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**Very low calorie ketogenic Diet and Common Rheumatic Disorders: a case report**

VLCKD and Rheumatic Disorders

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## **Abstract**

### **BACKGROUND**

The scientific literature provides evidence that nutritional ketosis can be an important support in the treatment of pathologies in which inflammation is present, as recent studies have shown that ketone bodies have anti-inflammatory activity in numerous diseases, including rheumatic diseases. We report the case of a 22-year-old woman with class I obesity and juvenile idiopathic arthritis who started treatment with a very low calorie ketogenic diet (VLCKD).

### **CASE SUMMARY**

The patient was a 22-year-old woman diagnosed with juvenile idiopathic arthritis at age 4 years and with a BMI of 30.8 kg/m<sup>2</sup>, waist circumference 80 cm, fat mass 28.1 kg, free fat mass 45.7 kg, and visceral adipose tissue 3.5 kg, assessed on bioimpedance analysis. She was treated using a commercial VLCKD weight-loss program (PNK® Method); this program provides high-biological-value protein preparations and natural foods. Each protein preparation contains 15 g protein, 4 g carbohydrate, 3 g fat, and 50 mg omega-3 DHA, with an energy content of 90–120 kcal. After four months on the program, the BMI was 28.6 kg/m<sup>2</sup>, waist circumference 73 cm, fat mass 23.2 kg, free fat mass 41.9 kg, and visceral adipose tissue 2.9 kg.

### **CONCLUSION**

VLCKD enabled the patient to reach her target weight and to reduce her joint pain and headaches. Laboratory inflammatory indices also normalized.

**Key Words:** VLCKD; Inflammation; PNK® Method; Weight loss; obesity; rheumatic disorders.

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**Core Tip:** A commercial weight-loss program (PNK® Method) was used, based on a VLCKD. VLCKD allowed the patient to achieve weight goal, better management of joint pain, headache episodes and normalization of inflammatory indices.

## INTRODUCTION

Nutritional ketosis has been used since the 1920s as a treatment for refractory epilepsy [1] and the very low calorie ketogenic diet (VLCKD) is currently gaining popularity as a potential therapy for obesity and metabolic disorders [2].

The Italian Association of Dietetics and Clinical Nutrition (ADI) gives the following indications for VLCKD: morbid obesity or obesity with comorbidities (including type 2 diabetes, dyslipidemia, hypertension, metabolic syndrome, obstructive sleep apnea syndrome, bone disease or severe arthropathy); the preoperative period of severe obesity with an indication for bariatric surgery; patients with severe comorbidities and overweight, necessitating rapid weight loss; non-alcoholic fatty liver disease (NAFLD); and drug-resistant epilepsy [3,4].

In addition to these established indications, the scientific literature advocates the use of nutritional ketosis in the treatment of chronic inflammatory diseases, as recent studies have shown that ketone bodies have anti-inflammatory activity in numerous diseases [5,6].

The ketone body  $\beta$ -hydroxybutyrate ( $\beta$ OHB) is elevated during VLCKD treatment, and there is increasing evidence that  $\beta$ OHB acts not only as an energy substrate but also as a signaling molecule [6].  $\beta$ OHB is a ligand for G protein-coupled receptors that bind short-chain fatty acids, including hydroxycarboxylic acid receptor 2 and free fatty acid receptor 3. It can attenuate oxidative stress in the spinal cord and kidney by

suppressing class I histone deacetylases (HDACs) [6] and has been shown to suppress NLRP3 inflammasome-mediated inflammatory disease [6–10].

Inflammatory rheumatic disorders induce chronic inflammation in joints and other tissues [11] and are characterized by an increased expression of several proinflammatory cytokines, including IL-1, IL-6, TNF- $\alpha$ , IL-23, and IL-17 [12].

A more recent review by Ciaffi *et al* suggests that the ketogenic diet (KD) could play a role in the treatment of patients with rheumatic musculoskeletal diseases as the KD can facilitate weight loss and modulate systemic inflammation, resulting in a rapid response to systemic therapy [13].

In obese patients, the VLCKD was significantly more effective than a standard low-calorie diet in terms of weight loss [14,15]. It has also been demonstrated that a VLCKD supplemented with omega-3 DHA has a significantly superior anti-inflammatory effect, despite non-significant differences in weight loss and metabolic improvement [16].

Given the potential benefits, a 22-year-old woman with a BMI of 30.8 kg/m<sup>2</sup> and who had been diagnosed with juvenile idiopathic arthritis at the age of 4 years, was started on a VLCKD.

## **CASE PRESENTATION**

### ***Chief complaints***

A 22-year-old woman attended outpatients at the Santa Margherita Nutritional Rehabilitation Institute, Pavia, Italy, for an endocrinology and dietary consultation. The patient reported gradual and persistent weight gain from the age of 10 years.

### ***History of present illness***

She had been diagnosed with juvenile idiopathic arthritis at age of 4 years, and occasionally presented headache and alternating episodes of constipation and diarrhea. At the time of her first consultation at this outpatients, she was on estrogen-progestogen therapy and had been prescribed naproxen 550 mg or 7.5 mg meloxicam as required.

### *Physical examination*

Weight (kg) was measured to an accuracy of  $\pm 0.05$  kg, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Bioimpedance analysis (Zeus, Cosmed, Italy) provided whole-body and compartmentalized values for fat mass (FM) and fat-free mass (FFM), visceral adipose tissue (VAT), and intra- and extracellular water analysis for estimating hydration status. Additionally, waist circumference (WC) was measured by a trained dietitian at the level of the umbilicus at the end of normal expiration using a non- elastic measuring tape.

The patient's baseline basal metabolic rate (BMR) was assessed by indirect calorimetry (Cosmed Q-NRG) at the first anthropometric and nutritional evaluation.

The patient never had significant limitations in physical activity.

### **FINAL DIAGNOSIS**

The patient had juvenile idiopathic arthritis and I grade obesity.

### **TREATMENT**

The initial dietary approach was a balanced, low-calorie diet based on World Health Organization (WHO) criteria (WHO, Washington, DC, USA) <sup>[17]</sup> adapted to the BMR calculated by indirect calorimetry.

Then, the patient was started on a commercial weight-loss program based on a VLCKD (PNK® Method, Barcelona, Spain). This program consists of high-biological-value protein products and whole natural foods. Each protein food provides 90-120 kcal and it's composed by 15 g protein, 4 g carbohydrate, 3g fat, and 50mg omega-3 DHA. The program consists of three phases: intervention, dietary re-education, and maintenance (Table 1).

The intervention phase consists of a very low calorie diet (600-800 kcal/day), with a low content of carbohydrate (20-50 g/day), and fat (10 g/day of olive oil). The intake of high-biological-value protein is fixed around 0.8 and 1.2 g per kg ideal body weight per day, in order to ensure the coverage of protein requirements. The intervention

phase is composed by 3 steps. In Step 1, patients consume 5 protein servings at high-biological-value and 2 portions of vegetables. The permitted vegetables are divided into two groups. Vegetables in group A have a very low glycemic index and include chard, celery, watercress, borage, broccoli, soybean sprouts, zucchini, lamb's lettuce, cauliflower, chicory, spinach, turnip greens, fennel, lettuce, cucumber, pickled gherkins, green peppers, mushrooms, radishes, and rocket; consumption of these vegetables is not limited. Vegetables in group B have a low glycemic index and include artichoke, eggplant, cabbage, asparagus, green beans, turnip, yellow and red peppers, leeks, and tomatoes; consumption is limited to 100 g per day.

During Step 2, a natural protein serving (100-150 g of meat, poultry, fish, or seafood, canned tuna in brine or two eggs) is consumed in place of one of the protein preparation, at lunch or dinner. Patients will therefore be consuming four high-biological-value protein preparations per day.

In Step 3, a fresh source of protein is introduced at both lunch and dinner, choosing between 100-150g of meat, poultry, fish, seafood, canned tuna in brine, or two eggs. In step 3, patients are therefore eating three high-biological-value protein preparations per day.

During the intervention phase, vitamin and mineral supplementation is provided in accordance with international requirements <sup>[18]</sup>. The composition is shown in Table 2.

During the dietary treatment, the patient followed a specially recommended physical activity program. During Step 1, 2, and 3 the recommended physical activity is anaerobic, with toning exercises to be performed preferably in the morning, at least 2 or 3 times a week; each exercise should be performed for 3 sets, with one minute of rest between sets, for a total of 30 minutes of physical activity. In steps 4 and 5, in addition to toning exercises to be performed at least 2-3 times a week, cardiovascular activity, such as walking or exercise bike of gentle or moderate intensity, is planned for about 50-60 minutes, twice a week.

## **OUTCOME AND FOLLOW-UP**



After the VLCKD period, the patient has been administered with a low-calorie diet; she reduced her BMI from I class obesity to overweight. Telephone contacts with the patient continue and new check-ups will be scheduled in order to monitor body weight.

## DISCUSSION

After two months, at the first follow-up visit, body weight remained unchanged (Table 4) and the patient reported increasing joint pain, for which the rheumatological team introduced hydroxychloroquine 200 mg/day. The patient was not satisfied with either the treatment or the dietary plan.

Given the failure of the low-calorie balanced diet, the nutrition team decided to switch to a VLCKD (the PNK® Method). The patient received multidisciplinary support from doctors, physical activity instructors, and nutritionist-coaches throughout follow-up.

The VLCKD intervention was started in early 2022, with a body weight of 79.9 kg. In Step 1, the patient lost 8 kg, from 79.9 kg to 72 kg, the waist circumference decreased from 82 cm to 75 cm, and the body composition improved, with a reduction in FM, from 29.4 kg (36.9%) to 25.3 kg (35.1%), and VAT, from 3.8 kg to 3.0 kg. At the follow-up visit at the end of Step 1, the patient reported a subjective feeling of well-being and the headaches had ceased.

Step 2 started in February 2022 and led to a further loss of about 4 kg (Table 4). At the follow-up visit at the end of Step 2, the patient reported tolerance of the dietary plan and that she performed the physical activity as defined in the PNK program. Her sleep pattern and quality had improved, as had her joint pain, and there had been no recurrence of the headaches. Body weight was 69 kg and the waist circumference 72 cm; FM and the VAT decreased to 23.2 kg and 2.7 kg, respectively (Table 4).

The patient next moved to Step 3 in April 2022. Body weight remained unchanged (69 kg) (Table 4). Contact with the patient took place by telephone, hence body composition measurements were not possible.

The patient did not lose weight during two weeks of Step 3, and the nutrition team therefore decided to progress to Step 4 (dietary re-education phase), moving the patient



to a low-calorie diet to favor dietary compliance. During this stage the patient regained some of the weight she had lost, reaching a weight of 72.8 kg (Table 4).

Step 5 was initiated in June 2022 after the patient had completed Step 4 and during this final step of the weight-loss phase, the weight remained practically unchanged (Table 4). Contact was by telephone, so again it was not possible to perform body composition analysis. The patient reported a feeling of well-being and good sleep quality, and there was no sensation of hunger.

Despite slight weight regain, the patient reported feeling better than before undertaking the VLCKD. We consider that this effect may be due as much to the beneficial effects of the nutritional ketosis or even the anti-inflammatory effect of the omega-3 DHA supplementation as to the weight loss. The serum inflammatory markers before and during the VLCKD are shown in Table 3.

A blood test was taken during the VLCKD and showed the following: lupus anticoagulant, negative; silica clotting time ratio, 0.96; Russel's viper venom time ratio, 1.05; ferritin, 10 ng/mL; erythrocyte sedimentation rate (ESR), 31 mm/h; complement component C3, 1.15 g/L; complement component C4, 0.19 g/L; rheumatoid factor, <20 IU/mL, and C-reactive protein (CRP), <5 mg/L. Protein electrophoresis trace did not reveal the presence of abnormal monoclonal components and the interferon-gamma release assay was negative.

The administration of a VLCKD would appear to improve all the parameters evaluated in order to assess inflammatory profile. In particular it's noteworthy the reduction of CRP values from 17 mg/L up to the normal range. Similar results were obtained by previous studies conducted in obese [14] and overweight subjects [18].

Anthropometric parameters at baseline and their changes during the dietary treatment are shown in Table 4.

Considering the entire weight loss diet therapy program, from the beginning to the end of the ketogenic phase, the patient lost 5.3 kg (from 78.3 to 73), with a greater weight loss at the end of steps 2 and 3 (-9.3 kg), always going to improve her wellbeing. In

steps 4 and 5 the patient gained 4 kg but it is very interesting to note how the improvement in body composition obtained during weight loss phase (with reduction of fat mass and preservation of fat free mass) has been maintained over time (step 4 and 5).

Finally, also the VAT, which is a well-known cardiovascular risk factor producing chronic low-grade inflammation <sup>[19]</sup>, has significantly reduced (-600 g) from the beginning to the end of dietary program.

The goal of healthy weight loss was therefore achieved, since <sup>9</sup> weight reduction has mainly affected fat mass, while lean mass was mostly preserved.

## CONCLUSION

The VLCKD allowed the patient to achieve her target body weight (reducing from class I obesity to overweight), with an improvement in her joint pain and the episodes of headache, and an improvement in serum inflammatory markers (reduction in CRP from 17 mg/L to 5 mg/L and ESR from 95 mm/h to 31 mm/h).

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