THE IMPACT OF AN EDUCATIONAL PROGRAM IN THE MANAGEMENT OF PATIENTS WITH CHRONIC HEPATITIS C

Emilia Rusu [1,2,3], ***Gabriela Radulian*** [1,2,3], ***Florin Rusu*** [2,4], ***Georgiana Enache*** [1], ***Andreea Diana Dragomir*** [1,2,3], ***Alice Stoica*** [4], ***Mariana Jinga*** [3,4], ***Coziana Ciurtin*** [6], ***Victor Stoica*** [3,5], ***Dan Mircea Chețа*** [1,2]

[1] "Prof. N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases - Bucharest, Romania.
[2] Healthy Nutrition Foundation - Bucharest, Romania.
[3] *"Carol Davila" University of Medicine and Pharmacy - Bucharest, Romania.*
[4] *"Dr. Carol Davila" Clinical Central Military Emergency Hospital - Bucharest, Romania*.
[5] Dr. I. Cantacuzino Clinical Hospital, Bucharest, Romania
[6] Lister Hospital, London, UK

Abstract

Introduction: *This study was designed to measure the impact of lifestyle changes, involving a diet therapy and physical exercises in patients with chronic hepatitis C (CHC).* ***Methods***: *The study was conducted during January 2008 - December 2009 at "Prof. N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases - Bucharest, Romania. We selected 67 patients (34 men/33 women). We performed anthropometric measurements (weight, height, BMI (body mass index), bioimpedance analysis (BIA) as well as fasting serum lipids (cholesterol, triglycerides, HDL-cholesterol), glucose profile (glucose, HbA1c), liver profile (ALT, AST, GGT, alkaline phosphatase, bilirubin, albumin, total protein), blood count for all patients at baseline.* ***Results***: *The average age was 53.91±10.19 years. Obesity was present in 32.8% (n=22) of patients at baseline. Total fat mass decreased with weight loss 2.21 kg (p = 0.0001) respectively 3.17 kg (p = 0.0001). Weight loss was accompanied by decreased resting energy expenditure. Triglycerides decreased from 158.11±7.63 mg/dl to 134.88±6.1 mg/dl, cholesterol decreased from 187.3±6.8 mg/dl to 168.65±4.42 mg/dl and HDL-cholesterol increased from 45.13±1.9 mg/dl to 47.2±1.39 mg/dl after 12 months. Aspartaminotransferase, alaninaminotransferese, gamma-glutamil transpeptidase decreased with significant differences.* ***Conclusions***: *Patients with hepatitis C undergoing an 1-year lifestyle intervention had significant improvements in fasting glucose, fasting insulin, HOMA-IR, lipidic profile, hepatic profile and adipose tissue distribution. The present study establishes the positive impact of an educational program in the management of patients with hepatitis C.*

key words: *hepatitis C, lifestyle change, HOMA-IR, body mass index*

Introduction

Chronic hepatitis C (CHC) has many features which suggest that this disease must be viewed not only as a viral disease, but also as a metabolic liver disease which implies: insulin resistance (IR), high prevalence of

steatosis, increased prevalence of impaired glucose tolerance, type 2 diabetes mellitus, changes in lipid metabolism.

Insulin resistance in chronic hepatitis C infection could be caused by an interplay between viral and host factors. Chronic hepatitis C infection per se generates multiple defects in hepatic insulin signaling pathways.

Eating adequate amounts of essential nutrients, coupled with an energy intake in balance with energy expenditure is essential to maintain health and to prevent or delay the development of obesity or malnutrition.

This study was designed to measure the impact of lifestyle changes, involving a diet therapy and physical exercises in patients with chronic hepatitis C.

Methods

The study was conducted during January 2008 - December 2009 at "Prof. N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases - Bucharest, Romania. We selected 67 patients (34 men/33 women). We performed anthropometric measurements (weight, height, BMI (body mass index)), bioimpedance analysis (BIA) as well as fasting serum lipids (cholesterol, triglyceride, HDL-cholesterol), glucose profile (glucose, glycated hemoglobin), liver profile (ALT, AST, GGT, alkaline phosphatase, bilirubin, albumin, total protein), blood count for all patients at baseline. All patients signed an informed consent before inclusion in the study.

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Based on the World Health Organization classification, overweight was defined as BMI between 25 and 29.9 kg/m^2, and obesity was defined as BMI over 30 kg/m^2 [1]. We also measured waist circumference (cm) in the middle between the 12th rib and the iliac crest. Arterial blood pressure was measured three times at the end of the physical examination with the subject in sitting position. Participants whose average blood pressure levels were greater or equal to 140/90 mmHg or with antihypertensive medication were classified as hypertensive subjects [2].

BIA method is a technology measuring the volume of a conductor through its length and impedance. Biospace developed the InBody using multi-frequency BIA technology in which the trunk and limbs are analyzed separately, and extra cellular fluid is accurately measured. InBody separates the body into 5 different cylinders with respect to the arms, legs, and trunk, and calculates the impedance of each. The InBody provides accurate results not only for healthy individuals but also for children, elderly, severely obese, athletes, and patients. The most clinically significant results were for body fat mass (BFM - kg) and protein mass (kg).

The liver fibrosis was non-invasively assessed using the Forn's index; a value < 4.2 excludes liver fibrosis and a value > 6.9 is a predictor for significant fibrosis. Forn's fibrosis index is based on platelet count, GGT, age and cholesterol levels, according to the formula: $7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{age}) - 0.014 \times (\text{cholesterol})$.

IR was determined using Homeostasis model assessment (HOMA-IR) (fasting insulin level (mUI/l) x fasting glucose level (mg/dl)/405; a HOMA-IR index value of more than 2.0 was considered as a criterion of

insulin resistance, and a higher value than 4.0 was considered as a prediabetic state.

CHC infection was defined by the presence of anti-HVC for a least 6 months and a positive HCV-viremia. Patients with other etiology of chronic liver diseases, hepatitis B, autoimmune liver disease, hemochromatosis, HIV infection, patients with a history of hepatotoxic or steatosis-inducing drug use, patients having an alcohol consumption more than 20g/day for women and 30 g/day for men, history of diabetes mellitus, pancreatitis were excluded from the study.

All patients received nutrition counseling in individual sessions every month in the first 6 months and 3 every months thereafter until 12 months; with clinical, biological and anthropometrical reevaluation at 6 and 12 months. All patients completed at baseline, 6 and 12 month a food frequency questionnaire.

The purpose of lifestyle changes of these patients was to decrease insulin resistance. The educational program included a description of the risk factors and their primary prevention, a distinct low calorie diet (with low fat, carbohydrate and sodium intake) and physical exercises of moderate intensity. The low calorie diet included: 27-30% of total calories from fat, less than 7% of total calories from saturated fat and less than 300 mg cholesterol per day, proteins 15-20 % of total calories, carbohydrates 50-60% of total calories and 25-35 grams of fibers/day. Regular physical activity includes 30 minutes of activities (e.g. brisk walking, jogging, cycling) 4-7 days a week. Patients were adviced to limit their alcohol consumption to 2 or fewer standard drinks per day. Smoking patients have been adviced to quit.

Statistics

Results for continuous data were expressed as mean ± standard error (SE). The comparison of mean value at baseline, 6 months and 12 months was performed with paired *t*-test. Pearson's and Spearman's correlation was used to measure the association between HOMA-IR and continuous variables normally distributed or categorical data. P-value less than 0.05 was considered significant. All statistical analyses were performed using SPSS 16 (Statistical Package for Social Software).

Results

The average age was 53.91±10.19 years. Obesity was present in 32.8% (n=22) of patients at baseline. An average weight loss of 3.17±0.058 kg of the initial weight was recorded parallel with decreased in calories consumption (p=0.0001). A 12-month obesity was present in 20.9% (n=14). (Figure 1).

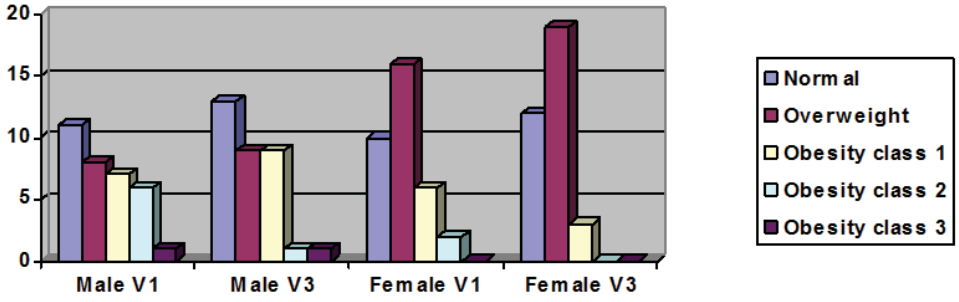

Figure 1. BMI and gender distribution

Total fat mass decreased with weight loss 2.21 kg (p = 0.0001) respectively 3.17 kg (p = 0.0001) (Table 1). Weight loss was accompanied by decreased resting energy expenditure.

Table 1. Clinical and biochemical characteristics before and after intervention

	Baseline		12 months after		
	Means	**SE**	**Means**	**SE**	**p value**
Weight (kg)	79.40	1.95	76.23	1.83	0.001
BMI (kg/m2)	27.71	0.72	26.63	0.52	0.001
Protein mass (kg)	10.82	0.29	10.63	0.26	0.001
Body fat mass (kg)	25.70	1.28	23.49	1.21	0.001
Cholesterol (mg/dl)	187.32	6.82	168.65	4.43	0.001
Triglycerides (mg/dl)	158.11	7.63	134.89	6.10	0.001
HDL-Cholesterol (mg/dl)	45.14	1.90	47.28	1.40	0.001
AST (U/L)	67.69	7.42	53.20	4.31	0.001
ALT (U/L)	78.41	7.40	64.59	6.56	0.001
Albumin (g/dl)	4.10	0.08	4.12	0.08	NS
Hemoglobin (g/dl)	14.01	0.20	13.78	0.15	NS
White blood cells *1000/ul	6.97	0.20	6.81	0.18	NS
Platelets *1000/ul	214.14	9.10	211.59	7.92	NS
INR	1.05	0.02	1.04	0.02	NS
GGT (U/L)	93.34	16.98	69.53	8.66	0.001
Bilirubin	0.83	0.09	0.79	0.04	NS
AST/ALT	0.95	0.05	0.91	0.04	0.001
AST/Platelets	0.46	0.09	0.36	0.06	0.001
Forn's	6.56	2.08	5.97	1.89	0.001
HOMA-IR	6.56	1.18	3.99	0.63	0.001
Adiponectin (ug/ml)	6.77	0.79	8.98	1.80	0.001
Leptin (ug/ml)	18.02	1.18	15.06	0.86	0.001
TNF-α (pg/ml)	13.91	0.81	12.80	0.77	0.001
IL-6 (pg/ml)	13.33	0.55	11.78	0.52	0.001
Resistin (ng/ml)	14.25	1.37	11.69	1.26	0.001
FPG (mg/dl)	125.19	7.08	107.99	4.81	0.001
FPI (uU/ml)	21.18	3.60	14.60	2.20	0.001
HbA1c (%)	6.36	0.20	6.23	0.14	0.001

In this study the prevalence of hypertension was 41.79%, higher in women than in men.

Before the study 57.14% (n=16) of the patients received antihypertensive treatment, intermittent and insufficient in most cases.

Mean SBP was 145.67±15.01 mmHg at the first visit, and 140.03±10.8 mmHg at the 3rd visit. Mean DBP at the first visit was 94.62±9.83 mmHg and 88.31±9.74 mmHg at the 3rd visit.

Triglycerides decreased from 158.11±7.63 mg/dl to 134.88±6.1 mg/dl, cholesterol decreased from 187.3±6.8 mg/dl to 168.65±4.42 mg/dl, and HDL-cholesterol increased from 45.13±1.9 mg/dl to 47.2±1.39 mg/dl after 12 months.

Aspartataminotransferase, alaninamino-transferase, gamma-glutamil transpeptidase decreased with significant differences. AST/ALT ratio, AST/Platelets ratio and Forn index had significant improvements. Albumin and bilirubin level were not significantly changed. Renal function, assessed by measuring serum creatinine and urea did not change during this period.

HOMA decreased from a baseline of 6.55 to 3.99 at 6 months with a means change of −2.56 ($p = 0.0001$) (Table 1). Fasting plasma insulin also decreased with weight loss.

Circulating cytokine levels: leptin, TNF alpha, IL-6, resistin decreased with weight loss (all $p < 0.0001$) (Table 1).

At baseline, by linear regression, HOMA-IR was correlated with body mass index, apparent liver disease duration, the serum levels of leptin, TNF alpha, IL-6 (positive correlation) and adiponectin (negative correlation) (Table 2).

Table 2. Univariate analysis of correlation between HOMA-IR and clinical and biological variables

Variables	HOMA IR	
	r	p
Age (years)	0.088	**0.16**
Gender	-0.148	**0.251**
BMI (Kg/m2)	0.307	**0.011**
WHR	0.00	**0.07**
Cholesterol (mg/dl)	0.035	**0.78**
Triglyceride (mg/dl)	0.04	**0.71**
HDL-cholestrol (mg/dl)	0.04	**0.69**
AST/ALT ratio	0.12	**0.09**
AST/platelets	0.019	**0.87**
AST (U/L)	0.298	**0.014**
ALT (U/L)	0.312	**0.008**
GGT (U/L)	0.258	**0.035**
Fasting glucose (mg/dl)	0.192	**0.0119**
Insulin (mU/l)	0.951	**0.0001**
C-peptide (pmol/l)	0.47	**0.001**
HbA1c	0.295	**0.015**
Adiponectin (ug/ml)	-0.066	**0.059**
Leptin (ug/ml)	0.337	**0.005**
TNF-α (pg/ml)	0.005	**0.0097**
IL-6 (pg/ml)	-0.077	**0.534**
Resistin	0.134	**0.028**
Viremia (copies/ml)	0.34	**0.049**
Apparent liver disease duration	0.29	**0.038**

Weight loss is explained by the decreasing amount of glucoses and fats; the quantity of proteins was similar. The decreased consumption of integral dairy products, saturated fats, refined carbohydrates, sugar, alcohol simultaneously with an increased consumption of low fat dairy products, fruits and vegetables was associated with an improvement in body weight and lipid profile.

Discussions

Weight reduction through dietary intervention is the cornerstone of management of obesity and/or NAFLD [3, 4]. We have reported previously that weight reduction with a low-fat, low calories diet effectively decreases plasma triglycerides, HOMA-IR and improves the fibrosis index [5]. However, intensive weight loss is difficult to achieve and maintain. Moderate weight loss of 3–7% is therefore a more realistic goal to be implemented in clinical practice [6]. Whether this level of weight loss could lead to adequate improvement in fatty liver and its associated metabolic disorders remains to be verified by larger studies. The effects of many popular diets on the fatty liver, such as the Zone [7] or the Atkins diet [8] are not known, although a recent abstract suggested that reduced carbohydrate intake may be of benefit [9]. In our study a normoglucidic diet (with limited refined carbohydrates, sugar, and increased fruit and vegetable, whole grains) was accompanied by improved insulin resistance (HOMA-IR), lipid and liver profile. The metabolic changes induced by the low carbohydrate, high protein diet brought some additional concern and perhaps precaution, as the fatty liver is prone to increased production of ketone bodies.

This study provides clinical evidence that HCV directly affects insulin resistance in a consecutive population of CHC subjects. Several pathogenic mechanisms may be involved in the effect of CHC on insulin resistance but adipocitokines and inflamatory citokines play an important part. Chronic HCV infection is specifically associated with IR even in the absence of type 2 diabetes mellitus and irrespectively of the presence of cirrhosis, and that high serum glucose levels have a fibrogenetic effect. Circulating levels of the cytokines - leptin, TNF alpha, IL-6, resistin decreased with weight loss (all $p < 0.0001$).

Limitations of the study are: there were only patients with chronic hepatitis C, we used the noninvasive methods to estimate steatosis and fibrosis and these indices are not so high sensitive and specify.

Conclusions

Patients with hepatitis C undergoing an 1-year lifestyle intervention had significant improvements in fasting glucose, fasting insulin, HOMA-IR, lipidic, hepatic profile and adipose tissue distribution.

The present study establishes the positive impact of an educational program in the management of patients with hepatitis C. This diet can generate weight loss, better glycemic control, without adverse effects on the hepatic and renal function.

Achieving therapeutic targets involves implementing an individualized education program, structured and continuously adapted to the biological and socio-familial conditions of the person, with its involvement in their treatment. Most people motivated quitting the diet on financial reasons.

Specific therapeutic education in the clinical management of diabetes mellitus, systematic and continuous, is an integral part of treatment.

The long term benefits can be highlighted only by long lasting studies, during which lifestyle improvements become a common thing.

Acknowledgments: The authors have no conflicts of interest directly relevant to the content of this paper.

A part of this study was supported by the Romanian National Authority for Scientific Research as a part of the PNCDI 2 program DIADIPOHEP 41-008/2007.

REFERENCES

1. **World Health Organization Obesity**: preventing and managing the global epidemic: report of a World Health Organization Consultation. Geneva, Switzerland. 1997.

2. **Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J.** The National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. JAMA **88**: 1882-1888. 2002.

3. **Torres DM, Harrison SA.** Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 134: 1682-1698, 2008.

4. **Van Gaal LF, Wauters MA, De Leeuw IH.** The beneficial effects of modest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord 21: S5-S9, 1997.

5. **Rusu E, Radulian G, Rusu F, Dragomir AD, Jinga M, Ciurtin c, Stoica V, Cheta DM.** Medical nutrition therapy in obese patients with Hepatitis C. *Obesity Reviews* 11 (Suppl 1): 182, 2010.

6. **Riches FM, Watts GF, Hua J, Stewart GR, Naoumova RP, Barrett PH.** Reduction in visceral adipose tissue is associated with improvement in apolipoprotein B-100 metabolism in obese men. J Clin Endocrinol Metab 84: 2854-2861, 1999.

7. **Cheuvront SN**. The Zone diet and athletic performance. *Sports Med* 27: 213-228, 2000.

8. **Landers P, Wolfe MM, Glore S, Guild R, Phillips L.** Effect of weight loss plans on body composition and diet duration. *J Oklah State Med Assoc* 95: 329-331, 2002.

9. **Amir R, Solga SF, Clark JM, Torbenson M, Cohen A, Diehl AM, Magnuson TH**. Dietary composition and fatty liver disease. *Hepatology* 34: 513A, 2003.

Correspondence Data:

Emilia Rusu, MD, PhD student

Diabetes, Nutrition and Metabolic Diseases Department, "Prof. N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Ion Movila Street, No 5-7, Floor 4, District 2, Bucharest, Romania

Tel: +0742959946

email: emiliarusumd@yahoo.com