HEALTH RISKS OF COMBINING WEIGHT LOSS DIETARY SUPPLEMENTS WITH A KETOGENIC DIET IN CASE OF INTENSE PHYSICAL EFFORT

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Abstract: *Nowadays, the "pro-thin" female beauty model became highly appreciated, especially among adolescents. In this regard, the modern society tends to achieve weight loss using diets characterized by reducing the carbohydrate intake combined with physical effort. Moreover, in the desire of a quick result, individuals combine muscle effort and restrictive diets with the consumption of supplements containing different active substances which sustain the weight loss. Among the widely used dietary supplements, the most of them contain as active substances caffeine, hydroxycitric acid, L-carnitine and synephrine. Starting from these premises, the aim of this study is to highlight the most important diet-weight loss dietary supplements interactions. Regarding the low carbohydrate intake, the risk of producing ketosis is also taken into consideration.*

Modern society imposes physical beauty models that are hard to reach without physical effort and/or a strict diet.(1) The "pro-thin" female beauty model highly appreciated especially among adolescents predisposes them to diseases associated with malnutrition and nutritional deficiencies during the growth period, but also to psychic disorders such as anorexia nervosa, whereas "ultra-masculine" models of beauty in man requires an increased muscle mass and less than 4% subcutaneous fat.(1) Dietary supplements are defined as concentrated foods that are designed to supplement a normal diet (supplements containing vitamins and minerals) or with nutritional or physiological effects, here there are included the weight loss dietary supplements (WLDS).(2) WLDS are aimed at reducing appetite, decreasing the absorption of trophins (fats, carbohydrates) and activating lipolysis. Studies show that the most popular vegetal compounds in WLDS are caffeine (CF), hydroxycitric acid (HCA), glucomannan, raspberry ketones, conjugated linoleic acid etc., which induce lipolysis by various mechanisms. Weight-loss diets aim at reducing carbohydrate intake and by altering the insulin/glucagon ratio in favour of the latter, to induce lipolysis and ultimately ketosis through low carbohydrate consumption.(3) During muscle effort, glucose and glycogen muscle reserves are the main source of energy for the body, and fatty acids can also be used by the β-oxidation.(4) The aerobic cell effort involves the use of glucose and then fatty acids as an energy substrate, the excess of acetyl-CoA exceeds the Krebs cycle's ability to use it and is transformed into ketone bodies. Often, in the desire of a quick result, individuals combine muscle effort with restrictive diets and consumption of WLDS, so the purpose of this study is to highlight the most important diet-WLDS interactions in case of caused by intense physical effort.

Biochemical bases of weight loss diets

Weight loss can be performed in several ways:

- by controlling appetite and feeling of satiety (mechanisms involving a mixture of active tissue compounds including serotonin and dopamine);
- muscle effort involving the use of energy reserves of carbohydrates (muscle glycogen) and lipids (triglyceride fatty acids) for energy production and thermogenesis, a hormone regulated process mainly by catecholamines, thyroid hormones and leptin;
- control of *de novo* synthesis of lipids or alteration of adipocyte differentiation and maturation;
- modifying the activity of adenosine monophosphate kinase (*AMP kinase)*, activating it determines lipolysis (by activating *tissue lipase*, favouring β -oxidation of fatty acids and inhibiting *de novo* fatty acid biosynthesis), glycogenogenesis (by activating *glycogen synthase* and inhibiting *glycogen phosphorylase*)
- altering the absorption of certain compounds by inhibiting digestive enzymes, especially *pancreatic lipase* and thus favouring the elimination of undigested compounds by feces.

Most weight loss diets aim to induce ketosis through low carbohydrate intake. If for the healthy adult recommended carbohydrate intake through diet is 200-350 g/day depending on physical activity level, in weight loss diet carbohydrate intake should be reduced to 20-50 g/day. The quality of the carbohydrates consumed is also extremely important, they should have low glycemic index, increased digestion time and high insoluble fiber content.(5) In the case of low carbohydrate intake, the insulin/glucagon ratio will be altered in favour of glucagon, leading to the use fatty acids as the body's energy source while glycaemia will be maintained within normal limits by gluconeogenesis. Acetyl-CoA resulted from β-oxidation of fatty acids enters mitochondria in the Krebs cycle, and the reduced coenzymes formed in the Krebs cycle are oxidized into the respiratory chain which, by coupling with oxidative phosphorylation, leads to ATP synthesis. In case of an imbalanced ratio between Acetyl-CoA and oxaloacetate obtained from glucose via *pyruvate carboxylase*, the rate of Krebs cycle is slowed down and excess Acetyl-CoA is used in the synthesis of ketone bodies.(6) The drastic low carbohydrate

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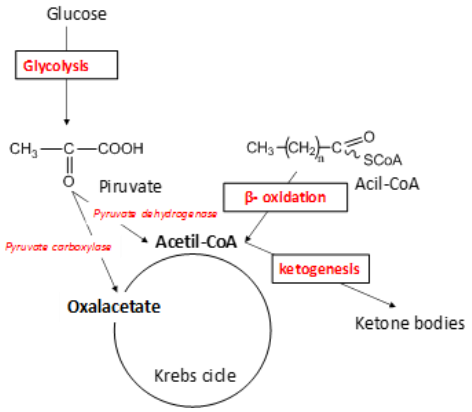
diets have a reduced long-term adherence, so recent studies show that an intake of 100-150 g carbohydrates/day would be more recommended.(7)

Figure no. 1. Ketogenic diet (schematic representation)



Studies on the long-term negative effects of ketogenic diets are scarce; the literature since the design of the study would require a long-term study (at least 2 years) in which intake of carbohydrates, fats and other energy substrates would be carefully controlled and the cost of such a study would be very high.(8) By analogy with diabetes mellitus, ketoacidosis is a medical emergency and new guidelines recommendation changed from glycaemia monitoring to careful monitoring of ketone bodies. Urinary elimination of ketone bodies in the form of salts depletes the alkaline reserve of the body leading to metabolic ketoacidosis.(9)

The most commonly used active substances in weight loss supplements

1. Caffeine. CF is a natural compound, purine alkaloid with a highly appreciated ergogenic effect in sports due to its central nervous system (CNS) stimulating mechanism, effective in sports requiring concentration and precision (10) (by blocking CNS purine receptors), by reducing CNS fatigue perception and thus increases the exercise capacity (11), by favouring skeletal muscle contraction (through releasing calcium from the endoplasmic reticulum). In WLDS, CF produces lipolysis by activating *sensitive hormone tissue lipase*, leading to the release of fatty acids from triglyceride deposits in adipose tissue and favoring aerobic metabolism by β-oxidation in mitochondria.(12) Often WLDS contain CF as pure substance and other sources of CF: Coffea Arabica, Guarana (Paullinia cupana), Green tea (Camilla Sinensis), Mate (Yerba mate). These DS contain a combination of CF with chlorogenic acid and catechin polyphenols (13), studies show that in these combinations, in addition to activating *tissue lipase*, CF also activates *carnitine acyl transferase* and *acyl-CoA dehydrogenase*, favouring the activated fatty acids entering the mitochondria by binding to the carnitine and activates the enzyme of the first step of β-oxidation.(14) Nowadays, besides lipolytic effect, studies show that CF reduces leptin resistance. Leptin secreted by adipocytes activates hypothalamus satiety centers to prevent over-feeding, but obese people develop hyperleptinemia and leptin resistance.(15) An animal study shows that CF also prevents glucose uptake in cells, thereby favouring the obtaining of energy by β-oxidation of fatty acids and ketogenesis by cell G-6-P deficiency.(16) The proven anti-obesity effects of CF have led to the development of medical devices with controlled release of CF, using hyaluronic acid to ensure penetration of skin layers.(17)

2. *Hydroxycitric acid.* HCA is a citric acid isomer important in the body by its involvement in mitochondria, in the Krebs cycle, but also for its role in transporting acetyl-CoA from its site of formation (into the mitochondria by β-oxidation of fatty acids or from oxidative decarboxylation of pyruvate catalyzed by the multi-enzymatic complex of *pyruvate dehydrogenase;* pyruvate is obtained by aerobic glycolysis when the formation of lactate is inhibited by Pasteur effect). Plant sources of HCA are vegetal extracts of Garcinia Cambogia or Hibiscus sabdarifa.(18) HCA has inhibitory effects on lipogenesis through the competitive inhibition of *ATP citrate lyase*, the enzyme that non-hydrolytically transforms the citrate into oxaloacetate and acetyl-CoA and the latter cannot be used in *de novo* biosynthesis of fatty acids. The cholesterol-lowering effect can also be explained by this mechanism, synthesis of cholesterol in cytoplasm also uses acetyl-CoA as precursor.(19) Indirectly, HCA also influences lipolysis by inhibiting the conversion of glucose to fatty acids via malonyl-CoA, the intermediate stage being citrate formation, causes the use of fatty acids as an energy substrate by the β-oxidation process and the excess of acetyl-CoA in mitochondria is converted into ketone bodies, the energy yield being much lower than in the Krebs cycle, followed by biological oxidation and oxidative phosphorylation and basically leads to the consumption of additional amounts of fatty acids in order to maintain energy cell homeostasis.(20) A review published by *Preuss H et al* indicates that HCA suppresses appetite by serotonin release in the cerebral cortex (21) and by its antioxidant effect prevents leptin resistance and inflammatory status characteristic for obesity. Free radicals are incriminated in the alteration of the oxidative use of energy substrates and the modification of food behaviour, while antioxidants reduce the release of leptin from adipocyte cell cultures following induction of inflammation with lipopolysaccharide.(22)

3. L-Carnitine. L-carnitine is structurally a non-proteinogenic amino acid extremely important in the transport of activated fatty acids in cellular mitochondria. The compound has both an ergogenic role in favoring “acute” physical effort, but also in post-exercise physical recovery by reducing the values of inflammatory biomarkers raised after intense exercise, improving endothelial function and oxygenation of myocytes after exercise, and reducing free radicals.(23) Regulation of the fatty acids metabolism by β-oxidation/*de novo* biosynthesis is accomplished by the *carnitine palmitoyl transferase I*/malonyl-CoA system. Post muscle effort malonyl-CoA deficiency, a key compound in *de novo* biosynthesis of fatty acids, activates *carnitine palmitoyl transferase* and therefore favours the entry of carnitine-bound fatty acids into mitochondria, which would explain the restoration of energy homeostasis after effort by intake of carnitine.(24) In case of WLDS with canitine, special attention should be given to the compound optical purity, the synthetic compound being a racemic mixture of D and L carnitine, but only the L isomer is biologically active while the D isomer is inactive and even potentially harmful. In addition, there is a competition between the enantiomers in the intestinal absorption phase, but also for the fixation in the mitochondrial membrane, the D isomer being able to produce L-carnitine depletion in the muscle and the heart and to produce myasthenia-like symptoms and cardiac arrhythmias.(25)

4. Synephrine. Synephrine is a derivative of ephedrine, para- hydroxyphenylethylamine extracted from bitter orange (Citrus aurantium). Ephedrine is a sympathomimetic included on the World Anti-Doping Agency’s forbidden list in sport, while the legal status of ephedrine derivative is different. There are numerous studies in the literature on the safety of synephrine use during muscular effort given the structural similarity to ephedrine, but the inconclusive and contradictory results, especially for cardiac stimulation, are attributed to the hydroxyl

group at the para-position of synephrine that modulates receptor affinity.(26) Unlike ephedrine which is a α, β-stimulator, synephrine preferentially stimulates β-3 adrenergic receptors and thus regulates lipid and carbohydrate metabolism and only a small part of α-1, β-1 and β-2 receptors. Activation of β-3 adrenergic receptors promotes lipolysis in white adipose tissue with free circulation of free fatty acids and brown adipose tissue thermogenesis.(27)

Possible interactions between diet and WLDS in case physical exercise

During exercise, carbohydrates are the main source of energy for the body. If the effort is longer, fatty acids will be used by β-oxidation as an energy substrate, with higher energy efficiency. If effort is performed during a ketogenic low-carb diet, glucose deficiency determines the orientation of mitochondrial excess of acetyl-CoA to the formation of ketone bodies.(28) DS that favour lipolysis (caffeine or syephrine), those that favour the entry of fatty acids into mitochondria (carnitine) or inhibit the use of acetyl-CoA in fatty acid or cholesterol biosynthesis (HCA) may exacerbate lipolysis and ketogenesis in low carbohydrate diets (less than 50 g carbohydrate/day).(29) Activation of the carbohydrates "saving" pathway by adrenaline released in physical effort conditions or the glucagon released in response to hypoglycemia will increase the lipolysis and at the same time worsen the ketosis.

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