Efficacy of a very low calories ketogenic diet (VLCKD) in obese patients with fibromyalgia or symptomatic knee osteoarthritis

(KD-FM-OA)

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SUMMARY

1. INTRODUCTION

Fibromyalgia is a chronic disorder of uncertain aetiology, characterized by widespread pain, muscle tenderness, and decreased pain threshold to pressure and other stimuli.[1] Its pathophysiology is still elusive, although evidence support a derangement in pain processing and modulation.[1] Clinical manifestations of fibromyalgia encompass a large range of symptoms including fatigue, unrefreshing sleep, cognitive and memory disturbances ("*fibro fog*"), anxiety, depression, chronic headache, gastrointestinal problems and more.[1]

Obesity is a well-known aggravating factor for musculoskeletal pain, such as in knee osteoarthritis.[2] Epidemiological data show that fibromyalgia patients have higher prevalence of obesity (40%) and overweight (30%) and that excess of body weight influences course and activity of fibromyalgia.[2] Similarly, obesity influences pain and progression of knee osteoarthritis.[3]

In the last years, a new nutritional approach – namely Very Low Calorie Ketogenic Diet (VLCKD) – has been proposed as a potential therapeutic option in different diseases that shares common clinical and pathophysiological features with fibromyalgia and osteoarthritis.[4]

The core characteristics of the VLCKD are the association of a high amount of fat, with low carbohydrate intake, usually a macronutrient ratio of fat to protein and carbohydrate combined equal to 3–4:1.[4] The objective is to achieve ketosis, leading to reduced insulin secretion and glycaemia within 48h.[4] Ketosis is achieved when less than 50 g of carbohydrates per day are introduced, with either restricted or unrestricted fat and calorie intake.[5]

VLCKD have been demonstrated to provide clear clinical benefits in different diseases - in particular refractory epilepsy[6] - and to achieve rapid weight loss in obese subjects who failed other dietetic interventions.[7] For their efficacy and safety profile, VLCKD entered as a therapeutic options in recent guidelines for management of obesity.[8, 9]

Furthermore, other studies evaluated the effect of VLCKD on conditions that shares common pathophysiological and clinical background with fibromyalgia. Accumulating evidence suggest positive effects on mood[10], cognitive functions,[11] as well as an improvement in nociception[12] and sleep quality.[13]

1.1 Aim of the study

On the basis of this background, aim of this pilot study is to investigate the effects of VLCKD in obese patients with fibromyalgia and symptomatic knee osteoarthritis.

2. STUDY DESIGN AND SETTING

2.1 Study design

Interventional study. Study procedures will be performed in agreement with current clinical practice guidelines[8, 9].

2.2 Study setting

Rheumatology Outpatient Clinic, Medicine & Rheumatology Unit, IRCCS Istituto Ortopedico Rizzoli, Bologna.

3. PATIENTS

3.1 General characteristics of patients

Adult patients with fibromyalgia or symptomatic knee osteoarthritis and comorbid obesity eligible to VLCKD as defined according to Italian Standards for Treatment of Obesity, released by the Italian Society for the Study of Obesity (SIO) and the Italian Association of Dietetics and Clinical Nutrition (ADI) (2016–2017)[9] and the recommendations of the Italian Society of Endocrinology (SIE) for VLCKD.[8]

3.2 Inclusion criteria

Age > 18 years and < 65 years
AND
Body mass index ≥ 30 kg/m^2
AND
Failed to achieve weight loss with standard low-calories diet
AND
Any of the following conditions: • BMI ≥ 35 kg/m^2 • Past diagnosis of type 2 diabetes without β-cell failure • Hypertriglyceridemia (fasting triglycerides ≥ 150 mg/dL) or taking lipid-lowering medications • Hypercholesterolemia (total cholesterol > 200 mg/dL) or taking lipid-lowering medications • Past diagnosis of arterial hypertension or taking blood pressure-lowering medications • Past diagnosis of non-alcoholic fatty liver disease • Past diagnosis of heart failure class NYHA I–II • Past history of myocardial infarction (> 12 months), stroke/minor stroke (> 12 months) • Past diagnosis of carotid atherosclerosis • Past diagnosis of polycystic ovary syndrome (PCOS) • Past diagnosis of neurodegenerative disorders
AND
Fibromyalgia classified according to 2016 Revisions to the 2010/2011 European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) criteria[14] *OR* Symptomatic knee osteoarthritis classified according to the ACR criteria[15]

3.3 Exclusion criteria

Exclusion criteria have been established on the basis of the abovementioned clinical practice guidelines[8, 9]:

- Age < 18 or > 65 years
- Currently pregnant or breastfeeding
- Past diagnosis of type 1 diabetes mellitus, latent autoimmune diabetes in adults, β-cell failure in type 2 diabetes mellitus, use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis)
- Past diagnosis of kidney failure and moderate-to-severe chronic kidney disease, liver failure, hearth failure NYHA III-IV, respiratory failure
- Past diagnosis of unstable angina
- Recent stroke or myocardial infarction (< 12 months)
- Cardiac arrhythmias
- Past diagnosis of eating disorders and other severe mental illnesses, alcohol and substance abuse
- Active/severe infections
- 48 h prior to elective surgery or invasive procedures and perioperative period
- Past diagnosis of rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, pyruvate carboxylase deficiency
- Allergy to protein-preparations ingredients
- Past or current history of gallstones

4. DIETETIC INTERVENTION

4.1 Very low-calorie ketogenic diet (VLCKD)

A personalized VLCKD will be prepared for each patient by specialized dietitians at IRCCS Istituto Ortopedico Rizzoli, Bologna using a combination of commercially-available ketogenic preparations and patient's handmade prepared meals (see attachment "VLCKD"). The commercial preparations will be ordered for free by an authorized supplier (see 9) on the basis of individual choices and preferences expressed during nutritional interview, and delivered by the seller to the Dietetic Service – IRCCS Istituto Ortopedico Rizzoli, and subsequently hand-delivered to patients by a dietician investigator.

Briefly, VLCKD is a nutritional intervention that mimics fasting through a marked restriction of daily carbohydrate intake, usually lower than 30 g/day (≃ 13% of total energy intake), with a relative increase in the proportions of fat (≃ 44%) and protein (≃ 43%) and a total daily energy intake < 800 kcal, depending on the amount and quality of protein preparations. Nonetheless, VLCKD should not be considered as a high-protein diet, since its daily protein intake is approximately 1.2–1.5 g/kg of ideal body weight (BMI 22.5 kg/m^2).

According to clinical practice guidelines[8, 9], VLCKD is based on protein preparations of high biological value derived from green peas, eggs, soy and whey. Each protein preparation is composed by approximately 18 g protein, 4 g carbohydrate, 3 g fat (mainly high-oleic vegetable oils) and provides approximately 100–150 kcal. Therefore, VLCKD is characterized by a low lipid content, mainly deriving from olive oil (≃ 20 g per day).

4.2 Weight loss program

The weight-loss program will be preceded by a free-diet phase (Phase 0, duration: 4 weeks), during which the patient will be invited to eat normal meals.

The ketogenic period will be dived in three different phases.

During the first phase (Phase 1, duration: 4 weeks), patients are allowed to eat four to six (depending on ideal body weight) of such protein preparations and low-carbohydrate vegetables. Patients will be instructed to maintain the intake of clear liquids (water, tea, coffee or unsweetened carbonated drinks) > 2 L/day.

In the next phases, the state of ketosis is still maintained, but one (Phase 2, duration: 2 weeks) or two (Phase 3, duration: 2 weeks) of the provided meals (lunch or/and dinner) are gradually replaced by natural protein meals (meat/fish/eggs/legumes).

Following the ketogenic period, carbohydrates are gradually reintroduced, starting from foods with the lowest glycaemic load (fruit, dairy products—Phase 4, duration: 4 weeks), followed by foods with moderate (legumes—Phase 5, duration: 4 weeks) and high glycaemic load (bread, pasta and cereals—Phase 6, duration 4 weeks). The gradual reintroduction of food items allows for a progressive nutritional education that supports long-term weight-loss maintenance.

Nutritional details of each phase are reported in the attachment "VLCKD".

5. ASSESSMENT OF DISEASE ACTIVITY

5.1 Assessment of fibromyalgia activity

Assessment of disease activity will be performed using validated Italian language self-administered tools (patient-reported outcomes, PROs) as suggested by the OMERACT proposal for Fibromyalgia Responder Index and Disease Activity Score[16], including:

1) Fibromyalgia Impact Questionnaire (FIQ)[17]

2) Short-Form 36 (SF-36)[18]

3) EuroQol (EQ-5D)[19]

4) Hospital Anxiety and Depression Scale (HADS)[20]

5.2 Assessment of knee osteoarthritis activity

Assessment of disease activity will be performed at weekly intervals using self-administered PROs as suggested by the OARSI Clinical Trials Recommendations: Design and Conduct of Clinical Trials of Rehabilitation Interventions for Osteoarthritis.[21]

1. Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index[22]
2. EuroQol EQ-5D
3. SF-36.

6. STUDY PROTOCOL

6.1 Study periods

As already mentioned, the study will be conducted following different periods:

1. **Free diet (4 weeks, Phase 0).** After recruitment (T-4), the patient will enter "free diet phase" in which he/she will be asked to follow a normal free diet for 4 weeks. During this period, a nutritional interview will be carried out by a trained dietician who will elaborate a personalized diet and order the ketogenic products on the basis of patient's preferences.
2. **VLCKD (8 weeks, Phases 1-3).** After the free diet period, the patient will start the VLCKD regimen as described (4.1 and "VLCKD" attachment). At the beginning of this period (T0) a box with the commercial products necessary to cover the whole study period will be hand-delivered by a dietician that will instruct the patient on the correct use and storage.
3. **Maintenance (12 weeks, Phases 4-6).** After VLCKD phase, the patient will start maintenance period as described (4.1 and "VLCKD" attachment).

6.2 Timing of disease activity and weight assessment

Study procedures are graphically summarized in the attachment "Study chart".

Patient-reported outcomes described in 5.1 and 5.2 will be obtained a T-4, T0, T1, T2, T3, T4, T5, T6, T7, T8, T12, T16, and T20. Patients will be instructed to fill the questionnaires at appropriate intervals and bring them at the subsequent office visits.

During the office visits (T0, T8, T12, T16, T20), a rheumatologist will perform medical interview with special focus on adverse events and routine musculoskeletal visit; weight and height will be measured and recorded.

6.3 Ketosis assessment

Ketosis assessment will be performed using urine strips (Siemens Multistix 10 sg) provided at time of enrolment (T0) at weekly interval from week T0 to T12. Patients will be instructed on correct usage of the strips and to take a picture of urine stick that will be sent by email to a dedicate address for evaluation.

7. SAFETY MONITORING

7.1 Blood tests

Following the abovementioned clinical guidelines[8, 9], safety will be monitored through regular blood and urine tests:

- Before VLCKD and every 4 weeks (T0-T4-T8): complete blood count (CBC), creatinine, blood urea nitrogen (BUN), uric acid, glucose, HbA1c, insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (serum), ALT, AST, γ-GT, total and direct bilirubin, Sodium, potassium, calcium, magnesium, inorganic phosphate, complete urinalysis and microalbuminuria, 25-hydroxyvitamin D, C-reactive protein
- Before VLCKD and at the end of VLCKD (T0-T8): Body composition by whole body DEXA

7.2 Adverse events monitoring

Adverse events will be systematically monitored during each office visits (see 6.1); any potential adverse event will be reported on CRF. In case of adverse event, the investigator, in agreement with the patient, will decide if continue or withdraw from the study. Furthermore, the patient and his/her general practitioner will be able to communicate to the study staff any suspect adverse events using the phone number reported in patient information sheet.

7.3 Women of childbearing age

In women of childbearing age, rapid pregnancy test will be obtained before ketogenic phase to exclude unacknowledged pregnancy. Patients will be instructed to immediately communicate to the study staff the event of unexpected pregnancy during ketogenic phase and to stop immediately the ketogenic diet. In this case, patient will be withdrawn from the study and referred for pregnancy nutritional consultation. No actions will be needed in case of pregnancy of a male patient's partner.

7.4 Insurance

Possible damages arising from participating in the present study will be covered by a study-specific insurance provided by IRCSS Istituto Ortopedico Rizzoli.

8. ETHICAL CONSIDERATIONS

Written informed consent will be obtained by all patients at recruitment. Study procedures will be performed according to the Declaration of Helsinki and clinical practice guidelines[8, 9].

9. STATISTICAL ANALYSIS

Given the exploratory nature of the study, an arbitrary number of 20 fibromyalgia and 20 symptomatic knee osteoarthritis patients will be recruited from Rheumatology Outpatient Clinic – IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy. Patients' associations will be involved for volunteer engagement.

Primary measures of efficacy (change in FIQ total score and WOMAC total score, for fibromyalgia and osteoarthritis, respectively) will be compared using paired-sample Student's T tests at time T-4, T0, T8, T20. Analysis of covariance (ANCOVA) will be used to evaluate the effect of baseline disease severity and BMI on change in primary efficacy measures.

Furthermore, other exploratory analyses will be performed:

- Change in secondary outcome measures at T-4, T0, T8, T20;
- Correlation between change in body weight ($\Delta weight_{T0\text{-}T8}$) and change in primary ($\Delta FIQ_{T0\text{-}T8}$ or $\Delta WOMAC_{T0\text{-}T8}$) and secondary outcome measures;
- Time course of %change in FIQ total score and WOMAC total score from T-4 to T20;
- Student's T test for difference in $\Delta FIQ_{T0\text{-}T8}$ or $\Delta WOMAC_{T0\text{-}T8}$ in patients who achieved and maintained ketosis during the ketogenic phase (urinary ketones > +5 from week 1 to week 8) vs patient who did not maintained ketosis.

Both per-protocol (PP) and intention-to-treat (ITT) analyses will be performed.

All analyses will be performed using the Statistical Software for Social Sciences (SPSS, IBM) version 23.

10. STUDY COSTS

No additional costs are attributable to this study except the provision for protein preparations required during the ketogenic phase of the diet. For this cost, we asked producers of VLCKD supplements a free supply of preparations to cover the requirements. Logistica Food srl, located in Manoppello (PE), Viale S.Tinozzi, 17 preliminary agreed (see attachment) to cover the requirements of the study. To preserve sensitive information of recruited patients, the orders covering product requirement for the entire study period will be anonymously placed by the Dietetic Service, IRCCS Istituto Ortopedico Rizzoli; subsequently the products will be hand-delivered by a dietician investigator to individual patients.

11. PUBBLICATION OF RESULTS

The results from this study will be published or shown at scientific conferences. The final publication of the study results will be written by the Principal Investigator.

12. SPONSOR ROLE AND RESPONSIBILITY

The promoter is the sole owner of the data and is responsible of all the clinical trial activities from study design, development, data collection, management, analysis, interpretation of data, writing and the decision to submit the report for publication written by the Principal Investigator.

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