Research Article

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Case control study for the effect of functional food consumption on biomarkers of patients with viral hepatopathy (Hepatitis B and C) and metabolic syndrome

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ABSTRACT

Introduction: The dissemination and adoption of healthy eating habits are crucial in promoting Public Health. Metabolic syndrome increases the risk of developing diabetes and cardiovascular disease, a leading cause of death. Viral hepatitis causes a high morbidity burden and a high incidence of hepatocellular carcinoma.

Objective: This case-control aims to investigate the impact of eating habits, especially functional food, on biomarkers of Metabolic Syndrome, Hepatitis B/C. The bibliographic lack of research on this matter was the impetus for this study.

Methods: 90 (aged> 18 years) patients participated in the study, equally distributed in the three diseases and 90 healthy controls. The cardiovascular-hepatic biomarkers evaluated were: HbA1c, CHOL, TG, HDL, SGOT, SGPT, NT-proBNP, U, and CR.

Results: The main groups of conventional and selected functional foods were recorded through their frequency of consumption and their effect on biomarkers (Statistically significant level, p-value <0.05). BNP was statistically significantly correlated (<300 pg./ml) with the consumption of wine, legumes, and honey, Urea with the consumption of fruits, Cr with the consumption of nuts and olive oil, and Cholesterol with the consumption of honey and herbs. Increased consumption of nuts was statistically significantly correlated with the improvement of BNP and U-values, vegetables with the improvement of SGPT, coffee fruits, and herbs with the improvement of SGOT values.

Conclusion: Our results agree with the international references, where the beneficial effects of functional foods are mainly captured descriptively and not in absolute values of biomarkers, as we have tried to highlight in our case-report study. Although in a small sample, the results highlight the beneficial effect of functional foods on cardiovascular-hepatic biomarkers. More prospective studies are needed for clearer results.

Keywords: Functional Food; Metabolic Syndrome; Hepatitis B; Hepatitis C; Biomarkers

INTRODUCTION

The dissemination and adoption of healthy eating habits is a crucial factor in advocating for individual health and a critical factor in promoting Public Health [1-4]. Functional foods provide health benefits, in addition to the nutrients they contain [5-6]. Metabolic syndrome is considered a worldwide pandemic disease; a disorder that affects the overall functioning of the body and is manifested by elevated cholesterol/triglyceride levels, weight gain with visceral fat deposition in the abdomen while increasing the risk of developing diabetes and cardiovascular disease, the leading cause of death [7-12]. Viral hepatitis [13], and hepatitis B and C, is a public health problem with a high morbidity burden and a high incidence of hepatocellular carcinoma, with significant social and economic consequences [14-17]. The lack of research in Greece on the effect of diet on biomarkers of metabolic syndrome and viral hepatitis B and C was the impetus for this study.

Metabolic syndrome (Mets) is the multifactorial entity that accelerates the onset of cardiovascular disease and type 2 diabetes [18-21]. It is a disease with no specific symptoms leading to its diagnosis. The diagnosis is made through laboratory indicators [22]. Manifested by increased cholesterol and triglycerides levels, a significant reduction in energy levels, and weight gain with visceral fat deposition in the abdomen. Criteria for the clinical diagnosis of metabolic syndrome NCEP-R(Network of Conservation Educators and Practitioners), NHLBI(National Heart, Lung, and Blood Institute), WHF(World Heart Federation), AHA(American Heart Association) 2005(Circulation 2009) are increased waist circumference (Caucasians ≥102cm for men and ≥ 88cm for women, elevated triglycerides or medication for TG(triglycerides)≥ 150mg/dl, reduced HDL(High-density lipoprotein) or treatment for reduced HDL<40mg / dL for men and <50mg / dL for women, increased blood pressure or antihypertensive treatment, SAP(Systolic Blood Pressure) ≥ 130mm and / or DAP(Diastolic Blood Pressure) ≥ 85mm Hg, elevated fasting blood sugar or antihyperglycemic therapy≥ 100mg/dl. At least three of the mentioned factors must be present to establish the existence of metabolic syndrome [23-26].

Hepatitis B (CHB, HBV) is a virus that is recorded as 100 times more contagious than HIV (Human Immunodeficiency Virus) and 10 times more contagious than HCV (Hepatitis C Virus) [27]. It is the most common carcinogen for humans after smoking. HBV infection is an internationally severe public health problem with significant morbidity and mortality. Internationally, the disease burden is estimated at approximately 250 million patients with HBV surface antigen (HbsAg, Hepatitis B surface antigen). 10 genotypes of the virus (A-J) have been identified [28]. HBV DNA: a positive result indicates the presence of the virus, which can be transmitted to others. A negative result usually means the virus cannot be transmitted to others [29,30].

Hepatitis C virus (HCV, CHC) [30] is a small, enveloped, single-stranded RNA virus, a disease with a high morbidity and mortality rate worldwide, particularly due to the high incidence of chronic infection complications in patients [31]. The global prevalence of HCV is 1% (71.1 million infected adults), with approximately 400,000 people dying each year from the disease, mainly due to cirrhosis of the liver and hepatocellular carcinoma [33]. The ability of the HCV virus to mutate led to the identification of 11 different genetic variants. Subtypes 1a and 1b are the most

common and account for about 60% of infections worldwide [32].

Many people infected with the hepatitis C/B virus are unknown in the health care system because they may be asymptomatic for years and seek medical attention only when they develop liver-related complications. When there are symptoms, the clinical picture consists of feeling tired, anorexia, nausea, vomiting, liver pain, diarrhea, and fever [34]. After 1-3 weeks, the above symptoms begin to subside, and the typical symptoms of hepatitis appear, which are jaundice (yellow color of the skin, mucous membranes), itching, discoloration of the stool, and hyperpigmentation of urine. Acute hepatitis with jaundice occurs in <10% of children <5 years of age and in 30-50% of adults. In other cases, there are no symptoms [35].

Functional foods are often referred to as "natural health products" or "healthy foods" [36]. They are not pills or powders but contain or are enriched with ingredients derived from natural materials or modified by technological or biotechnological means. The actual definition for these functional foods, as provided by the Functional Food Center (FFC), is as follows: "Natural or processed foods that contain biologically-active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms." [37]. Although there is scientific data about the effect of functional foods on cardiovascular diseases and metabolic syndrome, there is not sufficient evidence about their possible role in hepatic biochemistry.

This study aimed to conduct a case-control study to investigate the effect of Functional Food on Hepatic Biochemistry and Cardiovascular Indices in patients with Viral Hepatopathy (Hepatitis B and C) and Metabolic Syndrome, where the existence of international research is incomplete.

MATERIALS AND METHODS

Subjects: The study was a 2-arm parallel case-control study and involved 90 patients (12 patients were excluded due to insufficient data). The 90 patients were divided into three groups of patients :

- 30 patients with Hepatitis C
- 30 patients with Hepatitis B
- 30 patients with Metabolic Syndrome

The sample collection was carried out randomly at the General Hospital of West Attica "Agia Varvara" - General Hospital of Nikaia "Agios Panteleimon." Each time a patient was admitted to the study, a control was entered by gender and age assimilation.

Admission criteria: To be admitted to the study, a patient had to be over 18 years of age and have been diagnosed with :

- HBsAg (+), anti-Hbc (Hepatitis B core antigen) IgM (Immunoglobulin M) (+) and HBV-DNA positive PCR (Polymerase Chain Reaction)
- Anti-HCV (+) and PCR HCV-RNA positive
- Metabolic Syndrome to meet all five criteria (increased waist circumference ≥102cm for men and ≥ 88cm for women., Increased triglycerides ≥ 150mg / dL, decreased HDL, or treatment for decreased HDL <50mg / dL, increased blood pressure or antihypertensive treatment SAP ≥ 130mm and/or DAP ≥ 85mm Hg, increased fasting sugar or antihyperglycemic treatment ≥ 100mg / dL).

Regarding the selection of healthy controls, it was carried out in personal interviews with the participants by the doctor-researcher without clinical symptoms, signs, or suspicion of any form of Metabolic Syndrome or Hepatitis

of any type (A, B, C, D history. These questionnaires were completed through Google Forms. People with normal liver biochemistry and cardiovascular markers were approached voluntarily and selected. To reduce the selection error, a random selection was made where possible (approximately 60% of the witnesses) through anonymous lists of residents in various areas of Attica (mainly Athens). 40% of the witnesses consisted of colleagues, friends, or relatives of the researcher who participated in the study and met the above criteria.

Ethics: The data collection was carried out with the written permission of the Scientific Council of the Hospital of West Attica "Agia Varvara" - General Hospital of Nikaia "Agios Panteleimon," with the approval of the bioethics committee of the hospital and according to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee "Ethical Principles for Medical Research Concerning Human Subjects. " The application protocol number was 4481/2021.07.08 and was approved by the decision of the 9th meeting of the Scientific Council of the General Hospital of West Attica "Agia Varvara" - General Hospital of Nikaia "Agios Panteleimon" on the 8th of September 2021. Written informed consent was obtained from all study participants to participate in the research. Study participants were informed about the purpose of the study, the confidentiality of the data, and the voluntary nature of the participation. The fundamental rules of ethics, science and research were observed during the present study.

Data Collection: The data collection and analysis were carried out between 01-07-2021 and 10-12-2021. The study was conducted in the outpatient clinics of the Hepatology-Pathology Clinic located at the General Hospital of West Attica "Agia Varvara" after the consent of the coordinator-Director of the Hospital of West Attica "Agia Varvara. “Highlight the difficulties in completing and collecting the COVID-19(Coronavirus disease 2019) pandemic questionnaires, which consist of the difficulty of reaching patients to achieve compliance with all measures to protect public health from the risk of pandemic spread.

Biomarkers: The processing of biomarkers HbA1c (Hemoglobin A1c), SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamate-pyruvate transaminase or serum glutamic-pyruvic transaminase), NT-proBNP (N-terminal prohormone of brain natriuretic peptide), CHOL (cholesterol), TG (triglyceride), HDL (High-density lipoprotein), U(urea), CR (creatinine) was performed with random access sample technology (RANDOM ACCESS) in Architect ci4100. Its operating principle is based on Chemiluminescence with a quality control (QC) system with Levey-Jennings's diagram display.

Study Questionnaires: A specially designed questionnaire based on bibliographic data was used for data collection. Specifically based on:

- Well-being: National Health Action for Youth Life.
- Le Prolepsis Institute: Benefits, Eating Habits
- National Action Plan for Public Health: 2021-2025
- NHANES – National Health and Nutrition Examination Survey

The questionnaire consisted of three sections:

The first section included questions regarding the study participants' demographic characteristics, gender, age, occupation, and educational level.

The second section was about the general and nutritional history of the participants and their eating habits during the research period.

The third section included questions about the frequency of consumption of conventional foods and functional foods that are literature-related to viral hepatitis and MS.

The contribution of the doctors and nursing staff of the outpatient clinics in the approach of both the patients and the healthy ones for completing the questionnaires was also significant.

Statistical Analysis: The Statistical Package for Social Sciences (SPSS) was used to record, edit, and analyze the results, and Google forms were used to display the graphs. Statistical analysis was performed using one-way ANOVA (difference through one characteristic-quantitative variable, between 3 or more populations-categorical variable), and P-value was calculated (statistically significant level, p-value <0.05). An F-test (used when comparing statistical models that have been fitted to a data set to identify the model that best fits the population from which the data were sampled) where the results are significant at the 5%, Post hoc analysis/Bonferroni test- Correction were conducted.

RESULTS

Demographic and General Characteristics of Patients – Healthy Controls: A sample of 90 patients and 90 healthy controls were collected from the study. The demographic characteristics of the patients who participated in the study are presented in the following graphs based on Google Forms.

Gender/ Age / Level of Education / Occupation: Great effort was made to reconcile patients and healthy controls with gender through personal calls. Due to the current situation (pandemic), we could not avoid minor discrepancies between healthy controls and patients.

Table 1. Frequency Of Gender, Age, Education in Patients and Healthy Controls

GENDER	METS	CHB	CHC	HEALTHY C.
Male	73.3%	76.7%	73.3%	77.5%
Female	26.7%	23.3%	26.7%	22.5%
AGE	**METABOLIC S.**	**CHB**	**CHC**	**HEALTHY C.**
18-35	26.7%	26.7%	21.2%	25.8%
36-46	40%	40%	33.3%	39.3%
47-57	26.7%	26.7%	24.2%	27%
58-68	6.7%	6.7%	24.2%	7.9%
EDUCATION	**METABOLIC S.**	**CHB**	**CHC**	**HEALTHY C.**
Primary	36.7%	43.3%	9.1	4.5%
Secondary	30%	40%	75.8%	6.7%
Higher	20%	3.3%	6.1%	5.6%
Postgra duate/ DR	13.3%	13.3%	9.1%	83.20%

Metabolic Syndrome (MetS): the largest percentage of patients 40% were aged 36-46 years old (n = 12) while the lowest percentage of 6.7% (n = 2) was aged 58-68 years. According to the Level of Education: 36.7% (n = 11) had received primary education, 30% (n = 9) had secondary education, 20% (n = 6) had university degree and only 13.3% (n = 4) held a master's degree. As far as the occupation is concerned: clear prevalence of private employees (55.2%, n = 16), with next, the profession of doctor (13.8% n = 4) and the freelancer (10.3%, n = 3) and the impressive thing was that only women were unemployed (3.4%). The large percentage of doctors with MS creates additional concerns for us in the sample (Table 1.).

Hepatitis B(CHB) (Table 1.)

- AGE: The largest percentage of patients 40% were aged 36-46 years (n = 12) while the lowest percentage (6.7% n = 2) were aged 58-68 years.
- Level of Education : 43.3% (n = 13) had received primary education, 40% (n = 12) had secondary education, 13.3% (n = 3) had university education and only 3, 3% (n = 1) held a master's degree.
- Occupation: Clear prevalence of private employees (63.3%, n = 19), self-employed 10%, unemployed 10% with a predominance of men (6.7%), civil servants and retirees the same percentage 6, 7%, private employees (48%) and public (32%) are quite close. There was also a significant difference in education. In the patients the secondary education clearly prevailed, while in the healthy ones, those of the higher education and it was impressive that the postgraduates prevail.

Hepatitis C(CHC) (Table 1.)

- AGE: The highest percentage of patients 33.3% were aged 36-46 years (n = 12) while the lowest percentage (3.0% n = 1) was aged> 68 year
- Level of Education: 9.1% (n = 3) had received primary education, 75.8% (n = 23) had secondary education, 6.1% (n = 1) were students of higher education, 9.1% (n = 3) university graduates and none had a master's degree
- Occupation: gross predominance of private employees (48.5%, n = 16), followed by the unemployed (24.3%, n = 7), with a predominance of men (18.2%) and 12.1% (n = 4) were civil servants.

Healthy (Table 1.)

- While in gender and education it was possible to have a proportion of percentages, between health and patients, in terms of level of education and occupation, there was a clear differentiation. Specifically, in the patients the private employees prevailed strongly while in the healthy ones the percentages between private employees (48%) and public (32%) are quite close. There was also a big difference in education. In the patients the secondary education clearly prevailed, while in the healthy ones, those of the higher education and it was impressive that the postgraduates prevail.

- AGE (n = 89): 39.3% were aged 36-46 years (n = 35) while the lowest percentage (7.9%, n = 7) was aged 58-68 years.

- Education Level (n = 81): 4.5% (n = 4) had received primary education, 6.7% (n = 6) had secondary education, 2.2% (n = 2) were 36.0% (n = 32) of higher

education students had a university degree and an impressive 47.2% (n = 42) had a master's degree.

Occupation: the percentage of private employees was 48.1% (n = 39), while second in percentage were civil servants 32.1% (n = 26). No unemployed were registered.

These differences may be explained by the fact that the patients' questionnaires were completed individually by patients who resided in West Attica and the main characteristics of these patients were:

- have a low income,
- several of them, intravenous drug users (IVDU-mainly hepatitis C patients),
- have a low level of education as many Roma live in the area.

Health questionnaires were completed （40%, as mentioned above） via Google Forms, a supplement that requires knowledge of computer and internet usage, and therefore a higher level of education that is usually consistent with the highest income.

***Eating Habits**:* A summary table for the frequency of the consumption of functional foods in healthy and patients' participants is quoted. From the frequency of consumption of functional food as we have recorded in Table 2, it becomes clear that the largest consumption of functional food by the group of healthy controls, except for the pomegranate whose consumption, is recorded the same. This apart from the obvious reason (they are healthy) may be because, in this sample as we have already mentioned there is a higher standard of living and education

Table 2: Frequency of Consumption of Conventional and Functional Food

Food	≥6t/ D Ay	4-5 Times/ Day	2-3 Times/ Day	Once/ Day	5-6 Times/ Week	3-4 Times/ Week	1-2 Times/ Week	2-3 Times/M Onth	Once/ Month	Nev Er
		H	E	A	L	T	H	Y		%
Juices			3.3	7.8	5.6	15.6	18.9	22.2	8.9	17.8
Fruits		1.1	15.6	30	7.8	22.2	14.4	6.7	1.1	1.1
Vegs	1.1		6.7	34.4	14.4	26.7	12.2	4.4		
Pomegra Nate				2.2	2.2		6.7	13.3	33.3	42.2
Fish						1.1	47.2	30.3	15.7	5.6
Legumes			1.1	2.2		2.2	68.9	18.9	4.4	2.2
Olive			23.3	43.3	16.7	6.7	5.6	3.3	1.1	
Herbs			4.5	16.9	4.5	19.1	19.1	12.4	16.9	6.7
Coffee		3.3	48.9	28.9	2.2	5.6	3.3	1.1	1.1	5.6
Honey			4.4	18.9	5.6	20	15.6	16.7	11.1	7.8
Nuts			5.6	17.8	8.9	11.1	30	13.3	8.9	4.4
Wine				5.6	2.2	7.8	18.9	22.2	20	23.3
		P	A	T	I	E	N	T	S	%
Juices				16.7	6.7	16.7	16.7	3.3		40
Fruits				51.7	3.4	24.1	13.8		3.4	3.4
Vegs				30		26.7	33.3			
Pomegra Nate						6.7	3.3	26.7	16.7	46.7
Fish			3.3			3.3	66.7	16.7	10	
Legumes						16.7	56.7	16.7	3.3	6.7
Olive	3.3		3.3	76.7	6.7	3.3	3.3	3.3		
Herbs		3.3		10	3.3	3.3	20	20	3.3	36.7
Coffee	6.7	3.3	6.7	66.7	3.3	3.3		3.3		6.7
Honey				13.3	3.3	13.3	26.7	20	16.7	6.7
Nuts				13.3		3.3	16.7	20	6.7	40
Wine		3.3			3.3		26.7	10	10	46.7

Biomarkers values: Regarding the biochemical hepatic and cardiovascular biomarkers in MetS, as we mentioned, the selected patients met all five factors of MS （Hypertension/Hdl/Hba1c-Glu/Chol/Tg, which in all had pathological values So, the other cardiovascular indices that we had defined from the beginning were measured: SGOT, SGPT, URINE, CREATINE, and NT-proBNP(Table 3.)**.** Regarding biochemical cardiovascular markers in hepatopathy patients, all cardiovascular markers were tested except SGOT and SGPT, whose values were pathological (Table 4.).

Healthy controls-participants' biomarkers values were within normal limits. (SGOT<40 IU/L, SGPT<56 IU/L, Urea <50 mg/dl, Creatinine <1,3 mg/dL, NT-proBNP <300 pg./dl, HBA1C%<6, Triglycerides <150 mg/dL, Cholesterol<200 mg/dl, HDL>50 mg/dl).

Statistical Data Analysis: Statistically significant differences were found between patients and nutrition in several biomarkers. Level of statistical significance ($p<0.05$).

Table 3. Variation of Biomarkers Values: SGOT, SGPT(MetS), UREA, CREATININE, *NT*-proBNP (MetS, Hepatitis B/C)

	METABOLIC	SYNDROME	
SGOT(IU/L)	**<40**	**40-60**	**>60**
	53.3%	33.3%	13.3%
SGPT(IU/L)	**<56**	**56-76**	**>76**
	23.3%	56.7%	0,2
UREA (mg/dl)	**METABOLIC S.**	**CHB**	**CHC**
<50	36.7%	43.3%	63.6%
50-70	43.3%	43.3%	33.3%
>70	0,2	13.3%	0,03
CREATININE (mg/dL)			
<1,3	36.7%	43.3%	63.6%
1,3-2,0	43.3%	43.3%	33.3%
>2,0	0,2	13.3%	0,03
NT-proBNP (pg./dl)			
<300	0,7	73.3%	60.6%
>300	0,3	26.7%	39.4%

Table 4. Variation of Biomarkers Values HBA1C, TRIGLYCERIDES, CHOLESTEROL HDL In Patients' Hepatitis B /C

HBA1C%	**CHB**	**CHC**
<5	23.3%	21.2%
5-5,4	43.3%	36.4%
5,4-6,0	23%	30.3%
>6	10%	12.1%
TRIGLYCERIDES (mg/dL)		
<150	30%	15.2%
150-200	30%	27.3%
200-250	23.3%	39.4%
250-300	16.6%	18.2%
CHOLESTEROL (mg/dL)	**CHB**	CHC
<200	30%	33.3%
200-250	46.7%	6.1%
>250	23.3%	606%
HDL (mg/dl)		
<200	50%	39.4%
200-250	40%	36.4%
>250	10%	24.2%

Table 5: Statistical analysis of MetS/CHB/CHC biomarkers with demographics and dietary habits. Level of significance: *p-value <0,05*

Gender (Men)	P-Value	Occupation (Private)	P-Value	Cr	P-Value	Urea	P-Value	Sgot	P-Value	Sgpt	P-Value	Bnp <300 Pg.	P-Value
MetS													
NUTS	**P=0.034**	HONEY	***p=0.033***	NUTS	***p=0.070***	HONEY	***p=0.088***	COF FEE↓	***p=0.002***	VEGS	***p=0.047***	NUTS	***p=0.048***
VEGS	**P=0.036**	MEAT	***p=0.028***	FRUIT	***p=0.139***	FRUIT	***p=0.044***	PASTA↓	***p=0.028***	WINE	***p=0.063***	LEGUMES	***p=0.071***
FRUITS	**P=0.121**	ALCOHOL	***p=0.076***					COLD CUTS↑	***p=0.026***	LEGU MES	***p=0.073***		
CHB													
ALCOHOL	***p=0.001***	JUICE	***p=0.076***	POME GRA NATE	***p=0.116***	NUTS	***p=0.172***	FRUIT	***p=0.005***			WINE	***p=0.033***
HONEY	***p=0.063***	POME GRA NATE	***p=0.118***	FISH	***p=0.161***	VEGS	***p=0.196***	HERBS	***p=0.047***			LEGUMES	***p=0.035***
NUTS	***p=0.065***							FISH	***p=0.065***			FRUIT	***p=0.075***
OLIVE OIL	***p=0.071***							POME GRANATE	***p=0.072***			COF FEE	***p=0.115***
CHC													
NUTS	***p=0.001***	ALCOHOL	***p=0.008***	NUTS	***p=0.019***	CHIC KEN	***p=0.057***	LEGU MES	***p=0.104***			HONEY	***p=0.039***
ALCOHOL	***p=0.085***	WINE	***p=0.101***	OLIVE OIL	***p=0.045***	LEGU MES	***p=0.059***	PASTA	***p=0.157***			PASTA	***p=0.148***
				CHIC KEN	***p=0.110***	HONEY	***p=0.106***					COF FEE	***p=0.217***
AGE		**EDUCATION**		**TG**		**CHOL**		**HDL**		**HBA1C**			
MetS (↑AGE)													
VEGS	***p=0.188***	HIGH/WINE	***p=0.031***										
SEA FOOD	***p=0.107***	LOW/ COLD CUTS	***p=0.056***										
HERBS	***p=0.151***												
ALCOHOL	***p=0.138***												
AGE		**EDUCATION**		**TG**		**CHOL**		**HDL**		**HBA1C**			
CHB(47-57)													
VEGS	***p=0.072***	HIGH/HERBS	***p=0.161***	↑MEAT	***p=0.033***	HONEY	***p=0.016***	NUTS	***p=0.155***	NUTS	***p=0.294***		
COLD CUTS	***p=0.092***	HIGH/VEGS	***p=0.280***	↑SAUSAG E	***p=0.062***	FISH	***p=0.114***	COF FEE	***p=0.188***				
								LEGUMES	***p=0.191***				
CHC(18-35)													
COFFEE	***p=0.022***	SECONDARY/ ALCOHOL	***p=0.210***	↓VEGS	***p=0.075***	HERBS	***p=0.049***	HONEY	***p=0.139***	HONEY	***p=0.137***		
PASTA	***p=0.078***	SECONDARY/ LEGUMES	***p=0.291***	FISH	***p=0.087***	COF FEE	***p=0150***			POME GRANATE	***p=0.137***		
				JUICE	***p=0.095***	VEGS	***p=0.177***			LEGUMES	***P=0.152***		

DISCUSSION

According to the World Health Organization, chronic non-communicable diseases such as cardiovascular disease, cancer, chronic lung disease, and diabetes are responsible for 63% of deaths worldwide. The main factors for the increased morbidity and mortality from these diseases are smoking, unhealthy eating habits, and insufficient physical activity. The United Nations General Assembly has declared 2016-2025 a Decade of Action for Nutrition, calling on all those responsible for stepping up their efforts to reduce all forms of malnutrition, such as malnutrition, obesity, and micronutrient deficiencies1. In addition, it has been estimated that between 1990 and 2003, deaths from viral hepatitis worldwide increased from 890,000 to 1,450,000. Life loss due to premature mortality increased from 31.0 to 41.6 million YLLs (Years of Life Lost), while disability-weighted life years have increased from 31.7 to 42.5 million DALYs (Disability Adjusted Life Years) [57-58]. It is worth noting that hepatitis C has a significant contribution to these increases, the DALYs of which increased by 43% for the above period, while in combination with hepatitis B represent 96% of deaths and 91% of the total DALYs of viral hepatitis [59]. With the 29.12.2020 Ministerial Decision "Defining Strategic Objectives of the Ministry of Health for the year 2021", it was defined as the 2nd Strategic Objective "Health and prosperity for all, at all ages" with Intervention Axis Improving eating habits and eliminating all forms of malnutrition (malnutrition, obesity), especially vulnerable groups such as infants, children, adolescents, pregnant women, nursing mothers and the elderly. In Greece, the population lives six months above the European average, but they are 25% sicker than the rest of Europe. There is an ambitious project, and it is a strategic choice of the Ministry of Health to make Prevention a "way of life" for all Greek citizens based on the principle of the World Health Organization "leave no one behind." The goal is a better quality of life for all, with the protection of human life. We should make a leap for a better and healthier life we deserve.

As mentioned above, the prevalence of MetS is reaching epidemic proportions, and since maintaining healthy eating habits is still a matter of clinical nutrition research, this study examined the effect of specific functional food (fruits/vegetables/pomegranates/wine/herbs), coffee/nuts/olive oil/legumes/fish-seafood/honey) in selected biomarkers. Metabolic syndrome is significantly associated with a fivefold increase in the risk of type II diabetes and doubles the risk of cardiovascular complications [39], the leading cause of death worldwide.

Liver patients are a particular group whose clinical course is directly related to diet, and few studies correlate it with biomarkers.

The first important finding of our case-control study-research was that the consumption of vegetables was statistically significantly increased in men, a fact that agrees with the study "Changes in Vegetable Consumption in Times of COVID-19—First Findings from an International Civil Science Project" by Irmgard Jordan et al. 2021[6], where an increase in the consumption of vegetables was found, especially among men during the pandemic (men are not known to be vegetable eaters). The beneficial effect of vegetables was statistically significantly correlated with improving SGPT values in MetS [39]. It was strongly correlated with improved urea values in CHB patients and triglyceride values in CHC patients [40]. Our findings are consistent with the results of studies where increased vegetable intake (RESOLVE diet) appeared to be the leading cause of improving body composition and metabolic health [41].

The following more critical finding was the statistically significant correlation between biomarkers

and the consumption of functional food where, as we have mentioned, there is a lack of studies. Specifically, we are referring to the consumption of nuts statistically significantly correlated with the improvement of BNP values in MS and U in patients with CHB. Our findings align with similar studies on functional foods. Regarding the cardioprotective role of wine, this was also found in the statistically significant correlation of the value <300 pgpg. / ml of BNP with the consumption of wine [42-44] and legumes in patients with CHB [45] and consumption of honey in CHC [46]. According to SGOT, there was a statistically significant correlation between price improvement in MetS with the consumption of pasta, coffee, fruits, and herbs in the CHB.

Regarding coffee, our findings align with those of the Hospital cohort study that showed the beneficial effect of coffee in stabilizing the ALT level [47,48]. The beneficial effect of herbs is confirmed by the study on the beneficial effect of tea, cinnamon, and curcumin which is mentioned in the literature [49]. As far as fruits are concerned, our findings are confirmed by studies on the beneficial cardioprotective action of fruits, berries [50], grapes, and pomegranate [51]. There is also a statistically significant correlation between the consumption of cold cuts (p = 0.026) and the increase in the value of the liver enzyme in MetS, as found in the study by Fabiani et al., 2019 [38].

As far as Urea is concerned, a statistically significant difference was found after fruit consumption in MetS, consistent with the studies on the beneficial effect of consuming fruits [50-52]. Regarding Cr (normal values) with the consumption of olive oil in CHC, a beneficial effect is reflected in studies concerning virgin olive oil [53], more general studies referred to in diet, and in the PREDIMED study on the Mediterranean Diet with nuts and olive oil [54]. Cholesterol levels showed a statistically significant correlation with the consumption of herbs in patients with MS, a finding that coincides with a study of cinnamon by Gupta-Jain et al., 2017 [45] and the use of curcumin by Azhdari et al., 2019 [55]. Regarding triglycerides (> 150 mg / dl), with meat consumption in CHB-MetS, as reported in the study by Fabiani et al., 2019 [38], for the intake of red and processed meat that was associated with a high risk of prevalence of the Metabolic Syndrome.

Statistically significant difference was reported between patients and health, in terms of Level of Education (p = 0.049). Patients had secondary education, while healthy people had higher education. It should be noted that the group of patients referred to people of lower standard of living (St. Barbara, Roma, IVDU). Level of Education again, where there was a statistically significant difference between the highest educational level and the average consumption of wine 1-2 times a week, a frequency that is considered beneficial to health as reported in studies on resveratrol, a component of red wine which activates sirtuins (SIRT1), which have a variety of biological effects, including cardioprotective, antioxidant, and anti-inflammatory effects and significantly reduces CRP [56]. Statistically significant increased consumption of nuts [54] in men and in all three diseases which may be explained by the fact that nuts are a snack that is easily supplied and accompanies many social activities that are still considered "male" in our society, such as watching sports programs.

Regarding the correlation of Cr (normal values), we did not find it to be statistically significant with fruit consumption [50-52], but only a strong correlation. The same with the consumption of pomegranate where it emerged statistically significant in the study of Hou et al., 2019 [51], while we again found only a strong correlation. HDL price improvement was strongly correlated with coffee consumption [48] and legumes in patients with CHB consistent with the findings of a study by Reverri et al., 2015 [56] on black beans that have a cardioprotective effect. HBA1C (price improvement) only a strong

correlation was detected with the consumption of honey, pomegranate, and legumes in patients with CHC while in the studies of Yeow et al., 2013 [46], Hou et al., 2019 [51], Reverri et al., 2015 [56] respectively, the correlation is statistically significant.

When we refer to olive oil, it is mean extra virgin olive oil and in terms of honey, the percentages were 80% thyme honey and 20% flowers.

There were some limitations in our case-control study regarding firstly, our demographic percentages. Specifically, in terms of gender the percentages in CHC and Mets (men = 73.3% / women = 26.7%) did not completely agree with those of health and CHB (men ~ 77% / women ~ 23%) and in terms of age, the rates in the different age groups, CHB, Mets were similar, but we had a significant difference in the rates of CHC patients, especially in the age group> 58 years where the percentage of CHC patients was ~ 21% vs. 7 % of health, CHB, Mets. Most of the patients were residents of West Attica with a high percentage of residents belonging to the Roma tribe with a low standard of living and education. As in any case-control study, the disadvantages focus on the researcher and the respondent's bias in the questions and answers respectively and the inability to accurately recall the eating habits of the respondents.

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CONCLUSION

A novelty of the research concerning the scientific community was its focus on the effect of eating habits, especially functional food, on biomarkers related to metabolic syndrome and hepatitis, an area where there

is a lack of research in the bibliography. With the increasing prevalence of Metabolic Syndrome worldwide, and the adverse effects of untreated hepatitis leading to increased hepatocellular carcinoma, all three diseases, if not treated promptly and effectively with appropriate treatment, will be a public health problem. With a high morbidity burden but also significant social and economic consequences. The study indicated a correlation of specific functional foods with biomarkers of metabolic syndrome and hepatitis. Nevertheless, more studies are needed, prospective epidemiological and interventional studies, to investigate further the possible role of functional foods on the pathophysiology of these diseases.

Abbreviations: MetS, Metabolic Syndrome. NCEP-R, Network of Conservation Educators and Practitioners. NHLBI, National Heart, Lung, and Blood Institute. WHF, World Heart Federation; AHA, American Heart Association. SAP, Systolic Blood Pressure. DAP, Diastolic Blood Pressure. CHB, Chronic Hepatitis B. HIV, Human Immunodeficiency Virus. HCV, Hepatitis C Virus. CHC, Chronic Hepatitis C. HBsAg, Hepatitis B surface antigen. HbcAg, Hepatitis B core antigen. IgM, Immunoglobulin M. PCR, Polymerase Chain Reaction. Anti-HCV, Hepatitis C Virus. HbA1c, Haemoglobin A1c. COVID-19, Coronavirus disease 2019.

SGOT, serum glutamic oxaloacetic transaminase. SGPT, serum glutamate-pyruvate transaminase or serum glutamic-pyruvic transaminase. NT-PROBNP, N-terminal prohormone of brain natriuretic peptide. CHOL, cholesterol. TG, triglycerides. HDL, High-density lipoprotein. U, urea. CR, creatinine. IVDU, Intravenous Drug User.

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REFERENCES:

1. 1 United Nations System Study Committee on Nutrition: Decade of Action on Nutrition 2016-2025. https://www.unscn.org/en/topics/un-decade-of-action-on-nutrition?pages=4;2016
2. World Health Organization (WHO): Healthydiet. https://apps.who.int/iris/bitstream/handle/10665/325828/EMROPUB_2019_en_23536.pdf/;www.emro.who.int/nutrition; 2019
3. World Health Organization (WHO): Nutrient requirements and dietary guidelines.
4. Hooper L, Abdelhamid A, Moore HJ, Douthwaite W, Skeaff CM, Summerbell CD: Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. BMJ. 2012, 345: e7666.
5. LeeMermel V: Old paths new directions: the use of functional foods in the treatment of obesity. Trends in Food Science & Technology 2004, 15(11):532-540. DOI: https://doi.org/10.1016/j.tifs.2004.03.0054
6. Jordan I, Keding BG, Stosius L, Hawrysz I, Janiszewska K, Heil AE: Changes in Vegetable Consumption in Times of COVID-19—First Findings from an International Civil Science Project. Front Nutr. 2021, 8: 686786. DOI: https://doi.org/10.3389/fnut.2021.686786
7. Kastorini C M, Milionis JH, Esposito K, Giugliano D, Goudevenos A J, Panagiotakos B D: Clinical Research Metabolic Syndrome the

Effect of Mediterranean Diet on Metabolic Syndrome, and its Components: A Meta-Analysis of 50 Studies and 534,906 Individuals Download Get rights and content open archive. Journal of the American College of Cardiology 2011, 57(11):1299-1313. DOI: https://doi.org/10.1016/j.jacc.2010.09.073

8. Alfawaz AH, Wani K, Alnaami MA, Al-Saleh Y, Aljohani JN, Al-Attas SO, Alokail SM, et al.: Effects of Different Dietary and Lifestyle Modification Therapies on Metabolic Syndrome in Prediabetic Arab Patients: A 12-Month Longitudinal Study. Nutrients 2018, 10(3):383. DOI: https://doi:10.3390/nu10030383
9. Akbari M, Tamtaji OR, Lankarani B K, Tabrizi R, Dadgostar E, Haghighat N, Kolahdooz F, et al.: The effects of resveratrol on lipid profiles and liver enzymes in patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Lipids in Health and Disease 2020, 19(1). DOI: https://doi.org/10.1186/s12944-020-1198-x.
10. Alfawaz AH, Wani K, Alnaami MA, Al-Saleh Y, Aljohani JN, Al-Attas SO, Alokail SM, et al.: Effects of Different Dietary and Lifestyle Modification Therapies on Metabolic Syndrome in Prediabetic Arab Patients: A 12-Month Longitudinal Study. Nutrients 2018, 10(3):383. DOI: https://doi:10.3390/nu10030383
11. Al-Ghalith GA, Vangay P, Knights D: The guts of obesity: progress and challenges in linking gut microbes to obesity. Discovery Medicine 2015, 19(103):81–88.
12. Chaiyasoot K, Sarasak R, Pheungruang B, Dawilai S, Pramyothin P, Boonyasiri A, Supapueng O, et al.: Evaluation of a 12-week lifestyle education intervention with or without partial meal replacement in Thai adults with obesity and metabolic syndrome: a randomised trial. Nutrition Diabetes 2018, 8(1):23. DOI: https://doi: 10.1038/s41387-018-0034-0
13. Bernal W, Auzinger G, Dhawan A, Wendon J: Acute liver failure. Lancet 2010, 376(9736):190-201. DOI: https://doi:10.1016/S0140-6736(10)60274-7.
14. Dos Reis Menta PL, Toulson Davisson Correia MI, Vieira Teixeira Vidigal P, Luciana Silva L D, Reixeira R: Nutrition Status of Patients with Chronic Hepatitis B or C. Nutrition in Clinical Practice 2015, 30(2):290–296. DOI: https://doi:10.1177/0884533614546168
15. World Health Organization (WHO): Combating Hepatitis B and C to reach elimination by 2030.
16. Himoto T: Diet and Nutrition for Hepatitis. Nutrients 2021, 13(4):1210. DOI: https://doi.org/ 10.3390/nu13041210
17. Himoto T, Masaki T: Current trends of essential trace elements in patients with chronic liver diseases. Nutrients 2020, 12(7):2084. DOI: https://doi: 10.3390/nu12072084
18. Akbari M, Ostadmohammadi V, Tabrizi R, Lankarani BK, Heydari ST, Amirani E, Reiter JR, et al.: The effects of melatonin supplementation on inflammatory markers among patients with metabolic syndrome or related disorders: a systematic review and meta-analysis of randomized controlled trials. Inflammopharmacology 2018, 26(4):899–907. DOI: https://doi.org/10.1007/s10787-018-0508-7
19. Michielsen CJRC, Hangelbroek WJR, Feskens JME, Afman AL: Disentangling the Effects of Monounsaturated Fatty Acids from Other Components of a Mediterranean Diet on Serum Metabolite Profiles: A Randomized Fully Controlled Dietary Intervention in Healthy Subjects at Risk of the Metabolic Syndrome.Molecular Nutrition & Food Research Journal 2019, 63(9). DOI: https://doi: 10.1002/mnfr.201801095
20. Saklayen GM: The Global Epidemic of the Metabolic Syndrome. Current Hypertension Reports 2018. 20(12). DOI: https://doi.org/10.1007/s11906-018-0812-z
21. Angelakis E, Armougom F, Million M, Raoult D: The relationship between gut microbiota and weight gain in humans. Future Microbiology 2012, 7(1):91–109. DOI: http://doi:10.2217/fmb.11.142
22. Kastorini CM, Panagiotakos DB, Chrysohoou C, Georgousopoulou E, Pitaraki E, Puddu PE, Tousoulis D, et al.: Metabolic syndrome, adherence to the Mediterranean diet and 10-year cardiovascular disease incidence: The ATTICA study. Atherosclerosis 2016, 246:87-93.DOI: http://doi:10.1016/j.atherosclerosis.2015.12.025.
23. Zafar U, Khaliq S, Ahmad HU, Manzoor S, Lone PK: Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links, Hormones 2018, 17:299–313. DOI: https://doi.org/10.1007/s42000-018-0051-3

24. García-García JF, Monistrol-Mula A, Cardellach F, Garrabou G: Nutrition, Bioenergetics, and Metabolic Syndrome. Nutrients 2020,12(9):2785. DOI: https://doi:10.3390/nu12092785
25. Kunduraci YE, Ozbek H: Does the Energy Restriction Intermittent Fasting Diet Alleviate Metabolic Syndrome Biomarkers? A Randomized Controlled Trial. Nutrients 2020, 12(10): 3213. DOI: https://doi: 10.3390/nu12103213
26. Srikanthan K, Feyh A, Visweshwar H, Shapiro IJ, Sodhi K: Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population.Int J Med Sci 2016, 13(1):25-38. DOI: https://doi.org/10.7150%2Fijms.13800.
27. Stanaway DJ, Flaxman DA, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, Abu-Raddad JL, et al.: The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016, 388(10049):1081–1088. DOI: https://doi:10.1016/S0140-6736(16)30579-7
28. Raptopoulou M, Papatheodoridis G, Antoniou A, Ketikoglou J, Tzourmakliotis D, Vasiliadis T, Manolaki N, et al.: Epidemiology, course, and disease burden of chronic hepatitis B virus infection. HEPNET study for chronic hepatitis B: a multicentre Greek study. Journal of Viral Hepatitis 2008, 16(3): 195-202. DOI: https://doi:10.1111/j.1365-2893.2008.01057.x
29. US Department of Health and Human Services/Centers for Disease Control and Prevention-Morbidity and Mortality Weekly Report (MMWR): Prevalence of Past or Present Infection with Hepatitis B Virus† Among Adults Aged ≥18 Years, by Race and Hispanic Origin — National Health and Nutrition Examination Survey, 1999–2018, 2020.
30. Nobel Prize in Physiology or Medicine: The discovery of Hepatitis C virus. Nobel Assembly Karolinska Institute, Retrieved 2020, from https://www.nobelprizemedicine.org/wp-content/uploads/2020/10/pm_eng_FINAL_2020.pdf
31. Yi YH, Kim YJ, Lee SY, Cho BM, Cho YH, Lee JG: Health behaviours of Korean adults with hepatitis B: Findings of the 2016 Korean National Health and Nutrition Examination Survey. World Journal Gastroenterology 2018, 24(28):3163-3170. DOI: https://doi:10.3748/wjg. v24.i28.3163.
32. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet 2017.
33. Moorman CA, Drobenuic J, Kamili S: Hepatitis C, false-positive, RIBA, anti-HCV, prevalence, predictive value positive:Prevalence of false-positive hepatitis C antibody results, National Health and Nutrition Examination Study (NHANES) 2007–2012. Journal of Clinical Virology 2017, 89:1-4. DOI: https://doi: 10.1016/j.jcv.2017.01.007
34. Gastroenterology Hepatology, 2(3):161-176. DOI: https://doi: 10.1016/S2468-1253(16)30181-9.
35. Saraswat V, Norris S, De Knegt RJ, Sanchez Avila JF, Sonderup M, Zuckerman E, Arkkila P, et al.: Historical epidemiology of hepatitis C virus (HCV) in select countries. Journal of Viral Hepatitis 2015, 2(1):6-25. DOI: https://doi:10.1111/jvh.1235
36. Konstantinidi M, Koutelidakis EA: Functional Foods and Bioactive Compounds: A Review of Its Possible Role on Weight Management and Obesity's Metabolic Consequences. Medicines (Basel) 2019, 6(3):94. DOI: https://doi: 10.3390/medicines6030094.
37. Halford JCG, Joanne A, Harrold JA: Satiety-enhancing products for appetite control: science and regulation of functional foods for weight management. Proceedings of the Nutrition Society 2016, 71:350–362. DOI: http://doi:10.1017/S0029665112000134
38. Fabiani R, Naldini G, Chiavarini M: Dietary Patterns and Metabolic Syndrome in Adult Subjects: A Systematic Review and Meta-Analysis Nutrients 2019, 11(9):2056. DOI: https://doi.org/10.3390/nu11092056
39. Denniston MM, Jiles BR, Drobeniuc J, Klevens RM, Ward WJ, McQuillan MG, Holmberg DS: Chronic Hepatitis C Virus Infection in the United States, National Health, and Nutrition Examination Survey 2003 to 2010. Annals of Internal Medicine 2014, 160(5):293-300. DOI: https://doi:10.7326/M13-1133
40. Stanaway DJ, Flaxman DA, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, Abu-Raddad JL, et al.: The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016, 388(10049):1081–1088. DOI: https://doi:10.1016/S0140-6736(16)30579-7

41. Tremblay A, Clinchamps M, Pereira B, Courteix D, Lesourd B, Chapier R, Obert P, et al.: Dietary Fibres and the Management of Obesity and Metabolic Syndrome: The RESOLVE Study. Nutrients 2020, 12(10):2911. DOI: https://doi:10.3390/nu12102911

42. Babio N, Toledo E, Estruch R, Ros E, Martínez-González AM, Castañer O, Bulló M, et al.: Mediterranean diets, and metabolic syndrome status in the PREDIMED randomized trial. Canadian Medical Association Journal 2014, 186(17):649–657. DOI: http://doi:10.1503/cmaj.140764

43. Tain YL, Yu HR, Huang LT: The Effects of Resveratrol in the Treatment of Metabolic Syndrome. International Journal of Molecular Sciences 2019, 20(3):535. DOI: https://doi:10.3390/ijms20030535.

44. Tresserra-Rimbau A, Medina-Remón A, Lamuela-Raventós MR, Bulló M, Salas-Salvadó J, Corella D, Fitó M, et al.: Moderate red wine consumption is associated with a lower prevalence of the metabolic syndrome in the PREDIMED population. British Journal of Nutrition 2015, 113(S2):121–130. DOI: https://doi:10.1017/S0007114514003262

45. Mou S, Li J, Yu Z, Wang Q, Ni Z: Research Note Keto acid-supplemented low-protein diet for treatment of adult patients with hepatitis B virus infection and chronic glomerulonephritis. Journal of International Medical Research 2013, 41(1);129–137. DOI:https://doi:10.1177/0300060512474758 imr.sagepub.com

46. Yeow SHC, Chin STS, Yeow JA, Tan KS: Consumer purchase intentions and honey related products. Journal of Marketing Research & Case Studies 2013. DOI: https://doi:10.5171/2013. 197440

47. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, DGEM (German Society for Nutritional Medicine), et al.: Guidelines on Enteral Nutrition: Liver disease. Clinical nutrition, 25(2): 285-294. DOI: https://doi:10.1016/j.clnu.2006.01.018.

48. Liu F, Wang X, Wu G, Chen L, Hu P, Ren H, Hu H: Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A Meta-Analysis. PLoS One 2015, 10(11). DOI: https://doi:10.1371/journal.pone.0142457.

49. Gupta-Jain S, Puri S, Misra A, Gulati S, Kalaivani-Mani K: Effect of oral cinnamon intervention on metabolic profile and body composition of Asian Indians with metabolic syndrome: a randomized double -blind control trial. Lipids in Health and Disease 2017, 16(1):113. DOI: https://doi:10.1186/s12944-017-0504-8

50. Curtis JP, Van der Velpen V, Berends L, Jennings A, Feelisch M, Umpleby AM, Evans M, et al.: Blueberries improve biomarkers of cardiometabolic function in participants with metabolic syndromeresults from a 6-month, double-blind, randomized controlled trial. Nutrient 2019, 109(6):1535–1545. DOI: https://doi:10.1093/ajcn/nqy380

51. Hou C, Zhang W, Li J, Du L, Lv O, Zhao S, Li J: Beneficial Effects of Pomegranate on Lipid Metabolism in Metabolic Disorders. Molecular Nutrition Food Research 2019, 63(16). DOI: https://doi:10.1002/mnfr.201800773

52. Nishiyama M, Ohtake N, Kaneko A, Tsuchiya N, Imamura S, Iizuka S, Ishizawa S, et al.: Increased Akkermansia muciniphila by a diet containing Japanese traditional medicine Bofutsushosan in a mouse model of non-alcoholic fatty liver disease. Nutrients 2021, 12(3):839. DOI: https://doi:10.3390/nu12030839

53. Sanchez-Rodriguez E, Lima-Cabello E, Biel-Glesson S, Fernandez-Navarro RJ, Calleja AM, Roca M, Espejo-Calvo AJ, et al.: Effects of Virgin Olive Oils Differing in Their Bioactive Compound Contents on Metabolic Syndrome and Endothelial Functional Risk Biomarkers in Healthy Adults: A Randomized Double-Blind Controlled Trial. Nutrients 2018, 10(5):626. DOI: https://doi:10.3390/nu10050626.10, 626

54. Silva ELMC, Pereira de Melo ML, Faro Reis FV, Chagas Monteiro M, Dos Santos SM, Quadros Gomes BA, Meller da Silva LH: Comparison of the Effects of Brazil Nut Oil and Soybean Oil on the Cardiometabolic Parameters of Patients with Metabolic Syndrome: A Randomized Trial. Nutrients 2019,12(1):46. DOI: https://doi:10.3390/nu12010046

55. Azhdari M, Karandish M, Mansoori A: Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. Phytotherapy Research 2019, 33(5):1289-1301. DOI: https://doi:10.1002/ptr.63232019;1–13

56. Reverri JE, Randolph MJ, Steinberg MF, Kappagoda CT, Edirisinghe I, Burton-Freeman MB; Black Beans, Fiber, and Antioxidant Capacity Pilot Study: Examination of Whole Foods vs. Functional Components on Postprandial Metabolic, Oxidative Stress, and Inflammation in Adults with Metabolic SyndromeNutrients 2015, 7(8):6139-6154; DOI: https://doi.org/10.3390/nu7085273

57. Ramos-Figueira ER, Avancini-Rocha-Filho J, Souto-Nacif L, Carneiro-D'Albuquerque L, Linetzky-Waitzberg D: Nutritional support for fulminant hepatitis. Nutrición Hospitalaria; 2015, 32(6);2427-2432. DOI: https://doi:10.3305/nh.2015.32.6.9769

58. Westbrook RH, Dusheiko G: Natural history of hepatitis. Clinical Journal of Hepatology 2014, 61(1): S58-S68. DOI: http://doi:10.1016/j.jhep.2014.07.012

59. 59. Wiktor SZ, Hutin YJ: The global burden of viral hepatitis: better estimates to guide hepatitis elimination efforts. Lancet (London, England) 2016, 388(10049):1030-1031