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Long term effects of ketogenic diet in obese subjects with high cholesterol level

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Abstract

Objective: Various studies have convincingly shown the beneficial effect of ketogenic diet (in which the daily consumption of carbohydrate is less than 20 grams, regardless of fat, protein and caloric intake) in reducing weight in obese subjects. However, its long term effect on obese subjects with high total cholesterol (as compared to obese subjects with normal cholesterol level) is lacking. It is believed that ketogenic diet may have adverse effect on the lipid profile. Therefore, in this study the effect of ketogenic diet in obese subjects with high cholesterol level above 6 mmol/L is compared to those with normocholesterolemia for a period of 56 weeks.

Materials and methods: In this study, 66 healthy obese subjects with body mass index (BMI) greater than 30, having high cholesterol level (Group I; $n = 35$) and those subjects with normal cholesterol level (Group II; $n = 31$) were selected. The body weight, body mass index, total cholesterol, LDL-cholesterol, HDL-cholesterol, urea, creatinine, glucose and triglycerides were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored at 8, 16, 24, 32, 40, 48 and 56 weeks of the treatment.

Results: The body weight and body mass index of both groups decreased significantly ($P < 0.0001$). The level of total cholesterol, LDL cholesterol, triglycerides and blood glucose level decreased significantly ($P < 0.0001$), whereas HDL cholesterol increased significantly ($P < 0.0001$) after the treatment in both groups.

Conclusion: This study shows the beneficial effects of ketogenic diet following its long term administration in obese subjects with a high level of total cholesterol. Moreover, this study demonstrates that low carbohydrate diet is safe to use for a longer period of time in obese subjects with a high total cholesterol level and those with normocholesterolemia. (Mol Cell Biochem **286:** 1–9, 2006)

Key words: blood glucose, cholesterol, HDL, ketogenic diet, LDL, low carbohydrate diet, obesity, triglycerides

Introduction

Ketogenic diet has been around in the medical literature for well over 70 years [1]. It has been known that fasting has beneficial effects on seizure control. For many years, it was used as an anti-convulsant for controlling seizures. In some cases it is actually better than the modern anti-convulsants at controlling seizures. Mild ketosis is a natural phenomenon that occurs in man during fasting and lactation. Post-exercise ketosis is a well known phenomenon in mammals, the diet mimics the effects of starvation [1–3].

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In this study a low carbohydrate diet (Ketogenic diet) in which the daily consumption of carbohydrate is less than 20 g, regardless of fat, protein and caloric intake is used. In subjects with ketogenic diet, the metabolic energy requirements are obtained from the adipose tissue and/or from dietary fat consumed by the subject. The ketone bodies, acetoacetic acid, β-hydroxybutyrate and acetone produced during the fat metabolism substitute for glucose in subjects with ketogenic diet. Furthermore, 1 g of protein can give away 0.5 g of glucose whenever patient is on ketogenic diet [4], thus it sustains positive nitrogen balance and ultimately preserves the lean body mass [5].

Currently, there is a wide popularity about ketogenic diet, prompting concerns regarding the use of ketogenic diet in weight reductions programs. However, very few studies evaluated their effect in cardiac risk factors [6, 7]. These studies indicated that application of ketogenic diet results in significant decrease in serum triglycerides, small increase in total and LDL cholesterol and moderate increase in HDL cholesterol in subjects with normal lipid profile. In another study it is shown that for every kilogram of weight loss, HDL cholesterol increases 0.009 and triglycerides decrease 0.015 mmol/L [8]. Elevated fasting triglyceride is found to be an independent risk factor for cardiovascular diseases [9]. On the other hand, numerous studies suggest that a high carbohydrate diet raise triglyceride levels and reduce HDL cholesterol along with insulin resistance [10, 11]. Interestingly, these changes in triglyceride and HDL levels were reversed by replacing saturated fat instead of carbohydrate [12, 13].

Considering the complications caused by high cholesterol level in the blood, the usual tendency is to modify the diet so as to eliminate cholesterol and unsaturated fat. In this regard, it is reasonable to believe that the best alternative in such a situation is to enable the cells to use excess lipids to produce energy, which also reduces obesity. The cells can be primed to this type of metabolism by using a high fat diet and by not providing carbohydrate, which is the usual source of fuel for the energy requirements in the body. Various studies have convincingly shown the beneficial effects of ketogenic diet in reducing weight in obese subjects as compared to other diet programs [14–20], its long term effect on the lipid profile of obese subjects with high total cholesterol as compared to obese subjects with normal cholesterol level is lacking. Therefore, the present study was carried out to demonstrate the changes in body weight, lipid profile, glucose, urea and creatinine that might occur after the administration of ketogenic diet throughout the period of study (56 weeks), in healthy obese subjects with hypercholesterolemia as compared to those obese subjects with normocholesterolemia.

Materials and methods

Obese subjects (BMI greater than 30) who attended the Consultation and training office in the Faculty of Medicine, Kuwait University, were included in the study. Medical history and clinical examination were carried out on all the subjects during each visit. Among the 997 obese subjects who attended the Consultation and training office, only 66 subjects (34 males and 32 females) were included in this study. 119 subjects refused to participate in this study, whereas 812 subjects who were suffering from other health related problems such as heart diseases, hepatic diseases, serum creatinine above 120 μmol/L and with history of weight loss medication were excluded from the study. All the subjects who were included in this study were Kuwaitis. The subjects were divided into two groups: Group I (21 males and 14 females), subjects with high cholesterol level above 6 mmol/L (normal 3.4–6.00 mmol/L); and Group II (13 males and 18 females), subjects with normal cholesterol level less than 6 mmol/L. Among the 66 subjects included in the study, 35 subjects belonged to Group I and 31 to Group II.

All 66 subjects received a ketogenic diet consisting of less than 20 g of carbohydrates in the form of green vegetables and salad and 80–100 g of proteins in the form of meat, fish, fowl, eggs, shellfish and cheese. Polyunsaturated and monounsaturated fats (5 tablespoons olive oil) were included in the diet. Gradually, the amount of carbohydrate is raised from the original 20 to 40 g in order to supply sufficient glucose to sustain the cells with few or no mitochondria such as erythrocytes, cornea, lens, renal medulla and leukocytes [4].

A list of recommended and restricted food in ketogenic diet is given in Table 1. In addition, micronutrients (vitamins and mineral; Centrum Select, Canada) in the form of 1 capsule/day were given to each subjects (Table 2). Twelve weeks later an additional 20 g of carbohydrate was given. During each visit, participants were asked regarding the adherence to the diet and adverse effects. All participants were asked to perform exercise in the form of 45 min walking daily.

Fasting blood tests were carried out in all the subjects. The subjects were subjected to liver and renal function tests, complete blood count, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL; directly measured), triglycerides (TG), urea and creatinine in the beginning after 8, 16, 24, 32, 40, 48 and 56 weeks. Biochemical analysis of lipid, liver, renal profiles and electrolytes were performed by Beckman CX 5 C E and complete blood count was carried out by Coulter MD II. The body mass index (the weight in kilograms divided by square of the height) was determined initially and after 8, 16, 24, 32, 40, 48 and 56 weeks. We standardized our results with daily internal and external quality control program with “Lab quality Finland”. During each

Table 1. Recommended and restricted food in ketogenic diet

Recommended food			Fully restricted food	
Proteins	Vegetables/Fruits	Oil	Carbohydrates	Fruits/drinks
Fish: Tuna, Sardine Prawns, Shrimps. Lobster	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	Olive oil (5 tablespoon, added to the salad	Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes	All fruit juices
Meat: Kababs, Sausages, Minced	Strawberry-6/day, Avocado	Flax seed oil		All soft drinks
Poultry: Chicken, Eggs	Berries-10/day			
Cheese: Full fat cheese				

Table 2. Composition of the capsule containing micronutrients

Vit. A	1000 IU
Beta-Carotene	3000 IU
Vit E	75 IU
Vit C	90 mg
Folic Acid	0.6 mg
Vit. B1	2.25 mg
Vit. B2	3.2 mg
Niacinamide	15 mg
Vit. B6	8 mg
Vit. B12	25 mg
Vit D	400 IU
BIOTIN	45 mcg
Pantathenic acid	10 mg
Minerals	
Calcium	200 mg
Phosphorus	125 mg
Iodine	0.15 mg
Iron	4 mg
Magnesium	50 mg
Copper	2 mg
Manganese	5 mg
Pottassium	80 mg
Chlorine	72 mg
Chromium	100 mcg
Malybdenum	25 mcg
Selenium	25 mcg
Zinc	15 mg
Nickel	5 mcg
Tin	0.010 mg
Vanadium	10 mcg
Silicon	0.010 mg
Other Ingredients	
Lutein	250 mg

Source: Centrum Select, Canada.

visit, enquiries were made regarding their adherence to the diet, exercise habits and any side effects or uncomfortable feelings they felt.

Statistical differences between parameters before and after the administration of ketogenic diet were analyzed by ANOVA and student- t test using a package (Stat view 4.02). Age, body mass index and all biochemical parameters were expressed as mean $\pm$ standard error.

Results

Among the 66 subjects who were included in this study, 35 subjects belonged to group I and 31 to group II. Their age ranged from 17 to 67. Only 49 subjects (74%) completed 56 weeks successfully. At 56 weeks, there were 26 subjects in group I (with high cholesterol level) and 23 in group II (with normal cholesterol level). Among the 49 subjects who completed the study, 25 were male and 24 were female subjects (Table 3).

The average age, weight, BMI and the baseline values of other biochemical parameters examined in this study are given in Table 4. There was a significant reduction ($P < 0.0001$) in the body weight (Fig. 1) and the BMI of males

Table 3. Number of patients at different stages of the study

	Group I (High Cholesterol) *N* (%)	Group II (Normal Cholesterol) *N* (%)	Total *N* (%)
Week-1	35 (100)	31 (100)	66 (100)
Week-24	34 (97.1)	28 (90.3)	62 (93.9)
Week-32	32 (91.4)	27 (87.1)	59 (89.4)
Week-40	30 (85.7)	26 (83.9)	56 (84.8)
Week-56	26 (74.3)	23 (74.2)	49 (74.2)

Table 4. Baseline values of different physical and biochemical parameters monitored in persons subjected to low carbohydrate diet (ketogenic diet)

	Total	Group I ($n = 35$)	Group II ($n = 31$)	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
Tot.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 BMI: Body mass index; Tot.Chol.: Total cholesterol.
Data is expressed as mean ± standard deviation.

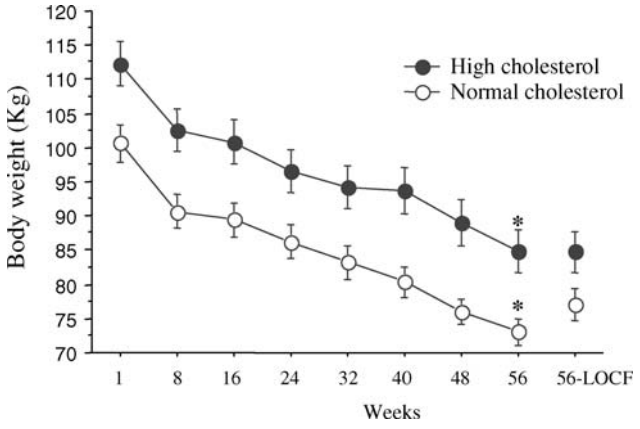

Fig. 1. Reduction in body weight at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia. The weights are expressed as mean ± SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

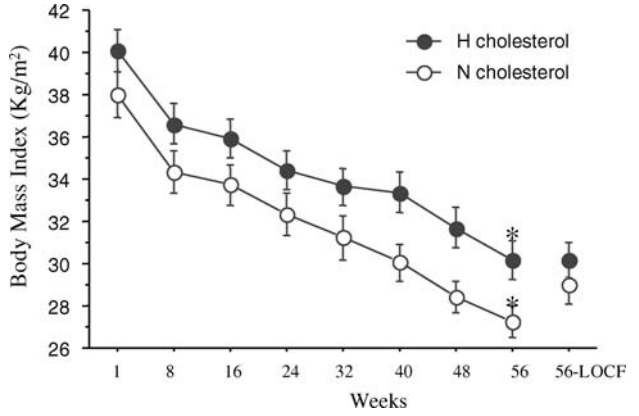

Fig. 2. Reduction in body mass index (BMI) at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia. The BMI are expressed as mean ± SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

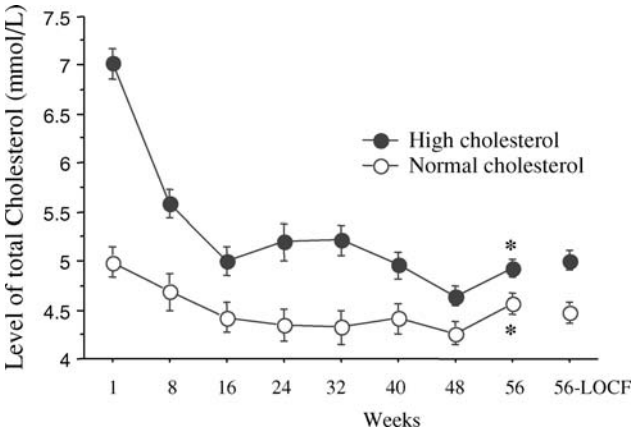

Fig. 3. Decreased levels of total cholesterol expressed as mean ± SEM, in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

and females in both Group I (high cholesterol) and Group II (normal cholesterol) throughout the program (Fig. 2).

There was a significant change ($P < 0.0001$) in the lipid profile of the subjects during the entire study period. The level of total cholesterol decreased significantly after week 1 until the end of the study (Fig. 3). HDL-cholesterol increased significantly (Fig. 4), whereas LDL-cholesterol decreased significantly (Fig. 5). The level of triglycerides significantly decreased from the start till the end of the study (Fig. 6). The blood glucose level of males and females decreased significantly ($P < 0.0001$) from the start until the 56th week (Fig. 7).The percentage changes in the various parameters observed at the end of the study and the statistical significance between week one and week 56 observations in total, group I and group II subjects are given in Tables 5 and 6 respectively. The changes in the level of urea and creatinine at week 1 and week 56 are given in Figs. 8 and 9 respectively. The changes in the levels of urea were statistically significant while changes in the levels of creatinine were not significant. The ratio of triglyceride/HDL, LDL/HDL and total cholesterol/HDL at week 1 and week 56 are given in Figs. 10, 11 and 12 respectively.

Discussion

Obesity has become a serious chronic disease in both developing and developed countries [21–24]. Furthermore, it

Table 5. Percentage changes in the various parameters observed at week 56 in persons subjected to ketogenic diet

	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
Tot.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 BMI: Body mass index; Tot.Chol.: Total cholesterol.
Data is expressed as mean $\pm$ standard deviation. Statistical significance between Group I and Group II are given.

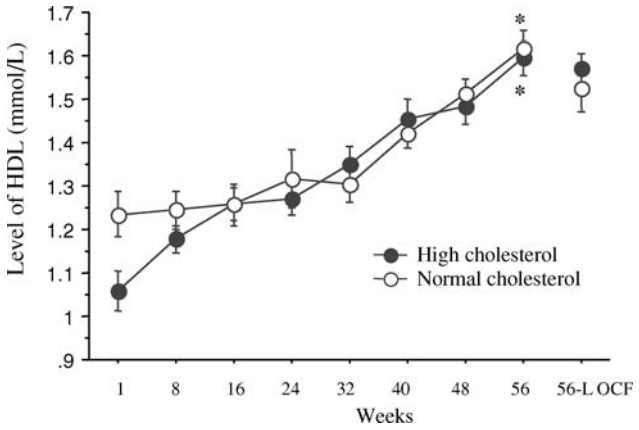

Fig. 4. Changes in the level of HDL-cholesterol expressed as mean $\pm$ SEM, following treatment with ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia for a period of 56 weeks. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

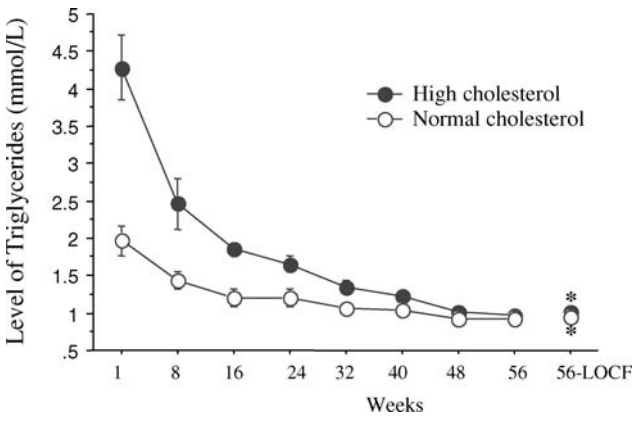

Fig. 6. Changes in the level of triglycerides in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean $\pm$ SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

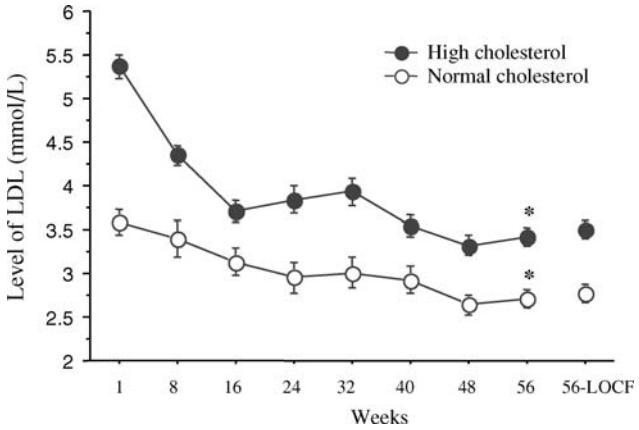

Fig. 5. Changes in the level of LDL-cholesterol following treatment with ketogenic diet at 8, 16, 24, 32, 40, 48 and 56 weeks in obese subjects with high level of cholesterol as compared to those with normal level of cholesterol. The levels of LDL-cholesterol are expressed as mean $\pm$ SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

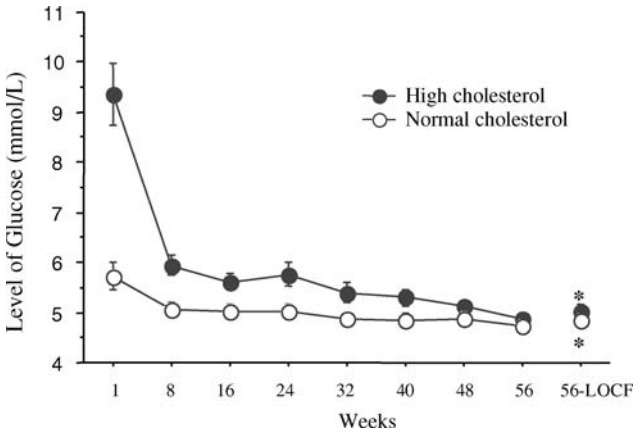

Fig. 7. Decreased levels of glucose expressed as mean $\pm$ SEM following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia at 8, 16, 24, 40, 48 and 56 weeks. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

Table 6. Statistical significance between week 1 and week 56 observation of various parameters studied in total, group I and group II subjects

	Total	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
Tot.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

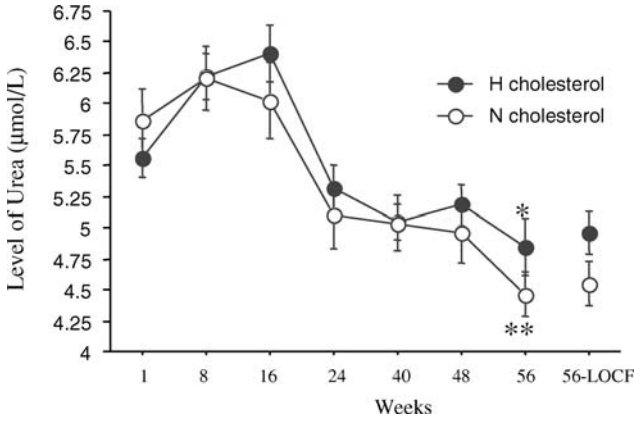

Fig. 8. Changes in the level of urea in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1 in hypercholesterolemic subjects. $^{**}p$ Value 0.0131 compared with week 1 in normocholesterolemic subjects.

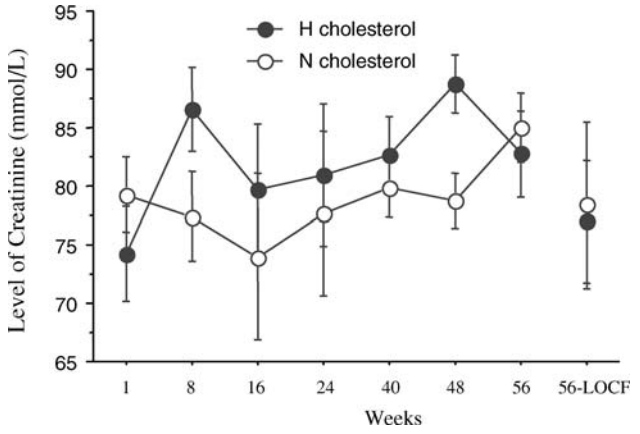

Fig. 9. Changes in the level of creatinine in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward.

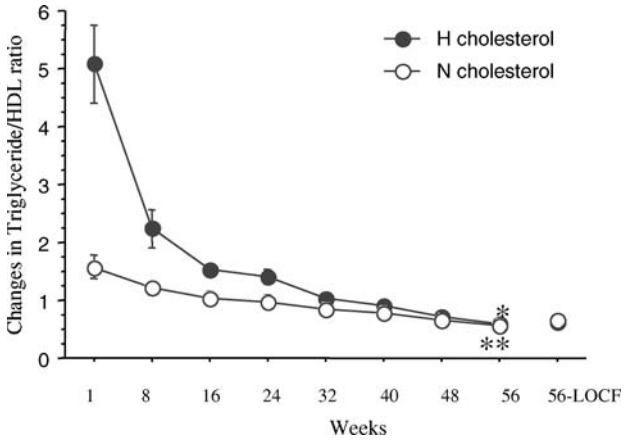

Fig. 10. Triglyceride/HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1 in hypercholesterolemic subjects. $^{**}p$ Value 0.0001 compared with week 1 in normocholesterolemic subjects.

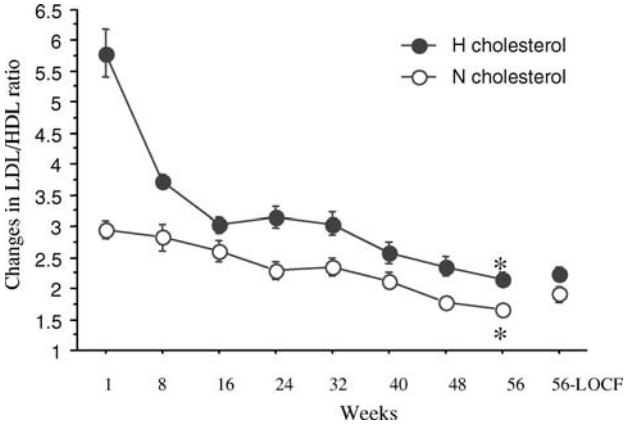

Fig. 11. LDL/HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. $^*p$ Value <0.0001 compared with week 1.

is associated with a variety of chronic diseases. It is estimated that in United States alone about 300,000 people die each year from obesity related diseases. There is a gradual increase in the number of obese people in United States [21–24]. A similar trend is observed in Kuwait and other Middle East countries. The different attempts for reducing weight by reduced calorie and fat intake combined with exercise have failed to show a sustained long term effect. Recent studies from various laboratories, including ours have shown that a high fat diet rich in polyunsaturated fatty acids (ketogenic diet) is quite effective in reducing body weight

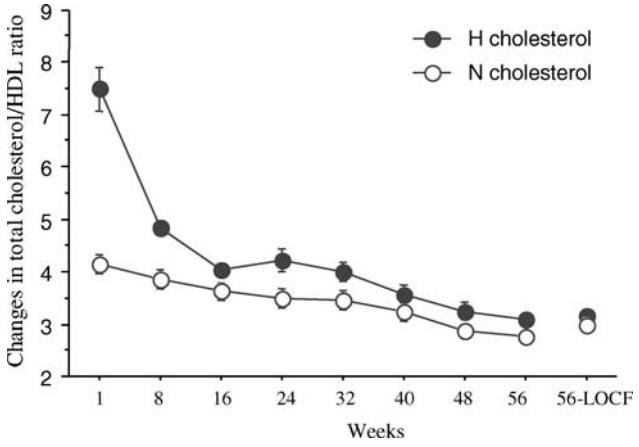

Fig. 12. Total cholesterol/ HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. $^{*}p$ Value <0.0001 compared with week 1.

and risk factors associated with various chronic diseases [1, 25–29].

These studies show the beneficial effects of ketogenic diet following its long term administration. It significantly reduces the body weight and body mass index. Furthermore, it decreases the level of triglycerides, and LDL-cholesterol [26–29].

The data presented in this study shows that both high and normal cholesterol groups showed reduction of LDL, however, there was no significant alteration between genders. The level of triglycerides significantly reduced after 8 weeks and showed a further gradual decrease in both groups till the end of the year. Similar changes occurred in males and females. Glucose level decreased significantly in both groups in males and females. As there were no significant differences in male and female subjects in all the parameters examined, the data of males and females in each group are pooled and presented together.

Majority of the subjects who attended the Consultation and training office in the Faculty of Medicine, Kuwait University, suffered from metabolic syndrome (visceral obesity, atherogenic dyslipedemia (i.e low level of high density lipoprotein and elevation of total cholesterol and triglyceride) and elevation of blood sugar. Various investigators have convincingly shown that triglyceride-rich lipoprotein plays a major role in atherogenesis [30–34] and fasting triglyceride is directly related to cardiovascular disease [35, 36], myocardial infarction, hypertension and diabetes mellitus [37, 38].

Ratio of total cholesterol/HDL and LDL/HDL are used as predictors of cardiac disease. Recent studies have shown that an increase in one unit in the LDL/HDL ratio and an increase in total cholesterol /HDL ratio is associated with a 53% [39, 40] and 49% [27], increase in the risk of myocardial infarction, respectively. In another study it is found that an increase in the ratio of LDL to HDL by one unit may even contribute to a 75% increase in the risk of myocardial infarction [38].

Unfortunately, one of the limitations of this study was that we were unable to estimate the fasting insulin level in these subjects. However, there was obvious improvement in their blood sugar level. In a similar study with low carbohydrate diet, Noakes *et al.* [41] have shown a 33% decrease in fasting insulin level along with improvement of fasting glucose level, blood pressure and reduction in body weight.

Other investigators have also shown that low carbohydrate diet had an influence in decreasing fasting triglyceride as well as the ratio of triglyceride to high density lipoprotein and improvement in blood sugar along with reduction in body weight [42–44]. Although, these studies did not compare the effects of ketogenic diet in subjects with hypercholesterolemia to those with normocholesterolemia, these studies collectively indicate that a low carbohydrate diet had more favourable outcomes with regard to weight and lipid profile than those who were on a conventional diet.

Regarding exercise most of the subjects as advised by their General Practitioners were following at least a daily walk of 45 min before participating in this program. However, they have not experienced any reduction in body weight. Thus, we have not introduced a new pattern of exercise together with this diet. On the other hand we just allowed them to continue with their routines. It should be noted that we have included about 5 tablespoons olive oil in the diet recommended to the participants in this programme. Historically, olive oil is one of the most characteristic components of Mediterranean diet [45]. It has a protective role in cardiovascular diseases, and various cancers, as well as to diminish the age-related cognitive decline [45–47]. Olive oil is rich in monounsaturated fatty acids and antioxidant substances. The health benefits of olive oil are attributed to these factors. Furthermore, it is shown that olive oil may have protective role for the dynamic blood cholesterol levels in a healthy population [47]. It should be noted that in our previous study [1], we have not included olive oil in the diet and the decrease in weight in obese subjects was similar in both the studies.

Administering ketogenic diet for a relatively longer period did not produce any significant side effects in subjects with high level of total cholesterol. Therefore, this study suggests that it is safe to use ketogenic diet for a longer period of time regardless of the total cholesterol level of the subjects.

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