

# Complete Cessation of Recurrent Cervical Intraepithelial Neoplasia (CIN) by the Paleolithic Ketogenic Diet: A Case Report

Csaba Tóth, Mária Schimmer, Zsófia Clemens\*

Paleomedicina Hungary Ltd, Evolutionary Medicine Working Group, Budapest, Hungary

\*Corresponding author: [clemenszsofia@gmail.com](mailto:clemenszsofia@gmail.com)

**Abstract Background:** Ketogenic diets have repeatedly been suggested for the treatment of cancer. To date, only a few case studies reporting long term benefits associated with such diets have been published. **Case report:** Here we present a case where recurrent cervical intraepithelial neoplasia (CIN), a premalignant condition of cervical cancer, was successfully treated with the paleolithic ketogenic diet. The patient had a history of high grade CIN in 2011, which was successfully treated with cervical conization and fractional curettage. In October 2015 she was found to have a recurrence of high grade CIN (HSIL: High Grade Squamous Intraepithelial Lesion). The patient was then commenced on the paleolithic ketogenic diet and her repeat Pap (Papanicolaou) smear three months later was found to have reverted to normal. The patient has remained on the paleolithic ketogenic diet for 26 months, her repeat smears have stayed normal, and she is free of symptoms and side effects. **Conclusion:** We conclude that the diet was effective and safe in this patient. As a major benefit the patient was able to avoid a hysterectomy, which is the standard treatment for recurrent high-grade CIN. We believe that the paleolithic ketogenic diet combines benefits of both paleolithic and classical ketogenic diets, while excluding their disadvantages.

**Keywords:** ketosis, evolutionary medicine, dietary intervention, cancer, metabolic therapy

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## 1. Introduction

Ketogenic diets have long been suggested as an alternative approach to cancer management [1]. Support for the ketogenic diet comes mainly from studies conducted on animals as well as research at the cellular level [2]. In contrast to the prevailing view of cancer as a predominantly genetic disease, Seyfried [2] suggested cancer as a metabolic disease emerging from respiratory insufficiency coupled with compensatory fermentation, an idea which can be traced back to the original theory of Warburg [3]. Seyfried suggested this altered energy metabolism to be common to all cancer types irrespective of the tissue type [2]. He also suggested that targeting this common metabolic component with the ketogenic diet would be more effective than targeting secondary and more variable components which is the case with many chemotherapy drugs [4].

Although human studies have shown that the classical ketogenic diet is relatively safe [1,5], they have provided little evidence that it is indeed beneficial in cancer. As far as we know only two cases of following the classical ketogenic diet have resulted in long-term survival [6]. Group studies that were carried out with the classical ketogenic diet were either limited in follow up duration [1,7] or reported no or uncertain benefit in terms of survival [8,9].

We have recently published a case where using the paleolithic ketogenic diet without any other treatment resulted in halted progression of soft palate cancer for 20 months [10]. The paleolithic ketogenic diet differs from the classical ketogenic diet in that it excludes food components that were not available in preagricultural times (milk, dairy, cereal grains, oilseeds, nightshades, vegetable oils, food additives, dietary supplements). It has been suggested that non-paleolithic food components induce pathological permeability of the intestine [11] and that of other barrier membranes, a factor thought to be involved in the cancerous transformation of normal tissues [12]. The paleolithic ketogenic diet that we use is close to the animal meat-fat based diet proposed by Voegtlin as being evolutionary adapted for humans [13].

Here we report a case of a patient with recurrent high grade cervical intraepithelial neoplasia (CIN) where following the paleolithic ketogenic diet reversed this condition as evidenced by gynecological cytology.

## 2. Results

### 2.1. Previous Medical History

The patient was a life-long non-smoker, had never used oral contraceptives and had three normal vaginal deliveries.

In 2011, at the age of 42, a high-grade squamous intraepithelial lesion was found on a routine Pap (Papanicolaou) smear and associated abnormal findings on colposcopy. The patient underwent cervical conization and fractional curettage in June 2011. Excision occurred with free margins. Histopathology of the excized specimen indicated high-grade CIN (HSIL: high-grade squamous intraepithelial lesion).

Between 2012 and 2014 consecutive gynecological ultrasound exams showed that the endometrial thickness decreased from 9.8 mm (in August 2012) to 2.7 mm (in January 2014). Testing for human papillomavirus (HPV) DNA, carried out in June 2013, was normal.

In February 2014 the patient started a popular version of the paleolithic diet with the aim of preserving health. The next two ultrasounds showed increasing thickness of the endometrium with 5.2 mm in December 2014 and 12.5 mm in May 2015 (Table 1). Due to the thickened endometrium fractional curettage was performed in June 2015. Histopathology indicated high-grade CIN (HSIL).

Pap smears between Sep 2011 and May 2015 were normal, but the smear in October 2015 (20 months after the onset of the popular paleolithic diet and four months after performing the fractional curettage) was found to be abnormal.

HPV DNA testing, performed in August 2015 (after 18 months on the popular paleolithic diet) showed the presence of low-risk types. Based on the abnormal histopathology, the abnormal cytology and the HPV positivity, the patient was offered abdominal hysterectomy. The patient asked for surgery to be postponed and contacted us for dietary guidance with the aim of avoiding a hysterectomy.

## 2.2. The Popular Paleolithic Diet

The patient had been following a popular version of the

paleolithic diet for 20 months between February 2014 and October 2015. In her diet vegetables, fruits and oilseeds predominated over animal-based foods. Besides animal fats, her diet also contained vegetable oils including coconut oil and olive oil. She was consuming sugar alcohols as sweeteners and was also taking multiple dietary supplements. She did not consume offal on a regular basis. This version of the paleolithic diet conforms neither to the paleolithic diet as originally described by Cordain [11] or Lindeberg [14] nor any of those versions in previously published clinical studies of the paleolithic diet [15,16,17,18]. We therefore refer to this diet as a 'popular paleolithic diet' because it appears to arise from a mixture of scientific and unscientific information, much of which is probably gleaned from dubious sources on the internet.

## 2.3. Paleolithic Ketogenic Diet

The patient was reluctant to accept a hysterectomy that was offered after the diagnosis of recurrent high-grade CIN. Shortly afterwards she contacted us, with the primary goal of avoiding a hysterectomy. We suggested the paleolithic ketogenic diet, which the patient started immediately. The paleolithic ketogenic diet is an animal fat-meat based diet with a fat: protein ratio of about 2: 1 (in grams). The diet excludes cereal grains, milk, other dairy foods, nightshades, oilseeds, vegetable oils (including coconut oil and olive oil), legumes, refined sugars, artificial sweeteners, food additives and all types of dietary supplements. Vegetables and fruits were restricted to less than 30% in volume. Red and fatty meats and a regular intake of offal from cattle and pork was encouraged. The patient was allowed to consume honey in moderation. Coffee consumption was limited to one coffee a day. The patient has now been on the paleolithic ketogenic diet for 26 months, and is currently still on it.

**Table 1. Pap smear, endometrial thickness (as shown by gynecological ultrasound) and HPV DNA testing data on the normal diet, popular paleolithic diet and the paleolithic ketogenic diet. ASC-US: atypical squamous cells of unknown significance**

	Pap smear	date	Endometrial thickness (mm)	date	HPV DNA	date
Normal diet	abnormal	24.05.2011				
	Conization, fractional curettage 21.06.2011					
	normal	27.09.2011	9.8	29.08.2012		
	normal	15.10.2013	8.4	15.10.2012	negative	07.07.2013
	normal	28.01.2014	2.7	29.01.2014		
Popular Paleolithic diet	normal	08.04.2014				
	normal	16.09.2014				
	normal	20.01.2015	5.2	12.12.2014		
	normal	19.05.2015	12.5	21.05.2015		
	Fractional curettage 09.06.2015					
	abnormal	08.10.2015			positive	28.08.2015
Paleolithic ketogenic diet	normal	14.01.2016				
	normal	28.04.2016				
	ASC-US	30.09.2016				
	normal	25.01.2017				
	normal	09.08.2017				
	normal	01.12.2017				

## 2.4. Follow up

### 2.4.1. Laboratory Workup and Urinary Ketones

A laboratory workup after 11 months on a paleolithic ketogenic diet (September 2016) was normal, and the low triglyceride and uric acid levels and mildly elevated cholesterol level were compatible with following the paleolithic ketogenic diet. Inflammation level as indicated by CRP was also low. The low thyroid stimulating hormone (TSH) level of the patient is compatible with a low carbohydrate diet (Table 2). The patient used urinary ketone strips on a daily basis which showed sustained ketosis except for during the summer months of 2016 when she reported 15 days of not being in ketosis and which was likely due to an increased consumption of fruits.

**Table 2. Laboratory measurements on the paleolithic ketogenic diet (on 20 Sep 2016)**

		reference range	unit
CRP	0.66	0-10	mg/l
Glucose	5.8	3.6-6.1	mmol/l
Carbamide	4	2.5-7.5	mmol/l
Creatinine	55	40-88	μmol/l
Total cholesterol	6.6	2.8-5.2	mmol/l
HDL cholesterol	1.87	1.09-2.29	mmol/l
Triglyceride	0.7	0.9-1.87	mmol/l
Uric acid	222	178-345	μmol/l
GOT	16	0-37	U/l
GPT	11	0-40	U/l
GGT	13	7-32	U/l
Iron	11.8	10.7-32.2	μmol/l
WBC	4.39	4.5-11	G/l
RBC	4.09	4-5.2	T/l
Hemoglobin	12.8	12-15.5	g/dl
Hematocrit	37.2	36-50	%
Thrombocyte	229	150-350	G/l
TSH	0.74	0.550-4.780	μIU/ml

#### Abbreviations:

CRP: C-reactive protein, HDL: high density lipoprotein, GOT: glutamate-oxaloacetate transaminase, GPT: glutamate-pyruvate transaminase, GGT: gamma-glutamyl transferase, WBC: white blood cell count, RBC: red blood cell count, TSH: thyroid stimulating hormone.

### 2.4.2. Cervical Cytology

During the follow up of 26 months the patient had six cervical cytology tests (Table 1). The first cytology follow up, performed at three months after diet onset (in January 2016), as well as the second one at six months on the diet (in April 2016) were normal. The third follow up at one year after diet onset (in Sep 2016) indicated atypical squamous cells of unknown significance (ASC-US) but no neoplastic alteration. This third cervical cytology was performed after a period of poor dietary compliance during which the patient was not in ketosis. After learning about the result of the abnormal cytology the patient went back to following the diet strictly. The fourth follow up, which was performed in January 2017 after going back to being compliant with the diet, showed normal results

again. The next two follow ups (in August 2017 and December 2017) also showed normal results.

### 2.4.3. General Condition

At diet onset the patient weighed 55 kg (BMI=20.7). On the paleolithic ketogenic diet she lost two kilograms. Currently her BMI is 19.9. She reports feeling generally well, and has no symptoms or side-effects due to the diet.

## 3. Discussion

CIN is regarded as a premalignant condition of cervical cancer [19]. Recurrence of cervical intraepithelial lesion after treatment is usually regarded as an indication for hysterectomy, a radical treatment of CIN. Upon recurrence our patient was offered a hysterectomy too. However, she opted for delaying hysterectomy and started the paleolithic ketogenic diet. Importantly, for the four years after the first conization and the fractional curettage she was disease-free as evidenced by regular gynecological cytology and ultrasound. Yet, while on the popular paleolithic diet, ultrasound showed endometrial thickening and both HPV DNA test and cervical cytology turned positive.

The diet denoted as "paleolithic" in the medical literature has been shown to confer several benefits in metabolic syndrome and associated conditions as also evidenced by a metaanalysis [20]. By definition, the paleolithic diet excludes foods that were not available in prehistoric times [11,14]. However, the paleolithic diet as published in clinical studies [15,16,17,18] differ from the diet we refer to as paleolithic ketogenic in important aspects including macronutrient ratios and the ratio of animal vs. plant based food components. Moreover, given the availability of internet-based, mainly non-scientific resources, several variants of the paleolithic diet abound which we collectively denote as popular paleolithic diet. These diets may also contain food components that should not be denoted as "paleolithic" according to Cordain [21].

We believe that the paleolithic diet (as described in previously published clinical studies) is inappropriate to fight autoimmune diseases and cancer. As we previously reported, recovery from Crohn's disease using the paleolithic ketogenic diet may be hindered by eating components of the popular paleolithic diet [22]. In another case study we reported that the popular paleolithic diet did not confer all the benefits that were provided by the paleolithic ketogenic diet in Gilbert's syndrome [23]. Previously we have published a case of soft palate cancer halted by the paleolithic ketogenic diet for 20 months [10]. We also reported successful management of cases of autoimmune conditions including type 1 diabetes [24,25] and cases with epilepsy [26,27] and metabolic syndrome [28] using the paleolithic ketogenic diet. In another case study we reported that a full dietary adherence is needed to halt disease progression in rectal cancer [29]. In a reply paper we summarized why the paleolithic ketogenic diet may be superior to the classical version of the ketogenic diet and why the standard treatment may be counter effective in the treatment of cancer [30].

Our patient with recurrent CIN started the paleolithic ketogenic diet under our guidance. Three months after diet onset her Pap smear cytology was reported as normal.

Follow up at three and six months after diet onset her Pap smear cytology was reported as normal. However, the 12 months follow up showed atypical cells of uncertain significance. This slightly abnormal Pap smear was preceded by a period of increased fruit intake and consequently the patient not being in ketosis. The patient then went back to following the paleolithic ketogenic diet strictly and her follow up tests at 15, 22 and 26 months were normal again.

Fluctuation of the grade of the cervical squamous cell pathology is common. However, in the long run the overall tendency of CIN is progressive even after treatment. Therefore a complete normalization of cervical cytology without any other treatment in a patient with recurrent high grade CIN is unlikely to be part of the normal course of the disease.

Ketogenic diets have been shown to be effective in controlling tumor growth in animal models [2]. In humans, the classical ketogenic diet has been shown to confer benefits in terms of reducing chemo/radiotherapy induced side-effects [2] but not in terms of prolonging survival. Previously, we reported a case with aggressive soft palate cancer successfully managed with the paleolithic ketogenic diet alone [10]. We believe that the state of ketosis, although required, is insufficient on its own in controlling tumor growth in cancer patients.

Increased permeability of the intestines and that of other membranes is known to be associated with an elevated level of inflammatory markers [31]. Both decreased barrier function [12] and inflammation are known to be associated with the development and growth of tumors [32]. We believe that the paleolithic ketogenic diet by excluding "non-paleolithic" food components normalizes the pathological permeability of the intestines as also seen in a published case of Crohn's disease [22], and likely through the normalization of intestinal permeability results in lowering inflammatory factors (as also showed in our previous case reports). In addition, ketosis, based on animal meat and fat may ensure optimal supply and bioavailability of vitamins, including vitamin C [33] the high blood level of which is important for the proper functioning of the immune system and also convey antitumor effects [34].

It is known that within the mitochondria beta oxidation of fatty acids is associated with the production of matrix water which is relatively low in deuterium. Depletion of deuterium has been suggested as one of the key elements of the antitumor effect of high fat diets. As a potential mechanism of action, it has been suggested that hydrogen bonding in DNA would be negatively impacted by elevated deuterium content given that NADPH-dependent DNA synthesis is subserved by the matrix water pool [35]. As a clinical parallel, there are metabolic profiling data showing that in lung cancer patients rapid progression was associated with serum markers of glycogenic substrates while ketogenic substrates were associated with prolonged survival [36]. More specifically, the importance of the quality and source of dietary fat in determining deuterium content and ratios was also stressed [37].

We conclude that the paleolithic ketogenic diet was safe and effective in our patient with recurrent cervical dysplasia. We believe that the paleolithic ketogenic diet combines benefits of both paleolithic and classical

ketogenic diets, while excluding their disadvantages. By using the paleolithic ketogenic diet the patient was able to avoid a hysterectomy which is thought to be otherwise inevitable knowing the progressive nature of this condition. As a major benefit the patient could preserve her cervix, reproductive capacity, social and sexual integrity, all of which contribute to general well-being.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## Informed Consent

Informed consent was obtained from the patient included in the study.

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