Med Sci Monit, 2001; 7(Suppl. 1): 282-286

Effect of high fiber vegetable-fruit diet on the activity of liver damage and serum iron level in porphyria cutanea tarda (PCT)

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key words: very-low-energy diet (VLED), porphyria cutanea tarda (PCT), liver, iron.

SUMMARY

Background: *During the treatment of coronary heart disease with a vegetable-fruit diet, we have observed the positive effect of the treatment on PCT patients. Therefore, we have now examined the short-term results of the diet on the selected PCT activity parameters. The study was approved by our Review Board.*
Material and methods: *A group of 13 male PCT patients (mean age 52 years) was evaluated. We assessed the body mass index (BMI), serum iron level, activity of transaminases (ALT, AST), severity of skin symptoms, and urinary porphyrins excretions, before and after a three-week period of vegetable-fruit diet. The diet was of natural vegetable/fruit products, and its daily caloric content was ca. 500 kcal/day.*
Results: *The mean BMI before and after the diet period were 26.8±4.7 vs. 25.8±4.3 ($p = 0.001$), the serum activities of ALT 122.0±60.7 U/l vs. 75.6±31.8 U/l, and of AST 91.8±56.0 U/l vs. 55.2±14.2 U/l ($p = 0.001$), respectively. The mean serum iron levels were 188.6±75.7 mg/dl vs. 140.2±56.4 mg/dl, serum ferritin concentrations 574±351 vs. 499±340 ng/ml ($p = 0.04$), respectively. Severity of skin lesions and urinary coproporphyrins excretion were significantly diminished during the diet; urinary uroporphyrins excretion was also lowered, but not to a statistically significant level.*
Conclusion: *In our group of PCT patients, we noticed the beneficial effect of the vegetable-fruit diet on selected disease parameters. The diet may be useful in the treatment of PCT and diseases associated with PCT.*

BACKGROUND

Porphyria cutanea tarda (PCT) develops in genetically predisposed subjects, in whom factors such as alcohol [1–2], HCV infection [3–4], or estrogen therapy [5] may cause the reduction of hepatic uroporphyrinogen decarboxylase (UROD) activity. The enzymatic block is associated with excessive production of uro- and coproporphyrins, whose photosensitizing properties result in typical photodermatoses. The clinical picture of the disease includes also liver damage, ranging from mild degenerative changes, through inflammatory or cirrhotic lesions, even to neoplastic ones.

The course of PCT is also associated with high iron levels in blood, as well as with the presence of iron deposits in hepatocytes. As iron inhibits UROD activity [6] and is one of the factors responsible for organ damage in PCT, the currently used therapy of the dise-

Sources of support: Study was supported by the Polish State Committee for Scientific Research (KBN) research grant No. 4P05B04113.

Received: 2000.12.30
Accepted: 2001.03.30

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ase is focused mainly on lowering the iron levels by repeated phlebotomies or desferrioxamine infusions (chelating iron) [7–10]. Together with iron depletion, UROD activity increases and porphyrin production is reduced, which leads to clinical remission. Other methods of treatment, making use of chloroquine [11], cimetidine [12], interferon [13], plasmaphoresis [14], hemoperfusion [15] – have proved less effective and their use is not very common.

As the treatment with phlebotomies is troublesome, often leads to anemia, and its discontinuation may lead to relapses of the disease, the search for alternative methods was initiated. During the recent years we have demonstrated the safety and usefulness of very-low-energy diet (VLED) in many clinical situations [16–18]. Our earlier, very promising results of VLED used in the treatment of patients with metabolic syndrome X [16-18], which often accompanies PCT, prompted us to use this type of therapy also in PCT patients.

The aim of the study was to asses the effect of very-low-energy vegetable-fruit diet on the activity of liver damage and serum iron levels in porphyria cutanea tarda.

MATERIAL AND METHODS

The study was carried out in a group of 13 patients of mean age 52 (40–73), in whom PCT was diagnosed on the basis of elevated urine levels of uro- and coproporphyrins and typical cutaneous lesions. The average duration of disease from the onset of first cutaneous lesions was 8±6.5 years. The patients reported in the anamnesis alcohol abuse in the past, but complete abstinence during the last months before the inclusion in the study.

Before and after treatment, the patients were weighed and their body mass index (BMI) was calculated, serum aminotransferase activity was assessed (alanyl aminotransferase, ALT, aspartyl aminotransferase, AST) as well as systemic iron turnover by determining serum iron levels and total iron binding capacity (TIBC), the degree of transferrin saturation was calculated and serum ferritin level determined by immunoenzymatic method using reagents manufactured by Abbott Laboratories.

The patients received very-low-energy diet (VLED), based on natural products of plant origin – mainly vegetables and some fruit – with energetic supply of ca 500 kcal/day. During that period, the patients ate only low-starch vegetables (e.g. carrots, celery, beetroots, cabbage, onions, tomatoes, peppers, lettuce, etc.) and some fruit, mainly those with low sugar content (apples, grapefruits and lemons). Vegetables and fruit were served raw (salads, juices) or cooked, stewed, fried, etc. The dishes were seasoned with herbs and a little salt, without fats. The patients drank still mineral water, herbal teas, vegetable broth. It was forbidden to eat any other products during the therapy.

Tables 1 and 2 present the contents of particular nutrients in VLED versus recommended dietary

Table 1. Energy and nutrient daily contents in very-low-energy diet and in recommended dietary standards [19].

Diet type	Energy (kcal/day)	Protein (g/day, % of total intake)	Carbohydrates (g/day, % of total intake)	Fat (g/day, % of total intake)	Cholesterol (mg/day)
Very-low-energy diet	511	15.0 (13%)	97.0 (84%)	4.0 (3.5%)	0
Recommended dietary standards	2800	85.0 (12%)	400.0 (57%)	95.0 (30%)	200
Very-low-energy diet / recommended dietary standards ratio	5.5	5.7	4.1	24	-

Table 2. Cellulose, mineral and vitamin daily content in very-low-energy diet and in recommended dietary standards [19].

Diet type	Cellulose (g/day)	Minerals (mg/day)				Vitamins				
						Carotene (µg/day)	(mg/day)			
		Ca	P	Fe	Mg		B1	B2	PP	C
Very-low-energy diet	42.0	556	306	22	145	17 968	1.0	1.0	7.0	342.0
Recommended dietary standards	27.0	800	800	12	400	5 000	1.6	1.7	19.0	60.0
Very-low-energy diet / recommended dietary standards ratio	1.6	0.6	0.4	1.8	0.4	3.6	0.6	0.6	0.4	5.7

standards [19] and the calculated ratios of these contents.

VLED, in comparison with recommended dietary standards, provides over 5-fold lower supply of energy and proteins, 4-fold lower supply of carbohydrates and even 24-fold less fat. Additionally, it is completely devoid of cholesterol.

As it follows from Table 2, VLED provides very little energy in comparison with traditional diets, but is richer in fiber, iron, carotene and vitamin C. The deficiency of calcium and magnesium in VLED was compensated by drinking 0.5 l of still mineral water 'Muszyna' (Poland) characterized by very high mineral content.

Statistical analysis of results was carried out using the STATISTICA 5.1, edition '97 software package (StatSoft Inc, USA). The statistical significance of differences was verified by Student-t or nonparametric tests appropriate for dependent samples. The study had been approved of by the Review Board of Medical University of Gdańsk.

RESULTS

The results, presented as mean values of the investigated parameters before the diet and after 2-week VLED, are listed in Table 3.

Almost all the parameters assessed before VLED exceeded the normal range. After two weeks of the diet a statistically significant reduction of body weight (BMI) was obtained, as well as reduced AST activity, serum iron and ferritin levels, and excretion of coproporphyrins with urine. ALT activity and urine levels of uroporphyrins were also considerably reduced, although the changes did not reach statistical significance, probably due to a small number of the studied. On the other hand, such parameters as total iron binding capacity (TIBC) or transferrin saturation, which had been within normal limits or slightly elevated prior to the diet, were not significantly changed after treatment. At the same time, we observed a clinical improvement manifested as rapid healing of cutaneous lesions.

DISCUSSION

Low energy supply in the form of vegetable-fruit diet proved to be a favorable factor in PCT patients, in whom, besides loss of weight, improvement of a number of metabolic disorders was obtained. The results suggest that in PCT there is a correlation between the diet and liver damage activity and iron turnover. Lützner [20] also observed that a restrictive diet of several weeks' duration resulted in reduced transaminase activity as well as urine uro- and coproporphyrin levels in a PCT patient.

Elevated aminotransferase activity can indicate the damage of hepatocytes, affecting both their cell membranes and subcellular elements such as mitochondria [21]. Although the mechanism of liver damage in PCT is unknown, it can be supposed that free radical reactions catalyzed by iron are one of the causes. [22]. Destructive effect of iron on the liver in PCT patients is particularly evident in case of insufficient antioxidative protection [23–24].

Very-low-energy fruit-vegetable diet combines multidirectional effects which may protect the liver from free radical reactions and thus prevent the increase of transaminase activity, because:

Table 3. Mean values of assessed parameters (± SD) before and after 2-week VLED and statistical significance of differences before and after the diet in PCT patient

Investigated parameter	Before diet	After 2-week diet	Statistical significance of differences before and after diet	Normal range
BMI (kg/m^2)	26.8±4.7	25.8±4.3	p=0.001	20.0–24.9
ALT activity (U/l)	122.0±60.7	75.6±31.8	n.s.	0–37
AST activity (U/l)	91.8±56.0	55.2±14.2	p=0.001	0–40
Serum iron level (μg/dl)	188.6±75.7	140.2±56.4	p=0.03	50–160
TIBC (μg/dl)	388.0±105.0	335.7±44.0	n.s.	250–410
Transferrin saturation (%)	49.2±19.0	41.4±18.0	n.s.	20–45
Serum ferritin level (ng/ml)	574.4±351.0	498.9±340.0	p=0.04	29–371
Excretion of uroporphyrins with urine (μg/l)	397.5±451.0	76.3±95.0	n.s.	0–9
Excretion of coproporphyrins with urine (μg/l)	219.9±309.0	71.7±68.0	p=0.001	0–37

n.s. - the difference statistically non-significant

- VLED reduces the amount of iron (which is an oxidant) in patients with PCT, as it follows also from our studies
- VLED is a rich source of antioxidative vitamins [25] (it provides 5.7-fold more vitamin C and 3. 6-fold more carotene than recommended by dietary standards) and flavonoids which are capable of neutralizing free hydroxide and superoxide radicals directly [26], or indirectly by chelation of iron and copper ions [27]
- the diet is associated with restricted calorific intake. Thus, it may inhibit the generation of endogenous free oxygen species [28] and induce the enzymes detoxicating free radicals [29] and repairing DNA [30–31].

The observation concerning reduction of iron levels and those of ferritin (regarded as a marker of tissue iron pools) resulting even from short-term treatment with VLED, seems most striking to us considering that the iron supply provided with this diet is almost two-fold higher than in the traditional one. One of the reasons for reduced iron levels may be more difficult absorption of iron of plant origin due to phytinates, as compared with heme iron of animal origin [32]. However, it should be emphasized that the diet did not result in the decrease of iron concentration below normal levels, but only in normalization of previously elevated concentrations. Thus, the improvement of self-regulatory mechanisms controlling the homeostasis of iron turnover at the cellular level seems to be more probable. Iron metabolism at the cellular level depends on appropriate co-ordination of iron supply, its storage and use, obtained by means of a hereditary regulation system. [33]. In order to obtain PCT remission, ca. 3.5 g iron should be eliminated from the patient's blood [34]. Under physiological conditions, iron can be excreted from the organism only in small daily amounts of ca. 0.24–0.6 mg [35], with desquamated epithelium or sweat. VLED may result in increased iron excretion with bile, but no evidence for that has been obtained so far.

High iron concentrations in PCT are associated with excessive production of uro- and coproporphyrins, due to the inhibition of UROD activity by iron. Therefore, reduction of iron concentration leads to improvement of porphyrin metabolism resulting from UROD activation [36]. Restricted calorific intake also affects the metabolism of porphyrin, because, as it is known, fasting may cause an attack of acute intermittent porphyria. Welland [37] observed that reduction of calorific supply by 60–80% leads to an increase of porphobilinogen and delta-aminolevulinic acid (ALA) excretion, whereas the administration of glucose inhibits their excretion [38]. Smith and El-Far [39] demonstrated on animal models than fasting inhibits the activity of coproporphyrinogen oxidase, thus reducing the conversion of coproporphyrinogen to protoporphyrinogen. The deficiency of protoporphyrinogen may reduce heme production and lead to the loss of feedback inhibition of ALA synthetase, which may cause an attack of acute porphyria. However, acute porphyria attacks due to restrictions of calorific intake may occur in genetically predisposed subjects only. In the animal model, fasting increased excretion of uro- and coproporphyrins with urine [40], whereas in PCT patients on very-low-energy diet the reduction of porphyrin excretion and clinical improvement manifested as rapid healing of cutaneous lesions was observed as early as after 2 weeks of dieting. On the basis of our experience it can be stated that repeated periods of VLED followed by normal, well-balanced diet helps to maintain the obtained results.

CONCLUSIONS

In the group of PCT patients we observed very favorable effects of very-low-energy fruit-vegetable diet on body weight and selected biochemical parameters, as well as clinical symptoms. In view of numerous clinical benefits obtained in the course of VLED, its use in the treatment of PCT should be considered.

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