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ASSESSMENT OF NUTRITIONAL STATUS IN PATIENTS WITH METABOLIC SYNDROME AND CHRONIC HEPATITIS C

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Abstract

Background and Aims*: The aim of the study was to assess nutritional status in patients with chronic hepatitis C and metabolic syndrome by different methods and to evaluate predictors of malnutrition.* ***Material and Methods****: This cross-sectional study was held in three centers from Bucharest and included 171 patients with chronic hepatitis C, divided into two groups according to the presence of metabolic syndrome (MetS). Anthropometric and biochemical parameters (including fasting plasma glucose, glycosylated hemoglobin, lipid profile, liver profile, complete blood count, and cytokines) were recorded. Nutritional status was assessed using Body Mass Index (BMI), Mini-nutritional assessment (MNA), Instant Nutritional Assessment (INA) and Nutritional Risk Index (NRI). We also recorded a malnutrition combined score. We considered patients to be malnourished according to the combined score if any score indicate malnutrition. Hepatic fibrosis was assessed using Forns index.* ***Results****: The average age was 53.14±8.3 years and 52% (n=89) were women. Using the combined score, malnutrition was present in 18 patients (10.5%). Multivariate logistic regression analysis showed that diabetes, hepatic fibrosis and IL-6 were independent risk factors for malnutrition (all p <0.05).* ***Conclusions****: Prevalence of malnutrition was high in patients with chronic hepatitis C (10.5%). In these patients diabetes, hepatic fibrosis and IL-6 were independent predictors for malnutrition.*

key words: *nutritional status, malnutrition, metabolic syndrom, chronic hepatitis C, insulin resistance.*

Background and Aims

The relationship between liver disease and nutritional deficiencies is of great importance because it is associated with adverse clinical effects. Prospective studies have shown that malnutrition is present in 65-90% of patients with advanced liver disease which leads to increased morbidity and mortality. In addition, the severity of malnutrition directly correlates with the progression of liver disease [1]. The worldwide prevalence of chronic hepatitis C is estimated to be 3%, and in Europe it is estimated to be 1% [2]. For Romania, the last statistical

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data show that the prevalence of hepatitis C infection is about 4.5% [3].

Metabolic syndrome is a condition characterized by obesity, hypoglycemia, hypertension, dyslipidemia and insulin resistance (IR). Cardiovascular disease and type 2 diabetes are the major consequences of MetS and became real public health problem worldwide [4]. Literature data suggests that IR, a very important link in the pathogenesis of MetS, plays a key role in inflammatory processes. It was also noted that there is an association between chronic hepatitis C and metabolic disorders [5].

Type 2 diabetes is a common complication of all liver disease independent of etiology, especially if liver disease is at an advanced stage. However, experimental and clinical data suggest that hepatitis C virus (HCV) has a direct role in the disruption of glucose metabolism. It was observed that patients with chronic hepatitis C that have reached the stage of cirrhosis may be more frequently type 2 diabetic than patients with cirrhosis of other origin [6]. In patients with chronic hepatitis C increased levels of oxidative stress and inflammation were evidenced. Thus, in a study by Mitsuyoshi et al. [7] evaluating 203 patients with chronic hepatitis C, HOMA-IR and serum levels of thioredoxin (a marker of oxidative stress) were significantly correlated with other specific alterations in insulin resistance (IR), even after adjustment for BMI. In patients with chronic hepatitis C, increased intrahepatic TNF-α leads to IR and to a high risk of developing type 2 diabetes [8,9].

The aim of the study was to assess the nutritional status of patients with chronic hepatitis C and metabolic syndrome by different methods and to evaluate predictors of malnutrition in these patients.

Material and Methods:

This was a multicenter, observational study including a total of 171 patients with chronic hepatitis C virus (HCV) infection, with or without metabolic syndrome (MetS). Patients were recruited from the National Institute of Diabetes, Nutrition and Metabolic Disease "N.C. Paulescu", "Cantacuzino" Clinical Hospital and Emergency Military Hospital, Bucharest, in the period September 2007 - December 2010. Every patient included in the study signed an informed consent and the study was approved by the local Ethics Committee.

Inclusion criteria, exclusion and clinical and laboratory evaluations were presented in detail in a previous article [10]. In brief the inclusion criteria were: men and women aged between 35 and 75 years, body mass index (BMI) over 25 kg/m2, diagnosis of chronic hepatitic C (CHC infection was defined by the presence of anti-HCV antibodies for a least 6 months and a positive HCV-viremia). Women with childbearing potential should be (eg, surgical sterility, being postmenopausal for at least 1 year), nonpregnant, nonlactating and use a medically accepted method of contraception. The exclusion criteria were: patients with other etiology of chronic liver diseases, hepatitis B, autoimmune liver disease, hemochromatosis, HIV infection, patients with history of hepatotoxic or steatosis-inducing drug use, currently on interferon treatment or during the last 12 months, patients having an alcohol consumption of more than 20 g/day for women and 30 g/day for men, history of pancreatitis; patients diagnosed with severe mental disease.

Patients included in the study were divided into two groups: patients with metabolic syndrome (MetS +) (N=111) and patients without metabolic syndrome (MetS -) (N=60).

MetS was defined using the Consensus Statement International Diabetes Federation (IDF) 2009 criteria [11]. Central obesity was defined as waist circumference (WC) over 94 cm in men, over 80 cm in women.

The followed anthropometric parameters were: weight, height, waist circumference, hip circumference, BMI. Biochemical parameters followed were: lipid profile (cholesterol, triglycerides, HDL-cholesterol), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), bilirubin, albumin, total protein and complete blood count.

To assess glucose metabolism we measured the following parameters: fasting plasma glucose - FPG (mg/dl), fasting plasma insulin - FPI (µUI/ml), C peptide (ng/ml) and HbA1c.

Serum C-peptide was measured by an electro-chemiluminescence immunoassay (Modular Analytics, Roche Diagnostics) with intra- and inter-assay coefficients of variation of 4.5% and 6.9%, respectively.

Determination of the concentration of insulin was performed by RIA (Abbott Axsym System), with intra- and inter-assay coefficients of variation of 4.5% and 6.9%, respectively.

HOMA-IR (Homeostasis model assessment of insulin resistance) was calculated according to the formula: FPI (µUIm/l) x FPG (mg/dl)/405 [12]. A HOMA-IR index value of more than 2.0 was considered as the criteria of insulin resistance [12].

Measurement of serum adipocytokines and pro-inflammatory cytokines including adiponectin (ng/ml), leptin (ng/l), resistin (ng/ml), TNF-α (pg/ml) and IL-6 (pg/ml), was performed by ELISA method (DIAMEDIX).

The liver fibrosis was non-invasively assessed using the Forns fibrosis index [13]; a value < 4.2 excludes liver fibrosis and a value > 6.9 is a predictor for significant fibrosis.

Nutritional status was assessed using body mass index (BMI), Mini-nutritional assessment (MNA), instant nutritional assessment (INA) and nutritional risk index (NRI). We also calculated a malnutrition combined score thus: we merged the results of the MNA, the NRI, the INA and BMI, into a single combined score. We considered patients to be malnourished according to the combined score if any individual score indicated the presence of malnutrition.

Mini-Nutritional Assessment (MNA) was based on a questionnaire that included a total of 18 questions divided in four areas: anthropometric assessment, general assessment, dietary assessment and self subjective assessment. This method was shown to have a good reproducibility and is easily accepted by patients, which makes it a very sensitive method. Interpretation of the results is as follows: MNA≥ 24 points - good nutritional status; MNA = 17 to 23.5 points - there is risk of malnutrition; MNA <17 points – malnutrition [14].

Nutritional Risk Index (NRI) is based on dosing serum albumin and calculating the ratio between current weight / usual weight [15]. The NRI is derived from the serum albumin concentration and the ratio of actual to usual weight, with the equation: NRI = (1.519 x serum albumin (g/dl)) + 41.7 x (present weight/usual weight). Test interpretation is done as follows: 100 - exclude malnutrition; 97.5-100 - slight malnutrition; 83.5 to 97.4 - moderate malnutrition; <83.5 - severe malnutrition.

Instant Nutritional Assessment (INA) is based on serum albumin and lymphocyte count. According to INA, the nutritional status of patients is divided into four degrees: first degree (albumin ≥3.5 g/dl; lymphocytes >1500 /mm^3), Second degree (albumin ≥3.5 g/dl; lymphocytes <1500/mm^3), third degree (albumin <3.5 g/dL; lymphocytes >1500/mm^3) and the fourth degree (albumin <3.5 g/dl; lymphocytes <1500/mm^3) [16].

Statistical Analyses

Data were reported as mean ± standard deviation (SD) for variables which are normally

distributed. The log-transformation was used for skewed data. The tests used for assessment of normality were Kolmogorov-Smirnov with a Lilliefors significance correction and Shapiro-Wilk statistic. Comparisons among groups were made by ANOVA for quantitative variables and the χ^2 test of independence for categorical variables. Logistic regression models with backward stepwise were done for estimating the risk factor for malnutrition. The performance of discrimination for age, triglycerides, IL-6, and Forns index was evaluated by an area under receiver operating characteristic (ROC) curve (AUC). Statistical analysis of data was performed using the SPSS 19.0 for Windows (Statistical Package for the Social Sciences, version 19.0; SSPS Inc. Chicago, IL, USA). A p-value < 0.05 was considered significant.

Results

Of the 171 patients, 52% (n = 89) were represented by women. The average age of enrolled patients was 53.14±8.3 years. Of the total number of patients 38% (n=65) had type 2 diabetes. The mean duration of diabetes in the patients with diabetes was 4.34±2.96 years. The mean duration of HCV hepatitis was 4.94±2.53 years.

Using the malnutrition combined score, malnutrition was present in 18 patients (10.5%). From these, 12 patients (66.7%) belong to the group with MetS.

Anthropometric and laboratory characteristics of the investigated population are shown in Table 1, according to the MetS group and the presence of malnutrition.

Patients with malnutrition had significantly lower weight, BMI, waist circumference, HbA1c, total cholesterol, HDL-cholesterol and albumin (all p < 0.05). Forns index, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) were significantly higher. The level of proinflammatory cytokines was significantly higher in patients with malnutrition (all p < 0.05), as shown in Table 1. The analysis of these parameters was performed according to the group (MetS + / MetS-).

Table 1. Characteristics of patients with and without malnutrition according to the MetS group.

	Group With Metabolic Syndrome (n=111)					**Group Without Metabolic Syndrome** (n=60)				
	Malnutrition + (n=12)		**Malnutrition - (n=99)**			**Malnutrition + (n=6)**		**Malnutrition - (n=54)**		
	Mean	**SD**	**Mean**	**SD**	**p**	**Mean**	**SD**	**Mean**	**SD**	**p**
Age (years)	57.75	6.16	53.33	7.48	0.152	52.33	10.4	51.85	9.65	0.294
Height (cm)	168.5	7.84	169.3	8.82	0.287	169.01	9.51	167.65	8.07	0.250
Weight (kg)	80.17	15.93	85.01	14.59	<0.001	63.66	9.07	73.43	14.39	<0.001
BMI (kg/m^2)	28.15	4.75	29.71	4.47	<0.001	22.62	2.17	26.14	3.82	<0.001
WC (cm)	95.17	13.01	9842	14.13	<0.001	74.51	7.60	87.31	14.07	<0.001
HC (cm)	93.06	9.00	97.98	9.15	<0.001	85.17	9.70	91.63	9.51	<0.001
Cholesterol (mg/dl)	184.9	45.4	209.3	47.04	0.005	183.5	56.21	186.85	34.51	0.002
Triglyceride (mg/dl)	171.9	65.61	171.9	51.52	<0.001	131.20	52.51	113.70	41.12	<0.001
HDL-C (mg/dl)	32.71	5.32	37.42	6.17	<0.001	36.50	10.41	48.02	11.80	<0.001
FPG (mg/dl)	104.2	24.8	111.4	31.2	0.005	95.31	3.09	96.97	32.14	0.007
FPI (uUI/ml)	18.61	11.36	14.12	7.16	0.003	14.31	2.80	10.82	5.49	0.004
HbA1c (%)	6.33	2.55	6.96	1.38	<0.001	5.31	0.18	5.95	1.10	<0.001

Table 1. *Continued.*

	Group With Metabolic Syndrome (n=111)					Group Without Metabolic Syndrome (n=60)				
	Malnutrition + (n=12)		Malnutrition - (n=99)			Malnutrition + (n=6)		Malnutrition - (n=54)		
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
C-peptide (ng/ml)	2.28	0.84	2.79	1.29	0.092	1.77	0.27	2.86	1.41	0.041
AST (UI/L)	76.95	41.40	61.77	31.95	0.027	73.31	32.11	49.60	28.10	0.021
ALT (UI/L)	98.4	56.02	74.53	43.08	0.008	78.01	37.81	57.40	3.04	0.011
GGT (UI/L)	82.17	62.12	75.81	56.96	<0.001	94.17	52.17	75.96	50.81	<0.001
Direct Bilirubin (mg/dl)	0.20	0.10	0.21	0.12	0.497	0.24	0.1	0.21	0.09	0.594
Forns Index	7.20	1.03	7.09	1.19	0.003	7.27	0.81	6.44	1.26	0.002
Hemoglobin (g/dl)	13.92	1.25	14.01	1.32	0.355	13.50	2.04	14.20	1.24	0.236
Platelet x 10^3/µL	238.58	69.5	221.04	54.6	0.723	195.01	20.61	219.87	58.90	0.399
Abumin (g/dl)	3.97	0.47	4.19	0.52	0.015	3.73	0.66	4.35	0.57	0.004
Log HOMA-IR*	0.72	0.24	0.68	0.16	0.429	0.93	0.07	0.53	0.18	<0.001
Log Adiponectin*	0.57	0.25	0.58	0.22	0.218	0.72	0.17	0.65	0.25	0.071
Log Leptin*	1.29	0.19	1.26	0.19	0.018	0.99	0.27	1.19	0.16	0.025
Log TNF alpha*	1.23	0.14	1.20	0.16	0.002	1.01	0.05	1.11	0.15	0.002
Log -6*	1.30	0.24	1.22	0.18	0.012	1.01	0.08	1.15	0.17	0.018
Log Resistin*	1.33	0.28	1.31	0.25	0.084	1.04	0.37	1.22	0.28	0.036

WC, waist circumference; HC, hip circumference, * data are log transformed

Malnutrition (evaluated both using each individual risk score and the combined malnutrition score) was not more common among patients with MetS as shown in Table 2. Obesity was present in 122 patients (71.4%) - 58 women and 64 men. Of these, 8 patients (4.7%) were malnourished according to the combined score.

Table 2. Prevalence of malnutrition according to the presence of the metabolic syndrome.

Variables	MetS - (N=60)		MetS + (N=111)		P value
	Number	Percentage(%)	Number	Percentage(%)	
BMI < 18.5Kg/m^2	0	-	0	-	-
MNA Score	0	-	2	1.2	0.298
NRI Score	6	3.5	12	7	0.870
INA Score	5	2.9	12	7	0.608
Combined Score	6	3.5	12	7	0.870

Table 3. Predictors of malnutrition after multivariate logistic regression analysis (Odds Ratio (ORs) and 95% confidence intervals (CI)).

Variables	Unadjusted ORs (95% CI)	p	BMI adjusted ORs (95% CI)	p
Age Group > 52.5 years	3.111 (1.04-9.881)	0.049	1.92 (0.49-7.46)	0.345
Diabetes	4 (1.2-13.3)	0.013	3.4 (1.01-6.72)	0.02
Triglycerides > 154.8 mg/dl	3.003 (1.021-8.836)	0.047	1.07 (0.27-4.19)	0.915
Forns Index > 6.9	26.9 (5.91-123.03)	0.001	7.8 (5.81-20.8)	0.001
IL-6 > 26.2 pg/ml	5.59 (1.55-22.87	0.004	18.8 (1.57-224.7)	0.02

A significant risk of malnutrition (evaluated using the combined malnutrition score) was recorded in patients over 52.5 years of age. Multivariate logistic regression analysis also showed that diabetes, hepatic fibrosis and IL-6 were significantly associated with malnutrition (all $p < 0.05$) as shown in Table 3.

Discussion

This is one of the few studies to evaluate the nutritional status of patients with chronic hepatitis C and metabolic syndrome. Most of the published studies focused on assessing nutritional status in patients with cirrhosis or those waiting liver transplantation, either diabetic or non-diabetic [17,18]. The novelty of this study is represented by the assessment of both nutritional status and cytokines in the early stages of chronic hepatitis C, before liver cirrhosis.

In the present study, proinflammatory cytokines levels were higher in patients with malnutrition compared to those without malnutrition. Association of high levels of proinflammatory cytokines and malnutrition was reported to be a strong predictor for increased morbidity in patients with metabolic syndrome [19].

As expected, BMI did not predict malnutrition in our patient cohort. Thus, BMI should not be used as a predictor of nutritional status in the general population and even less in patients with chronic diseases.

The results of different studies have demonstrated that MNA score is a quick and sensitive tool, allowing a better assessment of nutritional status which is applicable on a broad scale [20].

Regarding patients with chronic hepatitis C and MetS nutritional status assessment should be a mandatory component of treatment and individualized nutritional intervention should be done as early as possible.

Patients with liver disease and metabolic syndrome should be encouraged to follow a nutritionally balanced diet. Protein and caloric restrictions are not justified except for encephalopathy episodes and then only for a short period [21].

Lifestyle intervention in these patients should include besides an individualized diet, measures aimed at optimizing daily physical activity and an adequate sleep program. All these lifestyle changes could have multiple beneficial effects in both cardiovascular risk reduction and reducing the degree of liver fibrosis, improving liver function and also increasing the quality of life. The most important result would be the reduction of mortality in these patients.

It has been proven that the first step in the treatment of malnutrition is to assess the nutritional status [22]. At this time there is no consensus on the use of a particular method for assessing nutritional status. It was noted that the use of clinical scores is more accurate than using a single nutritional parameter [23]. Evaluation of sensitivity is necessary for choosing nutritional score used for various categories of patients.

There are several strengths of our study, including standardized clinical and anthropometric measurements used to support the diagnosis of malnutrition. Another strength is the use of malnutrition combined score, which reduces the risk of errors of interpretation.

Potential study limitations should also be considered. One of the limitations is the fact that the population studied is rather small, Caucasian origin, having a middle-aged and a specific pathology. This is why the study findings cannot be extrapolated to other populations. Another limitation of this study is that although it has made some adjustment for potential confounders, we cannot exclude the possibility

of residual confounding by unmeasured factors or confusion.

Conclusions

Prevalence of malnutrition was high in patients with chronic hepatitis C (10.5%). In this cohort of patients, advanced age, diabetes, hepatic fibrosis and IL-6 were independent predictors for malnutrition. Assessment of nutritional status in patients with chronic hepatitis C and metabolic syndrome brings important benefits by identifying those with malnutrition risk. Applying nutritional support measures could lead to lower cardio-metabolic risk and also to decreased mortality.

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