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ROLE OF VERY LOW-CALORIE KETOGENIC DIET (VLCKD) IN NAFLD ANALYSIS OF A CLINICAL CASE

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a relevant issue in public health because represents a major cause of chronic liver diseases worldwide. Approximately 20% to 30% of adult population has NAFLD, making it the most common liver disease in developed countries [1,2]. NAFLD is the result of fat accumulation in the liver (with fat representing more than 5% of whole liver weight) in absence of excessive alcohol consumption (usually evaluated using thresholds of 20 and 30 g/d for women and men respectively [3].

NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis and cirrhosis and promoting hepatocellular carcinoma development [4].

NAFLD is a multifactorial disease and the exact mechanism is unknown. It is usually associated to one or more conditions that contribute to the metabolic syndrome (MS) (diabetes mellitus, obesity, hypertension, and hyperlipidemia) and therefore is considered as its hepatic manifestation [5-9].

Several therapeutic interventions for NAFLD have been proposed over the last decades but any of these proved to be safe and effective [10,11]. Among therapeutic interventions there are weight reduction (e.g., low-calorie diet, exercise and bariatric surgery), insulin sensitizer agents and incretins, lipid lowering drugs (e.g., statins), antioxidants (e.g., vitamin E) and treatment of vitamin D3 deficiency [12]. Pharmacological therapies have not been always successful in reducing liver steatosis or inflammation [12,13]. On the other hand, other drugs, such as thiazolidinediones, have some success in improving liver histology but have undesirable side effects such as weight gain [14].

Epidemiological evidence suggests a tight relationship between unhealthy lifestyle (mainly related to diet and physical inactivity) and NAFLD [15] and therefore there is a general consensus on considering healthy diet and regular physical activity as the cornerstones in the treatment of NAFLD [4,12,16]. In addition, these interventions have been demonstrated also effective for improving conditions of MS and the related risk of cardiovascular disease (CVD) [17].

For all these reasons, a structured programme aimed at lifestyle changes towards healthy diet (with a 7%-10% weight loss in overweight/obese patients) and routinary physical activity is the most advisable for the treatment of NAFLD [4].

Nonetheless, lifestyle modification is usually difficult to achieve and maintain, above all in the long term, for a variety of reasons [27,28]. In particular, many patients have difficulty to find motivation to change their unhealthy lifestyle although most of them are well aware of the importance of healthy diet and habitual physical activity. Centis et al [18] report NAFLD cases have scarce readiness to physical activity change, and 50% of cases were classified in either the precontemplation or contemplation stage of change, i.e., refractory to increase exercise [19].

For these reasons there, in order to increase the success of the approach laying on lifestyle change towards a healthy diet and habitual physical activity, there is the need to move from the traditional prescriptive approach to an individualized, multidisciplinary, empowerment-based intervention, tailored on patients' preferences.

In this study we tested the effectiveness of nutritional counseling on reduction of NAFLD severity, weight loss, metabolic and anthropometric indexes and liver enzymes.

Keywords: *Non-alcoholic fatty liver disease, NAFLD, very low-calorie ketogenic diet, liver enzyme*

Introduction

Lifestyle modification with a focus on healthy eating, weight loss when needed, and regular exercise remain the cornerstone of therapy in adults and children. When recommending healthy food choices, a ketogenic diet has been shown to be a good alternative to a western diet [20].

NAFLD is thought to be a negative consequence of ectopic hepatic lipid accumulation, in the setting of insulin resistance. Steatosis—characterized by triglyceride deposition in hepatocytes—underscores the close connection between visceral adiposity, NAFLD, and the carb-laden, high-fat Western diet. Visceral adipose deposition stimulates inflammatory cytokine release and systemic insulin resistance, and diets high in saturated fat and simple carbohydrates lead to free fatty acid delivery to the liver, stimulating de novo lipogenesis, oxidative stress, and lipo-toxicity [21].

Most recent advances in the management and treatment of Non-alcoholic fatty liver disease (NAFLD) show that a multifaceted approach is likely to achieve the best outcomes. Our study evaluates the effectiveness of 6 months. The approach was effective on the reduction of NAFLD severity, weight, body composition, cardiovascular disease risk factors and the normalization of metabolic index, as well as liver enzymes. This study strengthens the hypothesis that ketogenic diet and more active lifestyle can be considered a safe therapeutic approach for reducing severity of NAFLD.

Once weight goal is achieved, it is mandatory to suggest an appropriate healthy lifestyle (physical activity and a balanced nutritional pattern such as Mediterranean Diet) for long-term body weight maintenance. The scheme of the stages of VLCKD is reported in Fig. 1 [22].

Methods

In this study an overweight patient with NAFLD is retrospectively analyzed, referring to the study by Dr. Lemasson (nutritionist biologist) between January and June 2019. The patient is a 63-year-old woman who has been excluded from other causes of liver disease, through viral markers (for hepatitis B and C), lack of alcohol intake in the anamnesis, presence of autoimmune or metabolic diseases, the use of drugs known to induce hepatic steatosis. For six weeks, the patient followed a very low-calorie ketogenic diet.

Standard liver tests were performed, including alanine aminotransferase (ALT), glutamic-oxaloacetic transaminase (GOT) and gamma glutamyltranspeptidase (GGT) at the beginning of therapy and after 6 weeks. The BMI was calculated as the body weight divided by the height squared (kg/m^2).

The evaluation of the body composition was carried out by bio-impedance with BIA-ACC (Biotekna).

Finally, the patient underwent hepatic elastosonography at the hepatology clinic of the Biella hospital, to describe the degree of steatosis according to the Stiffness score (KPa), a semi-quantitative classification, which ranged from 0 (no steatosis) to 4 (severe steatosis). For ethical reasons and according to international recommendations, no liver biopsies were performed.

Very low-calorie ketogenic diet protocol

VLCKD is a nutritional protocol that resembles fasting through a marked restriction of daily carbohydrate intake, usually lower than 30 g/day (≃ 13% of total energy intake) along with a relative increase in the proportions of fat (≃ 44%) and protein (≃ 43%) and a total daily energy intake < 800 kcal [22].

The VLCKD protocol is a weight loss nutritional program based on a high-biological-value protein (coming from milk, peas, whey and soy) preparations diet and natural foods. Each protein preparation contains 18 g protein, 4 g carbohydrate, 3 g fat (mainly high-oleic vegetable oils) and provides approximately 100–150 kcal. This protocol is divided in three stages: active, re-education, and maintenance.

Active stage

The active stage is characterized by a very low-calorie diet (600–800 kcal/day), low in

carbohydrates (< 50 g daily from vegetables) and lipids (only 10 g of olive oil per day). The amount of high-biological-value proteins ranged between 0.8 and 1.2 g per each Kg of ideal body weight in order to preserve lean mass and to meet the minimal daily body requirements. This stage is further divided in 3 ketogenic phases: in phase 1, the patients eat high-biological-value protein preparations five times a day, along with vegetables with low glycemic index. In phase 2, one of the protein servings is replaced by natural proteins such as meat/egg/fish either at lunch or at dinner. In the phase 3, a second serve of the natural protein low in fat replaced the second serve of biological protein preparation. Being a very low caloric nutritional pattern, it is recommended to supplement patients with micronutrients (vitamins, such as complex B vitamins, vitamin C and E, minerals, including potassium, sodium, magnesium, calcium; and omega-3 fatty acids) according to international recommendations. This active stage is kept until the patient loses most of weight loss target, about 80%. Therefore, the ketogenic phases are variable in time depending on the individual and the weight loss target. The active stage generally lasts between 8 and 12 weeks in total.

Re-education and maintenance stage

After the ketogenic phases, the patient is switched to low-calorie diet. At this point, the patients will progressively reintroduce different food groups and in the meantime participates in a program of alimentary re-education in order to maintain weight long term. Carbohydrates are gradually reintroduced, starting from foods with the lowest glycemic index (fruit, dairy products—Phase 4), followed by foods with moderate (legumes—Phase 5) and high glycemic index (bread, pasta and cereals—Phase 6). The daily calorie intake in the reintroduction period (Phases 4–6) ranges between 800 and 1500 kcal/day. After the reintroduction of food there is a maintenance stage which includes an eating plan balanced in carbohydrates, protein, and fat. The main target of this stage is to keep lost weight and to promote healthy lifestyle. In this stage the calories consumed ranged between 1.500 and 2.000 kcal/day, depending on individual.

Results

The patient strictly followed the prescribed diet and reported increased physical activity. During the observation period, no other treatment for NAFLD was initiated. Considering the entire period, we describe weight reduction and a slight increase in BMR in the patient (Table 1). In particular, the reduction in recorded weight was 7.9 kg, with a reduction in fat mass of 9.4 kg (Figure 2).
Considered hepatic metabolism, the value of GAMMA GT has decreased by 28 U/l. Finally, the initial hypertransaminasemia showed the normalization of the transaminase value at the end of the treatment (Table 2).

Hepatic elastography showed the patient reduced Stiffness score. In particular, the hyperechogenicity of the hepatic parenchyma, an ultrasound parameter directly linked to the accumulation of fat, was improved. At the time of the check, at the end of the treatment, no signs of hepatic disease and fibroscan are constantly improving, so that the hepatologist suspends the pharmacological treatment.

Discussion

Despite the rapid recognition of NAFLD in the last ten years, treatment directed at the treatment or prevention of this condition remains to be defined. Given the high prevalence of NAFLD in overweight patients, the prevention of hepatic fat accumulation and weight reduction remains the cornerstone of the treatment of hepatic steatosis and management must focus on the treatment of the metabolic syndrome and therefore NAFLD it is often considered an individual entity in clinical practice. Essential in the management of NAFLD, is implying a dietary change to reduce body weight and increase exercise, in order to reduce insulin resistance and normalize transaminase levels.

The occurrence of hepatic steatosis and its progression to fibrosis and cirrhosis is a long process that includes consecutive steps. Hepatic steatosis is a consequence of an altered balance between fat accumulation and oxidation, both regulated by insulin. Fatty liver is often associated

with insulin resistance and type 2 diabetes is associated with a two to five-fold increased risk to develop NAFLD. The ideal treatment for NAFLD would reduce liver damage and its progression. Therefore, drugs for the treatment of NAFLD should reduce body weight, improve insulin resistance and metabolic alterations, reduce the link between adipose tissue and liver function by acting as anti-inflammatory and immunomodulatory agents blocking oxidative stress. NAFLD patients are generally overweight or obese. A well-balanced diet and increased physical activity are associated with improved liver enzymes, lipid and glucose metabolism in about 40% of overweight patients with NAFLD. Our results are in agreement with these studies and we confirmed a direct correlation between lifestyle changes and BMI, insulin resistance and accumulation of liver fat.

With the limitations imposed by the fact that a single case has been analyzed, we indicate that a dietary regime and an increase in physical activity, improves after a short time, liver damage, BMI and accumulation of liver fat and, therefore, we suggest the potential role of the ketogenic diet for the treatment of overweight patients with NAFLD.

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Table 1. Variation in body composition.

	January 2019	June 2019
WEIGHT	88,6 kg	80,7 kg
BMI	34,6	31,9
BMR	1413 kcal	1445 kcal
TDEE	2049 kcal	2096 kcal
FAT MASS	40,3 kg	30,9 kg
FREE FAT MASS	48,3 kg	49,8 kg
MUSCLE MASS	17 kg	17,5 kg

Table 2. Variation in blood parameters.

	January 2019	June 2019
GAMMA GT	65 U/l	37 U/l
TRANSAMINASI AST/GOT	24 U/l	15 U/l
TRANSAMINASI ALT/GPT	33 U/l	18 U/l
GLUCOSE	88 mg/dl	66 mg/dl

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Figure 1. Scheme of the stages of VLCKD.

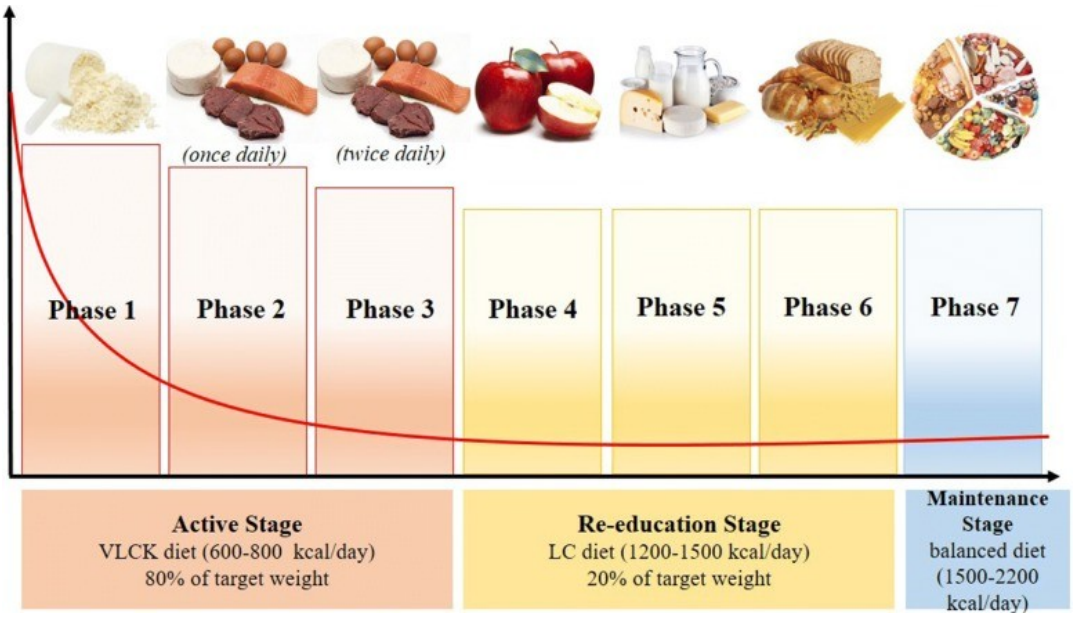
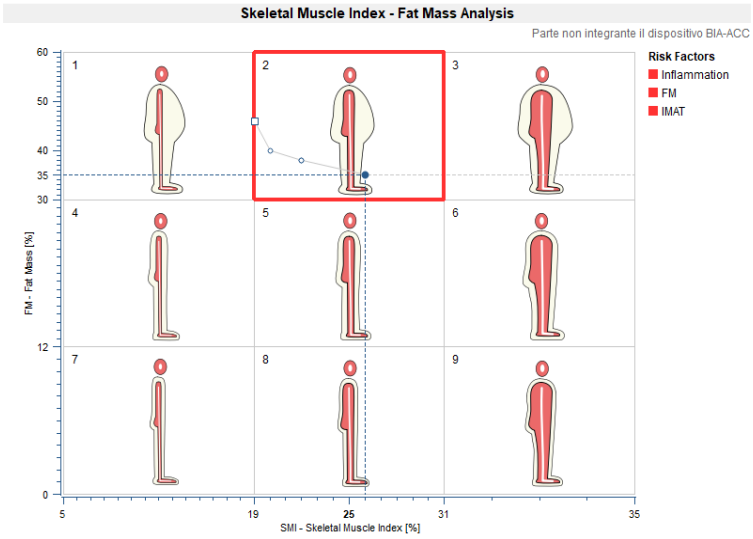
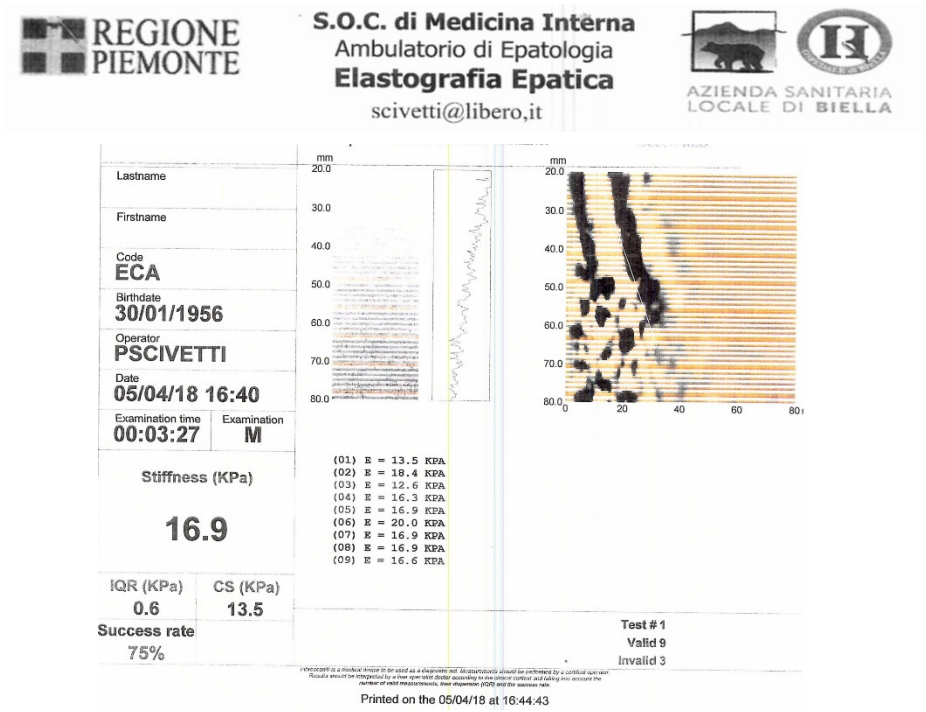


Figure 2. Variation of the body composition of the patient during treatment.



Attached 1. Fibroscan pre- treatment

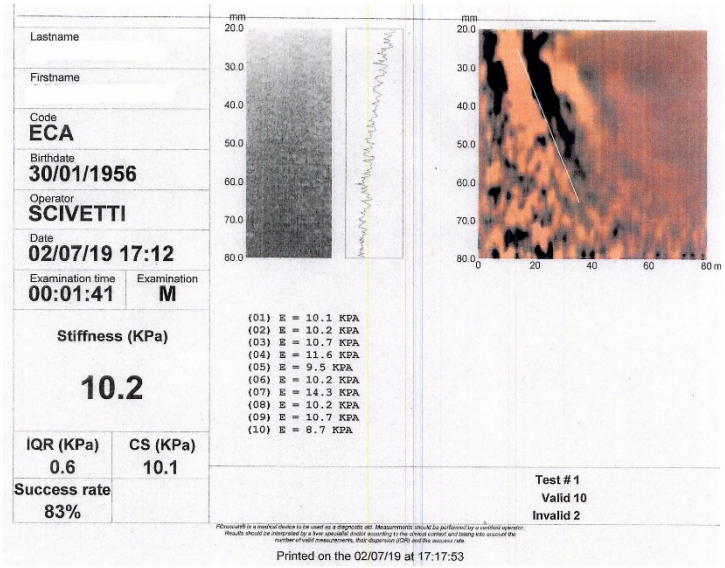


Biella, 05/04/2019

The patient underwent a liver elastography with the following results:
Stiffness value = 19,9 IQR = 0,6

STAGE OF FIBROSIS = F4 (cirrhosis).

Attached 2. Fibroscan post- treatment



Biella, 02/07/2019

The patient underwent a liver elastography with the following results:

Stiffness value = 10,2 IQR = 0,6

STAGE OF FIBROSIS = F3 (numerous septa without cirrhosis).