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## A review of low carbohydrate diet and its metabolic consequences

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**Abstract**

Diets low in carbohydrate (low-CHO diets) has become the focus of international attention because of the recent WHO recommendations to reduce the overall consumption of sugars and rapidly digestible starches that lead to high glycaemic responses. Low-CHO diets contain less than 100 g CHO/day with a nutrient distribution being 50–60% from fat, less than 30% from CHO, and 20–30% from protein. Following a low carbohydrate diet, there is a shift towards more fat and less carbohydrate oxidation to provide energy to skeletal muscle. This review summarizes recent work on low carbohydrate diet and fat metabolic adaptations to a low carbohydrate diet along with metabolic changes.

**Keywords:** low carbohydrate diets, metabolic changes, fat oxidation, glycaemic response

**Introduction**

Diets low in carbohydrate (low-CHO diets) has become the focus of international attention because of the recent WHO recommendations to reduce the overall consumption of sugars and rapidly digestible starches that lead to high glycaemic responses. Low-CHO diets contain less than 100 g CHO/day with a nutrient distribution being 50–60% from fat, less than 30% from CHO, and 20–30% from protein (Crowe *et al.*, 2003) [1]. Low-CHO diet' based on a consumption of  $\leq 50$  g CHO/day and involves several steps, starting with a 2-week 'ketogenic induction' period, during which the goal is to reduce CHO intake to  $<20$  g/day. Common metabolic changes take place when a person follows a low-CHO diet is ketosis (formation of ketone bodies). Ketone bodies (acetone, acetoacetate, and  $\beta$ -hydroxybutyric acid) are by-products resulting from a partial oxidation of fatty acids in the liver (Crowe *et al.*, 2003) [1]. When CHO availability (liver glycogen and exogenous CHO supply) is reduced in the short term to a significant degree, the body will be stimulated to maximize fat oxidation. In that condition, ketone bodies become an important respiratory fuel for the body. Several studies reported high drop-out rates and adverse effects in individuals that follow strict low-CHO diets such as dehydration, headache, constipation, hypoglycaemia, elevation of blood uric acid levels, vitamin deficiencies (Westman *et al.*, 2002, Crowe *et al.*, 2003, Samaha *et al.*, 2003 and Iqbal *et al.*, 2004) [1, 2, 3, 4].

**Hormonal changes**

The hormonal changes associated with a low carbohydrate diet include: a reduction in the circulating levels of insulin along with increased levels of glucagon. This activates - phosphoenolpyruvate carboxykinase, fructose 1,6-biphosphatase, and glucose 6-phosphatase. Inhibits - pyruvate kinase, 6-phosphofructo-1-kinase, and glucokinase. These changes favor gluconeogenesis (production of glucose from certain amino acids and glycerol). Gluconeogenesis will be enhanced to maintain a sufficient amount of circulating glucose for the central nervous system and the red blood cells.

**The ketone bodies - an important respiratory fuel**

When dietary CHO are chronically limited, the body utilizes at least part of its reserves of glycogen in order to meet demands for blood glucose maintenance. Glycogen stores in the body are small, with approximately 70 -100 g stored in the liver and about 400 g in muscle. Most of these glycogen stores are reduced significantly within 48 h of total CHO restriction (especially in the liver), but total depletion may take a much longer time depending on the

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Daily amount of CHO consumed and on the daily energy expenditure. In the liver in the well-fed state, acetyl CoA formed during the  $\beta$ -oxidation of fatty acids is oxidized to CO<sub>2</sub> and H<sub>2</sub>O in the citric acid cycle. When the rate of mobilization of fatty acids from adipose tissue is accelerated, during very low carbohydrate intake, the liver converts acetyl CoA into ketone bodies such as Acetoacetate and 3-hydroxybutyrate. Therefore, ketone bodies flow from the liver to extra-hepatic tissues (e.g., muscle and brain) for use as a fuel; this spares glucose metabolism via a mechanism similar to the sparing of glucose by oxidation of fatty acids as an alternative fuel. There is at present no consensus for CHO cut-off limit to induce ketosis, because this may vary on individual basis. However, intakes below 50 g of CHO /day are generally reported to induce ketosis. The use of ketone bodies replaces most of the glucose required by the brain. On average, 1.6 g of amino acids is required to synthesize 1 g of glucose. Thus, to keep the brain supplied with glucose at rate of 110 to 120 g/day, the breakdown of 160 to 200 g of protein (close to 1 kg of muscle tissue) would be required. The body limits glucose utilization to reduce the need for gluconeogenesis and so spare muscle tissue. In comparison with glucose, the ketone bodies are a very good respiratory fuel. Hundred gram g of glucose yields 8.7 kg of ATP, whereas 100 g of 3-hydroxybutyrate yields 10.5 kg of ATP and 100 g of acetoacetate yields 9.4 kg of ATP (Watford *et al.*, 2000) [5].

#### Diabetic ketoacidosis vs. Dietary ketosis

Detection of the ketone bodies in the urine of diabetic patients is a danger signal that their diabetes is poorly controlled. In *severely uncontrolled diabetes*, if the ketone bodies are produced in massive *quantities*, they are associated with ketoacidosis. In this life-threatening complication of diabetes mellitus, the acids 3-hydroxybutyric acid and acetoacetic acid are produced rapidly, causing high concentrations of protons, which overwhelm the body's acid-base buffering system (pH <7.35). However, during very low carbohydrate intake, the regulated and controlled production of ketone bodies causes a harmless physiological state known as dietary ketosis. In ketosis, the blood pH remains buffered within normal limits (pH range 7.35 to 7.45). Mild ketosis may offer therapeutic potential in a variety of different common and rare disease states, such as: (i) Diseases of substrate insufficiency or insulin resistance; (ii) Diseases resulting from free radical damage; and (iii) Disease resulting from hypoxia (Veech *et al.*, 2004) [6].

#### Effects on blood glucose, insulin response and weight

Significant decreases in fasting and postprandial glucose responses have been observed after consumption of low-CHO, high-fat diets, especially in diabetic subjects. This may be due to reduction of the abnormally high hepatic glucose output observed in these subjects with poor metabolic control. During a keto-acid infusion, hepatic glucose output and glycaemia decreased in both non-diabetic individuals and in patients with NIDDM (Type 2), suggesting that ketosis may lower basal hepatic glucose output in subjects consuming a low-CHO diet (Henery *et al.*, 1990) [7]. Low-CHO diets result in a reduction of the circulating insulin level, which promotes degradation of triacylglycerol into free fatty acids and glycerol (Sharman *et al.*, 2002, 2004 and Clifton *et al.*, 2004) [8, 9, 10]. Elevated levels of circulating fatty acids will promote their utilization as a fuel by muscle, which will promote fat loss. Volek *et al.*, 2010 [11] reported that a very-low-

carbohydrate diet resulted in a significant reduction in fat mass and a concomitant *increase in lean body mass* in normal-weight men due to elevated  $\beta$ -hydroxybutyrate concentrations which played an important role in preventing catabolism of lean tissue. Individuals who are on *ad libitum* low-CHO diet experience a rapid initial weight loss. Induction of a rapid initial weight loss with low-CHO diets may be due to (i) reduction in overall caloric intake, which may be the result of a great limitation of food choices by minimizing CHO intake (Brehm *et al.*, 2003) [12], (ii) to the initial increase in circulating  $\beta$ -hydroxybutyrate, which may suppress appetite (Meckling *et al.*, 2002) [13] and (iii) to the satiating effect of low-CHO diets containing relatively high amounts of protein (Layman *et al.*, 2003 and Johnston *et al.*, 2004) [14, 15]. Initial weight loss may also be explained by a reduction of glycogen stores from liver (5% of liver weight) and muscle (1% of muscle weight). Each gram of glycogen is stored with approximately 3 g of water. Therefore a weight loss of 1-2 kg can be achieved within the first week of the diet because of substantial glycogen reductions in liver and muscle and excretion of the liberated water in urine. Depending on the rate of glycogen depletion this process may last up to 7-14 d, after which weight loss slows (Bray *et al.*, 2010) [16].

#### Effects on lipid profiles

A low insulin level activates HMG-CoA-lyase (enzyme of ketone bodies synthesis) and inhibits HMG-CoA reductase (enzyme of cholesterol synthesis in the liver), which may provoke a decrease or a stabilization of the blood cholesterol and the LDL-C. Low-CHO, high-fat diets have a significant reduction in fasting serum triacylglycerol and postprandial lipaemia.

#### Effects on insulin sensitivity and insulin resistance

Significant decreases in fasting and postprandial insulin responses after the low-CHO, high-fat diets have been observed. Under circumstances of ketosis, it was shown that the consumption of a polyunsaturated fat-rich low-CHO diet (70% fat, 15% CHO and 15% protein) for 5 days induced a greater level of ketosis and improved insulin sensitivity without negatively affecting total or LDL-C levels, compared to a traditional very low-CHO diet high in saturated fats in healthy subjects (Rutenberg *et al.*, 2004) [17]. Studies reported that altered fatty acid metabolism contributes to insulin resistance because of alterations in the partitioning of fat between the adipocyte and muscle or liver. This change leads to the intracellular accumulation of fatty acid and fatty acid metabolites in these insulin-responsive tissues, which leads to acquired insulin signalling defects and insulin resistance resulting in a reduced glucose transport (Shulman, 2000) [18]. Fatty-acid-induced alterations in upstream insulin signalling events, resulting in decreased GLUT 4 translocation to the plasma membrane.

#### Effects on cardiovascular health

Short-term studies suggest that low-CHO diets help to reduce fasting insulin and glucose levels, improve blood pressure and lipid disorders that are characteristic of atherogenic dyslipidaemia by favouring an increase of LDL size, an increase of HDL-cholesterol levels and a decrease of plasma triacylglycerol. Low-CHO diets significantly decreased several biomarkers of inflammation (hs-CRP, hs-TNF $\alpha$ , hs-IL-6, s-ICAM-1, s-P-selectin), which play a key role in all stages of the pathogenesis of atherosclerosis. Fat loss, however, achieved is the driving force underlying the

reductions in most of the inflammatory markers (Sharman *et al.*, 2004) <sup>[9]</sup>. An increased plasma homocysteine level (+6.6%) was observed in individuals that follow strictly a low-CHO diet for several months. The mechanism of the observed increase in homocysteine is unknown at present (Clifton *et al.*, 2004) <sup>[10]</sup>. The effects of homocysteine on endothelial and vascular function and blood coagulation increased CVD risk (Refsum *et al.*, 2004) <sup>[19]</sup>.

### Effects on bone health

Low-CHO diets possess negative impact on bone health because of urinary calcium loss. Low-CHO diets generate acidosis (because of the presence of ketone bodies in blood), which promotes calcium mobilization from bone to buffer blood and maintain a neutral pH, finally leading to an increase of urinary calcium. Blood acidification is known to increase glomerular filtration rate and decrease renal tubular re-absorption of calcium with a concomitant increase in activity of osteoclasts and inhibition of osteoblasts, further increasing bone resorption. Study confirmed that consumption of a low-CHO diet leads to an increase in urinary calcium loss without an increase in compensating intestinal calcium absorption and a decrease in markers for bone formation (Reddy *et al.*, 2002) <sup>[20]</sup>.

### Low CHO diet and kidney health aspects

Multiple aspects of very-low-CHO, high-fat, and high-protein diet likely contribute to a potential for kidney stone formation. Low-CHO diet enhances ketone bodies production which may remain elevated for several months (3 months or more) (Foster *et al.*, 2003) <sup>[21]</sup>. Ketone bodies-induced acidosis, results in hypocitraturia and in an increase of uric acid (Reddy *et al.*, 2002) <sup>[20]</sup>. Urinary citrate is an important inhibitor of calcium crystal formation and a low urinary level increases the risk of calcium stone formation while patients on the very-low-CHO diet have also hypercalciuria (Westman *et al.*, 2002) <sup>[2]</sup>.

### Conclusion

One of the common metabolic changes take place when a person follows a low-carbohydrate diet is ketosis. Low-carbohydrate intakes result in a reduction of the circulating insulin level, which promotes high level of circulating fatty acids, used for oxidation and production of ketone bodies. When carbohydrate availability is reduced in short term to a significant amount, the body will be stimulated to maximize fat oxidation for energy needs. Literature shows that low-carbohydrate diets acutely induce a number of favourable effects: a rapid weight loss, decrease of fasting glucose and insulin levels, reduction of circulating triglyceride levels and improvement of blood pressure. Some less desirable immediate effects: increased urinary calcium loss, increased plasma homocysteine levels, increased LDL-cholesterol have been reported. The long term effect of the combination of these changes is at present not known. However, these undesirable effects may be associated with consumption of a low-carbohydrate, high-protein, low-fat diet, because this type of diet induce favourable effects on feelings of satiety and hunger, help preserve lean body mass, effectively reduce fat mass and beneficially impact on insulin sensitivity and on blood lipid status while supplying sufficient calcium for bone mass maintenance.

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