patients completed the drug allergy diagnostic work-up with a conclusive result: 39 patients (46%) had the final diagnosis of confirmed drug allergy and in 45 (54%) drug allergy was excluded, representing the study group and the control group, respectively.

Seventy-nine per cent of the patients were female and the mean age was  $39.58 \pm 13.3$  years, range [18 – 77].

The two groups were homogeneous concerning socio-demographic and general clinical characteristics. There were significant differences concerning the drug allergic reactions between the two groups. More details about the sample used in this study are presented in a previous publication from our group [25].

Regarding BMI, 42.2% of patients had normal weight, 36% were overweight, 19.3% obese and 2.4% underweight. According to the IDF criteria, 57.6% of the women and 41.2% of the men presented central obesity. As already described in our previous work [25], patients with drug allergy revealed significantly higher obesity-related parameters (anthropometrics and evaluated by bioimpedance) and also higher systemic inflammatory markers, compared to controls.

### Dietary inflammatory index (DII) and drug allergy

Globally, the 84 subjects revealed an anti-inflammatory diet pattern with a mean DII of  $-3.38 \pm 0.9$  (min -4.66, max -0.93).

No significant differences were found in DII scores between patients with confirmed drug allergy and controls ( $-3.37 \pm 0.95$  vs  $-3.39 \pm 0.86$ ,  $p = 0.985$ ).

Analyzing the 39 patients with confirmed drug allergy, no differences were observed in DII scores regarding the clinical manifestations, the type or the severity of the reactions (Table 1).

### Dietary inflammatory index (DII) and obesity parameters

There were no significant correlations between DII scores and anthropometric measurements or body composition by bioimpedance analyzed as continuous variables, neither in the globality of the evaluated individuals, nor in the patient group or in the control group (Table 2).

**Table 1. Patients with drug allergy: DII scores and characteristics of the reaction.**

	DII score	P value
<b>Type of reaction</b>		
Immediate reactions, Median (IQR)	-3.58 [(-4.03)—(-3.01)]	0.751
Non-immediate reactions, Median (IQR)	-3.21 [(-4.23)—(-2.72)]	
<b>Severity of reaction</b>		
Severe reactions, Median (IQR)	-3.40 [(-4.00)—(-3.05)]	0.975
Mild/moderate reactions, Median (IQR)	-3.57 [(-4.11)—(-2.73)]	
<b>Anaphylaxis</b>		
Yes, Median (IQR)	-3.32 [(-4.03)—(-3.00)]	0.729
No, Median (IQR)	-3.64 [(-4.15)—(-2.74)]	
<b>MPE</b>		
Yes, Median (IQR)	-3.21 [(-4.54)—(-1.60)]	0.894
No, Median (IQR)	-3.58 [(-4.00)—(-3.02)]	

IQR- interquartile range, MPE- maculopapular exanthema

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## Dietary inflammatory index (DII) adipokines levels, biochemical and other parameters

With respect to adipokines levels, a significant and negative correlation was found between DII and adiponectin levels, when all the individuals ( $r = -0.254$ ,  $p = 0.021$ ) and the control group ( $r = -0.311$ ,  $p = 0.040$ ) were considered, but not the drug allergy group ( $r = -0.225$ ,  $p = 0.175$ ) (Table 3). Regarding the other assessed parameters, including biochemical parameters, no significant correlations were observed with DII, except for triglycerides in the drug allergic group ( $r = 0.359$ ,  $p = 0.032$ ) (Table 3).

## Macronutrients, micronutrients and drug allergy

In Tables 4 and 5 the dietary parameters are described according to macronutrients and micronutrients, respectively. We found that the drug allergic patients presented a significantly higher intake of mono-unsaturated fatty-acids (MUFA) compared to controls ( $19.8 \pm 3.7$  vs  $17.8 \pm 4.0$ ,  $p = 0.021$ ). No other statistically significant differences were observed.

**Table 2. Correlations between DII and anthropometric/bioimpedance parameters.**

DII	All individuals (n = 84)		Drug allergy group(n = 39)		Control group(n = 45)	
	R value	P value	R value	P value	R value	P value
BMI (kg/m <sup>2</sup> )	0.096	0.387	0.111	0.507	0.086	0.575
Waist circumference (cm)	0.070	0.528	0.040	0.813	0.098	0.524
Hip circumference (cm)	0.072	0.517	0.117	0.483	0.001	0.997
Waist/Hip	-0.012	0.911	-0.038	0.820	0.013	0.932
Fat mass (kg)	0.009	0.940	-0.011	0.949	-0.004	0.981
Body fat percentage (%)	-0.038	0.739	-0.063	0.711	-0.028	0.854
Trunk fat mass (kg)	0.015	0.894	-0.003	0.986	-0.012	0.938
Trunk fat percentage (%)	-0.34	0.761	-0.056	0.742	-0.029	0.854
Trunk lean mass (kg)	0.126	0.262	0.141	0.404	0.104	0.500
Fat free mass (%)	0.115	0.307	0.145	0.391	0.113	0.465
Lean mass (kg)	0.122	0.278	0.153	0.365	0.128	0.408

BMI-Body mass index; BMR- Basal metabolism rate; All variables were analyzed as continues

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Table 3. Correlations between DII and adipokines levels, biochemical parameters and other parameters.

DII	All individuals (n = 84)		Drug allergy group (n = 39)		Control Group (n = 45)	
DII	R value	P value	R value	P value	R value	P value
Leptin (ng/ml)	-0.107	0.334	-0.078	0.643	-0.157	0.305
Adiponectin (ng/ml)	<b>-0.254</b>	<b>0.021</b>	-0.225	0.175	<b>-0.311</b>	<b>0.040</b>
Ratio leptin/adiponectin	0.006	0.954	0.082	0.626	-0.057	0.060
Total cholesterol (mg/dl)	-0.065	0.568	-0.068	0.689	-0.064	0.686
HDL cholesterol (mg/dl)	-0.188	0.097	-0.301	0.070	-0.088	0.577
LDL cholesterol (mg/dl)	-0.001	0.994	-0.011	0.951	-0.012	0.942
Triglycerides (mg/dl)	0.138	0.229	<b>0.359</b>	<b>0.032</b>	-0.084	0.596
Glucose (mg/dl)	0.053	0.643	0.174	0.302	-0.095	0.556
Systolic BP (mmHg)	0.025	0.829	-0.051	0.775	0.024	0.880
Diastolic BP (mmHg)	0.010	0.932	0.095	0.595	-0.080	0.616

HDL-high-density lipoprotein; LDL- low-density lipoprotein; BP- Blood pressure

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Table 4. Macronutrients intake and drug allergy diagnosis.

	Confirmed drug allergy (N = 38)	Excluded drug allergy (N = 45)	P value
Calories (kcal), Mean (SD)	2457.3 (648.7)	2488.7 (550.7)	0.812
Protein (g), Mean (SD)	111.2 (32.4)	113.6 (25.1)	0.697
Carbohydrates (g), Mean (SD)	266.8 (74.8)	284.6 (79.2)	0.298
Fibre (g), Mean (SD)	31.0 (11.7)	31.2 (11.3)	0.914
Total fat (g), Mean (SD)	106.4 (31.5)	101.3 (26.1)	0.418
Cholesterol (mg), Mean (SD)	349.3 (109.8)	338.1 (92.3)	0.616
Linolenic acid(g), Median (IQR)	1.4 (1.1–1.7)	1.3 (1.1–1.8)	0.877
Trans fat (g), Median (IQR)	0.9 (0.7–1.2)	0.9 (0.7–1.1)	0.844
Sodium (mg), Mean (SD)	2112.3 (696.0)	2228.5 (608.9)	0.419
Water (%), Mean (SD)	1573.5 (515.4)	1626.8 (461.9)	0.621
Alcohol (g), Median (IQR)	1.7 (0.0–5.2)	1.7 (0.0–10.9)	0.464
Caffeine (mg), Median (IQR)	81.3 (31.4–105.1)	78.8 (19.2–86.4)	0.187
Protein (TEV), Mean (SD)	18.0 (2.0)	18.3 (2.2)	0.477
Carbohydrates (TEV), Mean (SD)	43.7 (7.2)	45.5 (5.5)	0.191
Simple sugars (TEV), Mean (SD)	18.1 (4.8)	19.4 (4.3)	0.178
Total fat (TEV), Mean (SD)	38.9 (5.3)	36.6 (5.5)	0.060
Polyunsaturated fat (TEV), Mean (SD)	6.5 (0.9)	6.3 (1.2)	0.695
Omega-3 (TEV), Mean (SD)	0.6 (0.1)	0.6 (0.1)	0.593
Omega-6 (TEV), Mean (SD)	5.2 (1.0)	5.1 (1.2)	0.558
Saturated fat (TEV), Mean (SD)	9.6 (1.7)	9.5 (1.5)	0.820
Linoleic acid (TEV), Mean (SD)	5.0 (1.0)	4.9 (1.2)	0.523
Monounsaturated fat (TEV), Mean (SD)	<b>19.8 (3.7)</b>	<b>17.8 (4.0)</b>	<b>0.021</b>
Linolenic acid(TEV), Median (IQR)	12.9 (9.9–15.4)	12.0 (10.0–16.0)	0.913
Trans fat (TEV), Median (IQR)	0.3 (0.3–0.5)	0.3 (0.3–0.4)	0.777
Ethanol (TEV), Median (IQR)	11.6 (0.0–36.2)	11.6 (0.0–76.3)	0.409

SD- standard deviation; IQR- interquartile range; TEV-total energy value

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Table 5. Micronutrients intake and drug allergy diagnosis.

	Confirmed drug allergy (N = 38)	Excluded drug allergy (N = 45)	P value
Vitamin A (RE), Mean (SD)	2313.2 (1183.1)	2483.5 (1342.0)	0.485
Niacin B3 (mg), Mean (SD)	26.2 (7.3)	28.6 (8.6)	0.625
Folate (mcg), Mean (SD)	418.7 (171.2)	420.4 (177.0)	0.890
Iron (mg), Mean (SD)	17.7 (4.9)	18.8 (6.2)	0.371
Magnesium (mg), Mean (SD)	418.4 (147.6)	408.6 (120.8)	0.166
Potassium (mg), Mean (SD)	4009.5 (1287.4)	4194.5 (1092.6)	0.496
Selenium (mg), Mean (SD)	121.1 (40.1)	117.1 (33.9)	0.173
Zinc (mg), Mean (SD)	13.5 (4.3)	14.0 (3.9)	0.231
Vitamin D (mcg), Mean (SD)	4.7 (2.0)	5.1 (2.0)	0.919
Vitamin E (mg), Mean (SD)	14.4 (4.4)	14.0 (4.4)	0.936
Thiamine B1 (mg), Median (IQR)	1.7 (1.5–2.1)	1.8 (1.5–2.2)	0.285
Riboflavin B2 (mg), Median (IQR)	2.1 (1.7–2.6)	2.2 (1.8–2.7)	0.344
Vitamin B6 (mg), Median (IQR)	2.3 (2.0–2.9)	2.6 (2.2–3.3)	0.091
Retinol (RE), Median (IQR)	374.8 (257.6–762.2)	329.5 (206.4–803.6)	0.694
Vitamin B12 (mcg), Median (IQR)	10.0 (7.7–13.3)	10.1 (7.5–12.3)	0.920
Vitamin C (mg), Median (IQR)	156.1 (114.0–230.0)	170.0 (118.5–245.1)	0.590
Vitamin K (mcg), Median (IQR)	13.0 (11.0–20.7)	13.6 (11.0–20.8)	0.923
Calcium (mg), Median (IQR)	919.4 (766.9–1237.3)	932.1 (838.6–1284.0)	0.609
Iodine (mcg), Median (IQR)	70.7 (33.6–99.5)	77.1 (42.8–102.9)	0.577

SD- standard deviation; IQR- interquartile range; RE- retinol equivalent (1RE = 1 mcg Vitamin A)

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### Physical activity and obesity, biochemical and other parameters

In terms of physical activity, the majority of individuals (48.8%) were sedentary, 26.2% irregularly active, 9.5% active and 14.3% intensely active. In the group of patients with drug allergy, 21 (53.8%) were classified as sedentary, 9 (23.1%) irregularly active, 4 (10.3%) active and 4 (10.3%) intensely active, while 8 controls (17.8%) were intensely active, 4 (8.9%) active, 13 (28.9%) irregularly active and 20 (44.4%) sedentary.

No differences with statistical significance were obtained between the 4 categories of physical activity regarding anthropometric/ bioimpedance, inflammatory and biochemical parameters assessed or with the DII scores.

## 4 –Discussion

To our knowledge, this is the first study applying the DII score in the assessment of patients with drug allergy. We found a slightly higher DII score in patients with drug allergy compared to controls but not achieving statistical significance. Nonetheless, the former group revealed significantly higher obesity parameters and leptin levels, as detailed in our previous work [25]. This result can be in part related to the general dietary pattern of our sample, but also to the sample size. Interestingly, the globality of the individuals of our study presented an anti-inflammatory DII (DII = -3.38), suggesting a Mediterranean diet pattern [6]. This DII score is considerably more anti-inflammatory than the few studies involving patients with asthma, performed in Australia [24] (DII asthma group =  $-1.40 \pm 0.2$ ; controls =  $-1.86 \pm 0.4$ ,  $p = 0.04$ ), in Portugal [36] ( $0.1 \pm 1.5$ ) and in EUA [23] (DII scores revealed a pro-inflammatory diet in all evaluated groups). Other studies carried out in our country also showed higher DII scores, particularly studies involving children [36, 37] or adolescents [19], but also adults ( $-0.35 \pm 1.88$ ) [38]. These differences might also reflect regional and age differences in dietary patterns.



In our study, no significant correlations were found between DII scores and obesity parameters assessed by anthropometric measurements or by bioimpedance. In very large sample studies, individuals with higher pro-inflammatory diets assessed by DII presented higher obesity parameters, such as BMI [20, 39, 40] and especially waist circumference [20]. With these results the authors discuss that a pro-inflammatory diet might contribute to increase or maintain obesity, especially abdominal obesity, in a population mostly overweight or obese [20]. It is well established that the link between obesity and diet is not exclusively related to the balance between energy intake and expenditure [6], but also with the inflammatory pattern of the diet and its potential to modulate the low-grade chronic inflammation state associated with obesity [12–15]. Several studies investigated and found associations between DII scores and inflammatory systemic markers, as CRP [14, 42], TNF- $\alpha$  [22, 42], IL6 [19, 23], C3 [19, 42], and also with biochemical parameters as triglycerides [41, 42], and other lipoproteins [41].

Within the inflammatory and biochemical parameters assessed in our study, we found a negative correlation between the DII scores and adiponectin levels, when all the individuals or only the control group were considered. This correlation was not present in the drug allergy group. Adiponectin is an anti-inflammatory adipokine that is downregulated in the obesity status [43]. A negative correlation with DII scores means that patients with lower DII scores or more anti-inflammatory diet, have higher adiponectin serum levels which is in accordance with the adiponectin role and with other studies [41]. Moreover, this correlation was observed in the control group, with less obesity parameters and leptin levels [25], but not in the drug allergic patients. We also observed a positive correlation between DII scores and triglycerides levels exclusively in the drug allergic group, illustrating that patients with a less anti-inflammatory diet have higher triglycerides levels. Also, this correlation was only present in the group with higher obesity parameters and systemic inflammatory parameters [25].

With respect to individual macro and micronutrients and other food components, we did not find any association with drug allergy, except for MUFAs, with higher intake in this group compared to controls. This is an unexpected result, as MUFAs have globally shown anti-inflammatory effects [44]. Moreover, this result does not take into account the whole diet and the interaction between its components, and a dietary pattern approach is more appropriate [13, 18, 44, 45]. Although, Heinrich *et al.* in 2001, used the European Community Respiratory Health Survey (ECRHS) that included 3,872 subjects, and concluded that a high intake of MUFAs might promote the development of allergic sensitization [46].

In terms of the potential role of the diet and its components in the development of allergic diseases and its outcomes, research is focused not only in dietary patterns [23, 24, 36, 43, 45], but also in individual nutrients and food components' [47–49] and their potential influence throughout life, including in fetal life [50]. Although some results are inconsistent, there is evidence that the Mediterranean diet pattern has a protective role [6, 44, 45, 47] and a Western diet pattern a deleterious one [6, 44]. This is mostly attributed to the high content in antioxidants, fibers, polyunsaturated fatty-acids omega-3 (w3-PUFAs) and MUFAs of the Mediterranean diet, combined with low amounts of saturated fatty-acids (SFAs) [6, 44, 45, 47]. Conversely, the Western diet is a high caloric diet, rich in SFAs and w-6 PUFAs, and with low intake of w-3 PUFAs, fiber and antioxidants [6, 44, 45, 47]. The role of individual nutrients and other food components is not yet clearly established in allergic diseases, although several have revealed potential effects. The ratio w3-PUFAs/w-6 PUFAs might be important [44, 45, 49], while fruits and vegetables have revealed to have the most consistent protective effects [42, 44, 47, 48], probably because they are rich in antioxidants such as vitamin C, E and  $\beta$ -carotene and also in flavonoids, isoflavonoids and polyphenolic compounds [45, 48]. On the other hand, vitamin A and D deficiency might influence the development of allergy and its outcomes [6, 47].

Physical activity was also evaluated in this study, as exercise has demonstrated an effect on total and abdominal adiposity [51], serum adipokines [52] and biochemical parameters [53].

No statistically significant differences were found between the 4 categories of physical activity regarding anthropometric/ bioimpedance, inflammatory and biochemical parameters evaluated, probably due to the reduced number of individuals in each category. We also analyzed a potential association between physical activity and DII scores, as both may reflect a certain type of lifestyle, but also here the sample size might have influenced the absence of a significant association.

The global anti-inflammatory diet pattern of our sample might represent a constraint to the results of our study. Other limitations of our study also deserve consideration. First, the sample size also did not allow the analysis according to the standardized terciles or quartiles as seen in other studies. Second, 14 nutrients/components were not included in the DII assessment, as no data was available in the Portuguese food composition database. Third, dietary habits were collected using self-reported information from FFQs and based on patients recall from the last 12 months. However, the use of a validated FFQ is considered an appropriate tool for this purpose and permits seasonality intake. This is not possible with 24h-Food questionnaires but, on the other hand, these questionnaires are more specific and do not have recall bias. Fourth, a trained nutritionist assisted the participants in our study. This fact could avoid some inaccuracies, but could also influence patients' answers, as they tend to respond according to social desirability [54]. Finally, the method used for the evaluation of physical activity was not based on objective measures and the question of the social desirability may also have influenced the patients' answers.

On the other hand, the prospective design, the randomization, the high number of dietary parameters evaluated, the assessment of a considerable number of potential confounders and the complete drug-allergy work-up were relevant in our study.

## 5- Conclusions

Globally the population assessed in this study revealed an anti-inflammatory diet profile. Although, we have found in a previous work that the same patients with drug allergy revealed higher obesity and inflammatory parameters, here the DII did not allow to distinguish between patients with drug allergy and controls. However, the DII scores correlated with triglycerides levels in drug allergic patients and inversely with adiponectin levels in the control group.

Larger studies are needed to clarify the potential role of the diet in drug allergy and its outcomes.

## Supporting information

**S1 File.**  
(SAV)

## Author Contributions

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