Review Article

# Prevention of Obesity Using Low Carbohydrate Ketogenic Diet

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**ABSTRACT**

This review focuses on the effect of low carbohydrate ketogenic diet on obese subjects presenting with various metabolic syndromes. Here, we provide data from our laboratory and from various other investigators on the therapeutic effectiveness of ketogenic diet on obese subjects. In this review we provide the rationale behind using ketogenic diet as a treatment of obesity and its beneficial role in neurodegenerative / neurological disorders, diabetes, hyperlipidemia, coronary diseases, cancer *etc.* Administering ketogenic diet for a relatively longer period did not produce any significant side effect. Therefore, based on the data presented in this review, it is recommended that it is safe to use ketogenic diet for a longer period of time for obesity and associated disorders.

KEY WORDS: coronary diseases, diabetes, hyperlipidemia, ketogenic diet, obesity

## INTRODUCTION

Although, historically obesity has been considered as a sign of a prosperous and wealthy society, today obesity has become a major health problem in both developed and developing countries. Obesity has been described as a disease entity since 1700s. Currently obesity levels are increasing at a remarkable level all over the world. Data from a recent survey by the US Center for Disease Control indicates that 66% of the US population are overweight, with 32.3% having a body mass index (BMI) of more than 30 kg/m$^2$[1]. It is estimated that about 300,000 people die each year from obesity related diseases[1]. A similar trend is observed in Kuwait and other Middle East countries[2].

## CLASSIFICATION OF OBESITY

Obesity has been defined by body mass index (kg/m$^2$) and waist circumference. According to the current classification of the World Health Organization (WHO), body mass index (BMI) greater than 25 is considered overweight[3]. An adult who has a BMI of 30 or higher is considered obese. Obesity is further classified into Class I (BMI > 30), Class II (BMI > 35) and Class III (BMI > 40) obesity. In addition to BMI, increased risk of obesity associated metabolic disorders is found in men with waist circumferences greater than or equal to 102 cm and in women with 88 cm[1]. This classification of obesity is primarily based on a Western population perspective[4]. Therefore, it is necessary to redefine obesity from an Asian or Middle Eastern viewpoint. In Asians, overweight has been suggested to start at BMI 23 and also lower waist circumference cut-offs for men and women have been recommended[4].

## HEALTH CONSEQUENCES OF OBESITY

Problems related to obesity affects almost every aspect of life[5-6]. The rise in obesity and its complications is a threat to global healthcare system. The obesity epidemic of the world is out of control and none of the current measures show any improvement in reversing this global crisis. Early measures to curb obesity and public awareness on

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**Table 1:** Obesity associated risks

| Mild risk | Moderate risk | Severe risk |
|---|---|---|
| • Low back pain<br>• Impaired fertility<br>• Increased risk during anesthesia<br>• fetal defects due to maternal obesity<br>• Cancer | • Coronary heart disease<br>• Hyperuricaemia<br>• Gout<br>• Osteoarthritis<br>• Complications of pregnancy | • Diabetes<br>• Dyslipidaemia<br>• Hypertension<br>• Gall bladder disease<br>• Sleep apnoea<br>• Breathlessness |

obesity associated diseases are the only way towards achieving a sustainable health service. Along with the appropriate measures taken to prevent obesity, priority should be given to the treatment of obesity related diseases. The health consequences of obesity can be categorized into mild, moderate and severe types depending on the risk involved (Table 1).

## CONTRIBUTING FACTORS TOWARDS OVERWEIGHT AND OBESITY

Obesity results from the interplay between genes and environment. Both genes and behavior may be needed for a person to become overweight. Other factors that regulate body weight are the diet preferences and the number of calories consumed. One of the genetic components of obesity is insulin resistance which is the probable common pathway for metabolic syndrome. It has been shown that diet choices and physical activity are the major contributing factors towards overweight and obesity. Caloric intake must be equal to the caloric expenditure to maintain a healthy body weight. Calorie, the unit of energy is defined as the amount of heat needed to raise the temperature of one gram of water by one degree Celsius at sea level. By eating roughly the same number of calories that the body requires, the body weight can be maintained in a stable condition. Obviously, weight gain occurs when more calories are taken than the body requires. The extra calories taken in are stored as fat within the body. However, this fact is true only when eating a lot of carbohydrate along with fat. On a diet with controlled amounts of carbohydrate, the body will switch from using glucose to fat for producing energy. This means that a person on low carbohydrate ketogenic diet (LCKD) can take in as much calories and still loose weight. In other words, a person while consuming 3,000 calories on LCKD will loose weight whereas taking in the same calories on a low-fat high carbohydrate diet will gain weight. So the assumption that the only way to lose weight is to strictly control the intake of calories needs to rewritten based on the type of diet. Furthermore, while on LCKD diet the appetite is usually diminished and a person will eat only fewer calories. Hence persons on LCKD will have to burn more fat for producing energy, which will lead to more weight loss.

Another factor that needs to be mentioned is the outcome of certain diet programs that restrict calorie intake. In such circumstances where diets with restricted calories are taken, so as to conserve energy, the overall metabolism in the body shifts into a slow survival mode. But after certain period, when it becomes inevitable for the person on the low calorie diet to go back to a higher-calorie diet, the body metabolism will still remain in its slow survival mode of burning calories slowly. Hence it becomes quite difficult to continue or maintain weight loss in such situations.

## OBESITY IN RELATION TO DIET PREFERENCES

Since obesity is the accumulation of excess of body fat, excessive fat intake has been discouraged. Less fat and exercise had become the slogan against obesity to be fit physically and maintain a healthy body. Well, for generations people have tried this recipe of low fat diet, yet they still get obese. Therefore, what we blindly believe about high carbohydrate diet could be completely baseless.

Various researchers have pointed out the bad effects of a high carbohydrate diet. It is the root cause of various chronic diseases. Several studies[7-18] have shown that a diet with a high glycemic load is independently associated with accelerated aging, development of cardiovascular diseases, type II diabetes and certain forms of cancer[7-9].

The glycemic index is a rating system for foods based on their ability to raise the level of blood glucose within two hours of their consumption[19]. When foods of higher glycemic index are eaten there is a rapid release of glucose into the bloodstream. The glycemic index of pure glucose or white bread is arbitrarily scored as 100[20]. Foods with high glycemic index induce a rapid release of insulin[19]. Thus eating foods with a high glycemic index lead to higher levels of circulating insulin. This rapid surge in insulin release can cause a relative hypoglycemic period within the postprandial period. The reactive hypoglycemia thus developed with foods of lower fat and higher carbohydrate content stimulates the appetite and thus leads to obesity[21]. The hyperinsulinemia developed following the consumption of foods with high glycemic index has been implicated in creating atherosclerotic plaques, that can lead to heart disease[22]. Insulin increases salt and water retention, a mediator of high blood pressure and correlates with high levels of triglycerol and low levels of high density lipoprotein (HDL) cholesterol. Now it is evident that high carbohydrate diets increase fasting

**Table 2:** Recommended and restricted food in ketogenic diet[66]

| Recommended Food | | | Fully Restricted Food | |
|---|---|---|---|---|
| **Proteins** | **Vegetables/fruits** | **Oil** | **Carbohydrates** | **Fruits/drinks** |
| **Fish:**Tuna,Sardine Prawns, Shrimps. Lobster **Meat:** Kababs, Sausages, Minced **Poultry:** Chicken, Eggs **Cheese:** Full fat cheese | Spinach, Watercress, Eggplant, Parsley, Mulberry, Coriander, Mint, Artichoke, Okra, Cabbage, Mushroom, Avocado, Leek, Carrot, Radish, Celery, Cauliflower, Green pepper, Lettuce, Cucumber, Tomato, 10-15 olives/day, Lemon, Strawberry -6/day, Avocado, Berries-10/day | Olive oil (5 tablespoon, added to the salad), Flax seed oil | Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes | All fruit juices All soft drinks |

plasma triglycerol concentrations[23-27] and decrease HDL cholesterol concentrations[28-30]. These changes are associated with enhanced atherogenesis[31]. However, it is found that short-term ketogenic diets improve the lipid disorders that are characteristic of atherogenic dyslipidemia[32]. Furthermore, high insulin levels lead to increased risk of breast cancer and polycystic ovarian syndrome[6,19,33]. In addition, other evidence indicates that consumption of a high–glycemic-index diet is associated with a higher risk of diabetes.

Excess sugar in the bloodstream also leads to the production of free radicals. Free radicals increase significantly one hour after sugar consumption and more than double after two hours. It has been proven that disrupting the oxidant-antioxidant status of the cell will lead to various diseases of the body[33]. Furthermore, increased sugar decreases the blood levels of vitamin E, which leads to a decrease in the natural ability of the body to fight against free radical damage.

Carbohydrates increase levels of triglycerol, total cholesterol, and low density lipoprotein (LDL) and decreases HDL cholesterol. High ratio of triglycerol to HDL has a 16-fold greater incidence of coronary events than those with the low ratio[10.19,22,32]. In several studies, insulin, insulin-like growth factors and carbohydrates were identified as risk factors for cancer. It is quite reasonable to believe that sugar contributes to the growth and metastasis of cancer since cancer cells utilize sugar as their energy source. In other studies it was found that sugar is a causative factor in kidney disease, liver disease and shortened life span. Although there is cumulative scientific evidence to show that high carbohydrate diets can cause more harm than previously thought, we are still unwilling to accept this fact.

Since the 1980's calories from fat intake dropped from 34 to 8%. However, no change in the trend of obesity has been noticed. Interestingly, even after all this; the negative image of fat is still in our mind. In fact, contrary to the common belief, high fat diet has certain therapeutic values. Since 1921, high fat diet was used as an effective alternative therapy to control intractable seizures[34]. In some cases, high fat diet was found to be far better than modern anticonvulsants. The common argument against the consumption of high-fat diet is that it causes obesity. However, recent studies show that the high fat diet can cure obesity. Since obesity results from genetic and environmental influences, an individualized approach probably is the best solution for tackling the obesity problems. Therefore, a low-carbohydrate diet combined with an exercise program, in our experience, can help selected patients to safely achieve weight loss and overcome several obesity associated diseases. As mentioned earlier, since lower insulin levels and less hunger are the physiologic effects of consuming foods with low–glycemic-index, persons who take in low-carbohydrate diets could successfully lose their weight. Furthermore, there is an increased calorie use *via* ketogenesis. Therefore, LCKD is a reasonable alternative for body weight loss for persons who are willing to adhere to this diet. Table 2 gives a brief list of recommended and restricted food in ketogenic diet.

**Low carbohydrate ketogenic diets**

LCKD is not new to our society. Even early man's prehistoric diets may have been low carbohydrate ketogenic diets[35]. Prior to its use as a diet for obesity, LCKD have been used in the treatment of diabetes[36] and pediatric epilepsy[34]. Also, studies on the therapeutic role of LCKD in obesity are not new at all. Since 1955, scientists were experimenting on the concept that fat can be eaten *ad libitum* and still induce weight loss in obese subjects. A high-fat diet changes the body's metabolism to a new direction. Incomplete oxidation of fatty acids by the liver, results in the accumulation of ketone bodies in the body. The condition in which ketone bodies are formed in excess of the body's ability to metabolize them is called ketosis. Since high-fat diet causes ketosis, they are generally called as ketogenic diets. Ketosis has a significant influence on suppressing hunger. Thus, a ketogenic diet is a good regulator of the body's calorie intake and it is the body's natural adaptation to starvation. However, this mild ketosis has been always confused by the

general public with the dangerous ketoacidosis which is associated with untreated type 1 diabetes. But these two conditions are quite different and virtually opposite. Diabetic ketoacidosis has high blood sugar while ketosis has a high blood level of ketone bodies. Is ketosis safe? If ketosis was bad for health, why does nature switch on to a situation similar to that of administering a ketogenic diet? Well, everyone approaches ketogenesis during the sleep portion of the diurnal cycle. Above all, who can ignore the fact that mother's milk, which has a high fat content, is the best natural food formula taken in during human development? It is also interesting to note that no species could have survived millions of years, if its members could not tolerate occasional brief periods of natural starvation, which results in ketosis.

**WHAT ARE KETONE BODIES?**

Ketone bodies result from the partial oxidation of free fatty acids and are synthesized only in the mitochondria of liver cells. There are three types of ketone bodies. They are: acetoacetate (AcAc), ß-hydroxybutyrate (BHB), and acetone. Ketone bodies are always being produced under normal dietary conditions but in amounts that are too small to cause any metabolic effects[37]. Triacylglycerol (TAG) stored in fat tissue breaks down into glycerol and three fatty acid molecules. This process is lipolysis and is regulated by hormones like glucagon, epinephrine *etc*. These hormones activate the hormone-sensitive lipase (HSL) that hydrolyzes fatty acid from carbon atom 1 and / or 3 of TAG. The remaining fatty acids are removed by other lipases that are specific for diacylglycerol or monoacylglycerol[38].

Fatty acids are classified into short-medium chain fatty acids consisting of 12 carbons or less and long chain fatty acids. Medium chain fatty acids are found in the maternal milk and in medium chain fatty acid oils. The free fatty acids that diffuse from adipose cells either bind with albumin in the blood or remain as free fatty acids. The albumin bound fatty acids are transported to other tissue to be oxidized and the unbound free fatty acids present in the blood reach the liver[38, 39]. The medium chain fatty acids enter the liver without any transporter whereas the long chain fatty acids, the major precursor for ketone bodies, need a special transporter called carinitine to enter the mitochondrial matrix and become oxidized[40].

The medium chain fatty acids become activated to fatty acyl CoA and undergo ß-oxidation to form fatty acetyl CoA whereas the long chain fatty acids become activated into fatty acyl CoA in the liver cytosol. The carinitine acyltransferase system moves the acyl CoA to the mitochondrial matrix where they undergo ß-oxidation to form acetyl CoA[40]. When there is an excess of acetyl CoA, more than that is required for providing energy through Kerb's cycle, the liver converts the extra acetyl CoA into ketone bodies[41,42].

The formation of ketone bodies occurs as follows. Two molecules of acetyl CoA are condensed to form a molecule of acetoacetyl CoA. Then a third molecule of acetyl CoA is added to acetoacetyl CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG CoA). Formation of HMG CoA is catalyzed by the hepatic enzyme, HMG CoA synthase. HMG CoA is then cleaved into acetyl CoA and acetoacetate by the action of another enzyme, HMG CoA lyase. Acetoacetate is either reduced to ß-hydroxybutyrate (BHB) through the action of BHB dehydrogenase or undergoes spontaneous decarboxylation to acetone which is excreted in the breath and urine[41,42].

Ketone bodies are used as an energy source in the body including the brain. BHB is converted to acetoacetate by the reversal reaction of BHB dehydrogenase, producing nicotinamide adenine dinucleotide phosphate (NADH). The acetoacetate, in turn, will bind to coenzyme A (CoA) provided from succinyl CoA molecules through thiophorase reaction producing acetoacetyl CoA. The acetyl CoA is further converted into two molecules of acetyl CoA, which will enter the Kreb cycle for production of energy[42].

**EFFECT OF KETOGENIC DIET IN PREVENTING OBESITY**

Recent studies from our laboratory have shown that the ketogenic diet is a natural therapy for obesity even in diabetic subjects. The weight and body mass index of the patients decreased significantly ($p < 0.0001$) from week 1 to 56 (Table 3). A similar significant ($p < 0.0001$) weight loss was observed in diabetic subjects who were on a LCKD diet (Table 4).

Several possible mechanisms on the role of very-low carbohydrate diet in reducing body weight have been suggested[43]. It is thought that major part of the weight loss following the administration of ketogenic diet can be attributed to the loss of water. Each 1 g of glycogen is stored in 3 gms of water. This means that the initial weight loss could be due to glycogen depletion and water excretion in urine. The weight lost in this manner will be gained immediately after stopping the ketogenic diet. Glycogen stores replenishes again with retention of a large amount of water as mentioned above[44,45]. Ketones have a diuretic effect and hence lead to an even greater water loss[44]. Furthermore, there is a

decrease in metabolic efficiency resulting in greater loss of energy in the form of heat[46] and in the form of ketones in urine, sweat, and feces.

In addition to the weight loss observed, very-low-carbohydrate ketogenic diets alter the metabolic rate by preserving more lean body mass[47]. Following the administration of ketogenic diet there is a preferential loss of fat mass and preservation of more lean body mass[47-49]. As mentioned earlier, ketone bodies especially BHB, has an effect on appetite suppression[50]. In addition, the high fat content in LCKD delays the digestion providing a sense of fullness[51]. Above all, the utilization of fat as body fuel, promote fat loss and therefore weight loss[52]. In addition to studies from our laboratory, several other studies have shown that low carbohydrate diets compared to low fat diets have a significant long term effect on the reduction of body weight[53-55].

## OTHER BENEFICIAL EFFECTS OF KETOGENIC DIET

Although, the main focus of this review is on the beneficial effects of ketogenic diet on obesity, we know that this review will not be complete, if some of the other beneficial effects of ketogenic diets are not mentioned. Therefore, we give here below, some well known beneficial effects of ketogenic diet on neuronal and cardiac efficiency and its therapeutic role in diabetes, heart diseases, cancer *etc*.

### Brain function

In humans, ketone bodies are the only additional brain energy source after glucose[56,57]. Hepatic generation of ketone bodies during fasting is a protective mechanism that spares the destruction of muscle from glucose synthesis. Historically, it is known that ketogenic diet is quite effective in antiepileptic treatments. However, how this diet works is still unclear? Several mechanisms that contribute to the anticonvulsant role of LCKD have been suggested. It is found that ketogenic diet increases the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain, which may be involved in the suppression of the seizure activity[58]. Furthermore, LCKD increases the level of polyunsaturated fatty acids (PUFAs), which functions as modulators of neuronal membrane excitability by inhibiting the sodium and calcium ion channels[59]. It is suggested that free radicals contribute to the development and progression of epilepsy. Thus, the anticonvulsant role of ketogenic diet could also be through the antioxidant mechanisms activated by fatty acids and ketones[60]. It has also been found that a ketogenic diet affects signal transduction in neurons by inducing changes in the basal status of protein phosphorylation[61]. Furthermore, ketogenic diet has beneficial influence on the brain energy metabolism[62].This is quite significant, as cerebral hypometabolism is a characteristic feature of those who suffer from depression or mania[62]. Interestingly, it is shown that a ketogenic diet reduces amyloid ß 40 and 42 in a mouse model of Alzheimer's disease[63].

### Cardiovascular Diseases

The common notion is that a ketogenic diet will cause high cholesterol, TAG, and cardiovascular disease because of the high fat it contains. In our previous studies and recent studies using ketogenic diet it is shown that LCKD decreased the level of triglycerol and LDL cholesterol and increased the level of HDL cholesterol[53,64-67]. Furthermore, administering a ketogenic diet for a relatively longer period of time did not show any significant side effects in the patients. A similar situation was found when obese subjects with high cholesterol

**Table 3:** Statistical significance between week 1 and week 56 observation of various parameters studied in normal subjects[67].

| | Normal Subjects (n = 33) | | |
|---|---|---|---|
| | **Week 1** | **Week 56** | **p-value** |
| Weight (kg) | 105.273 + 15.377 | 74.923 + 11.384 | < 0.0001 |
| Total chol (mmol/l) | 5.479 + 1.293 | 4.650 + 0.495 | 0.0020 |
| HDL (mmol/l) | 1.237 + 0.270 | 1.621 + 0.177 | < 0.0001 |
| LDL (mmol/l) | 4.030 + 1.148 | 2.807 + 0.496 | < 0.0001 |
| TG (mmol/l) | 1.827 + 0.981 | 0.861 + 0.179 | 0.0001 |
| Glucose (mmol/l) | 5.127 + 0.440 | 4.726 + 0.529 | 0.0069 |
| Urea (μmol/l) | 5.563 + 1.299 | 4.419 + 0.743 | < 0.0001 |

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

**Table 4:** Statistical significance between week 1 and week 56 observation of various parameters studied in diabetic subjects[67].

| | Diabetic Subjects (n = 31) | | |
|---|---|---|---|
| | **Week 1** | **Week 56** | **p-value** |
| Weight (kg) | 108.081 + 21.245 | 83.536 + 18.030 | < 0.0001 |
| Total chol (mmol/l) | 6.755 + 1.086 | 4.878 + 0.533 | < 0.0001 |
| HDL (mmol/l) | 1.033 + 0.264 | 1.586 + 0.211 | < 0.0001 |
| LDL (mmol/l) | 5.160 + 0.892 | 3.379 + 0.608 | < 0.0001 |
| TG (mmol/l) | 4.681 + 2.468 | 1.006 + 0.205 | < 0.0001 |
| Glucose (mmol/l) | 10.481 + 3.026 | 4.874 + 0.556 | < 0.0001 |
| Urea (μmol/l) | 5.778 + 0.905 | 4.972 + 1.050 | < 0.0111 |

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

**Table 5:** Baseline values of different physical and biochemical parameters monitored in persons (high cholesterol / normal cholesterol) subjected to low carbohydrate diet (ketogenic diet) [66]

| | Total | Group I (n = 35) (High cholesterol) | Group II (n = 31) (Normal cholesterol) | p-value |
|---|---|---|---|---|
| Age (years) | 42.9 + 10.8 | 45.5 + 9.2 | 39.9 + 11.8 | 0.0731 |
| Weight (kg) | 106.9 + 18.3 | 112.3 + 19.3 | 100.7 + 15.3 | 0.0168 |
| BMI (kg/m$^2$) | 39.1 + 6.1 | 40.1 + 6.1 | 38.0 + 6.1 | 0.1385 |
| Total chol (mmol/l) | 6.1 + 1.4 | 7.0 + 0.9 | 5.0 + 0.8 | < 0.0001 |
| HDL (mmol/l) | 1.1 + 0.3 | 1.1 + 0.3 | 1.2 + 0.3 | 0.0076 |
| LDL (mmol/l) | 4.6 + 1.2 | 5.4 + 0.8 | 3.6 + 0.7 | < 0.0001 |
| TG (mmol/l) | 3.2 + 2.3 | 4.3 + 2.6 | 2.0 + 1.1 | < 0.0001 |
| Glucose (mmol/l) | 7.7 + 3.4 | 9.4 + 3.7 | 5.7 + 1.5 | < 0.0001 |

HDL = high density lipoprotein; LDL = low density lipoprotein; TG =Triglyceride
Data is expressed as mean + standard deviation

level and obese diabetic subjects were treated with LCKD for longer period, suggesting that it is safe to use ketogenic diet in both diabetic subjects (Table 3, 4) and in subjects with high cholesterol level (Table 5, 6). Further studies revealed that despite the increase of cholesterol intake with ketogenic diet, there is no significant increase in the total cholesterol or LDL[53,64-67]. This may be due to the low insulin level which will activate HMG CoA lyase, the enzyme responsible for ketone formation and inhibit HMG CoA reductase, the enzyme responsible for cholesterol formation[68]. In a recent study from our laboratory on experimental rats, we have convincingly shown that LCKD enhances cardiac tolerance to global ischemia as compared to rats fed on a high carbohydrate diet [69]. In addition, ultra structural studies have shown that there was a decrease in the number of mitochondria in rats fed a high carbohydrate diet and an increase in the number of mitochondria in those fed a LCKD as compared to the normal diet group, confirming the physiological observations on cardio-protective function of LCKD[69]. It should be noted that pre-historic diets were high in dietary protein and fat. However, these pre-historic societies were relatively free of several cardiovascular diseases that exist today in our society[35].

**Diabetes mellitus and insulin resistance**

In the pre-insulin era LCKD has been used for diabetes treatment instead of medications[70]. The results from our laboratory show that LCKD has significant beneficial effects in obese diabetic subjects following its long-term administration (Table 3, 4). The blood glucose level decreased significantly from the start until the 56th week. A similar situation was found when obese subjects with high cholesterol level were treated with LCKD for a longer period. As previously mentioned, these studies suggest that it is safe to use ketogenic diet in both obese diabetic subjects and subjects with high cholesterol level (Table 5, 6). Furthermore, LCKD may be effective for improving glycemia and reducing medications in patients with type 2 diabetes.

Insulin resistance is a characteristic feature of Type 2 diabetes[71]. Insulin resistance is defined as the inability of insulin to produce its usual response at concentrations that are effective in normal individuals. As mentioned earlier, the content of carbohydrate in the diet is the most important factor that influences

**Table 6:** Percentage changes in the various parameters observed at week 56 in persons (high cholesterol / normal cholesterol) subjected to ketogenic diet[66]

| | Total (n = 66) | Group I (n = 35) High cholesterol | Group II (n = 31) Normal cholesterol | p-value |
|---|---|---|---|---|
| Weight (kg) | -25.9 + 6.3 | -25.8 + 6.7 | -26.0 + 5.8 | 0.9065 |
| Total chol (mmol/l) | -19.3 + 17.0 | -29.2 + 9.4 | -6.2 + 16.2 | 0.0005 |
| HDL (mmol/l) | 52.3 + 43.8 | 63.7 + 52.7 | 37.1 + 20.6 | 0.1778 |
| LDL (mmol/l) | -28.2 + 20.1 | -33.5 + 19.5 | -21.3 + 19.1 | 0.1331 |
| TG (mmol/l) | -59.0 + 32.1 | -69.8 + 32.6 | -44.7 + 25.7 | 0.0537 |
| Glucose (mmol/l) | -31.0 + 25.0 | -44.0 + 22.6 | -12.8 + 15.1 | 0.0004 |

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation. Statistical significance between Group I and Group II are given.

**Table 7:** Statistical significance between week 1 and week 56 observation of various parameters studied in group I (high cholesterol) and group II (normal cholesterol) subjects[66].

| | Total (n = 66) | Group I (n = 35) High cholesterol | Group II (n = 31) Normal cholesterol) |
|---|---|---|---|
| Weight (kg) | < 0.0001 | < 0.0001 | < 0.0001 |
| BMI (kg/m$^2$) | < 0.0001 | < 0.0001 | < 0.0001 |
| Total chol (mmol/l) | < 0.0001 | < 0.0001 | 0.0170 |
| HDL (mmol/l) | < 0.0001 | < 0.0001 | < 0.0001 |
| LDL (mmol/l) | < 0.0001 | < 0.0001 | < 0.0001 |
| TG (mmol/l) | < 0.0001 | < 0.0001 | 0.0002 |
| Glucose (mmol/l) | < 0.0001 | < 0.0001 | 0.0034 |

BMI = Body mass index, Chol = cholesterol, HDL = high density lipoprotein; LDL = low density lipoprotein; TG =Triglyceride

the glycemic level. LCKD appear to improve glycemic control and le ssen the need for exogenous insulin and hypoglycemic medication[67,72]. Furthermore, LCKD significantly improved the insulin sensitivity by up to 75%[54,73]. In a recent study on experimental rats from our laboratory, we have demonstrated that LCKD ameliorated the diabetic state and helped to stabilize hyperglycemia. In addition to its therapeutic effect, LCKD had a significant protective role against the diabetogenic action of streptozotocin (STZ) [74]. STZ is selectively cytotoxic to the ß-cells of pancreatic islets. Therefore it is commonly used to induce diabetes in experimental animals[74].

**Osteoporosis**

A link between low fat diet and osteoporosis has been suggested. Very-low-fat diets are considered to be low in calcium content. Women on low-fat diets excrete most of the calcium they consume. Therefore, they are more prone to osteoporosis. On the other hand recent studies indicate that a high fat diet can rectify this situation[75].

**Cancer**

The relation between high fat diet and cancer is close to reality now. It has been found that altered energy metabolism and substrate requirements of tumor cells can provide a target for cancer therapy. Two major metabolic alterations found in cancer cells are the increase in glucose consumption and aerobic glycolysis, the conversion of glucose to lactic acid *via* the reduction of pyruvate even in the presence of oxygen. In addition, there are defects in ketone body metabolism[71,76]. These metabolic changes in cancer cells may provide a rationale for therapeutic strategies that inhibit tumor growth by LCKD. It has been shown that cancers, specifically brain tumors grow minimally on a LCKD[77]. These studies suggest that treatment with LCKD is a safe and effective alternative therapeutic option for malignant brain cancer. In addition, ketone bodies function as anti-inflammatory agents through the reduction of reactive oxygen species and increase of glutathione peroxidase activity[78].

## SIDE EFFECTS OF KETOGENIC DIET

It is noticed that some individuals on ketogenic diet may experience a bad breath. However, vast majority of individuals do not develop medical problems. As in the case of any form of diet with restricted caloric intake, ketogenic diet is also deficient in minerals and water-soluble vitamins [79]. In order to overcome this side effect, subjects on ketogenic diet are given multi vitamin and mineral supplements daily to avoid such deficiencies.

Another criticism of ketogenic diet is the reduction of fruits, vegetables and whole grains, which are considerd to be healthy foods. However, it should be noted that LCKD can include a wide range of healthy vegetable as mentioned in Table 2. It has been suggested that chances of having increased formation of kidney stones could be another side effects of LCKD. Factors that could enhance the stones formation could be the limited fluid intake and increased production and the decreased excretion of uric acid. Also, similar to suppression of food intake, ketone bodies are involved in the suppression of thirst, leading to reduced fluid intake. Thus hyperuricemia gives rise to urate stone formation. It is suggested that with 5% carbohydrates composition in the diet this situation can be prevented[80]. However, it should be noted that, in our studies we have observed a decrease in serum level of urea (Tables 3, 4).

Constipation is also a noted side effect of LCKD. This could be due to the decreased fiber content and as mentioned above the suppression of thirst by ketones leading to dehydration. Also, with increased absorption / digestion of foods, there is a decrease in the stool volume. This situation can be easily avoided by increasing the fiber content by taking in vegetables in the diet, increasing fluid intake and using sugar-free laxatives[34,81]. Apart from these, the data presented in this review from our laboratory and from the studies of various investigators show that chronic ketosis without caloric restriction poses no danger to maintaining a healthy body.

## CONCLUSION

The data presented from the various studies conducted at the Faculty of Medicine, Kuwait University, in a population comprising of Kuwaiti and non-Kuwaiti subjects and the results of several investigators mentioned in this review show that a ketogenic diet (consisting of 30 gms carbohydrate,

1 gm/kg body weight protein, 20% polysaturated, 80% polyunsaturated and monounsaturated fat) induces a miraculous weight loss in normal obese subjects as well as obese subjects with diabetes and hyperlipidemia. In addition to weight loss, there was a significant decrease in the level of triglycerols, total cholesterol, LDL-cholesterol and glucose whereas there was an increase in the level of HDL in these patients. Also, recent studies have shown that LCKD may actually be cardio-protective. All these studies clearly indicate that it is safe to administer ketogenic diet for a relatively longer period.

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