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Impact of ketogenic diet on insulin and thyroid hormones in a healthy cohort

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***Abstract*---**Objective: To determine the effect of a ketogenic diet (KD) on the levels of insulin and thyroid hormone in healthy adult individuals. Methodology: This single-arm comparative experimental study was conducted at the Clinical trial room and Physiology laboratory, Khyber medial university, Peshawar. A total of 46 individuals were selected falling under the inclusion criteria. Ketogenic diet was given to the participants for four weeks. Blood was obtained from subjects on day 1, and after 29 days. Paired sample t test was used for pre- and post-trial comparison and ANOVA was used for comparison at day 0, and 29th day. Results: Mean age was 29.8±5.28 years. The mean value of thyroid stimulating hormone (0.005), T3 (<0.001) and insulin (0.003) statistically decrease from day 1 to day 29. But mean value of T4 increased from day 1 (6.26±0.8301) to day 29 (7.70±0.931). However, there was no significant difference for thyroid releasing hormones (TRH) on day 1 and day 29 (0.139).

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Conclusion: The KD statistically reduced the level of TSH, T3, TRH and Insulin while T4 level increases. The clinicians should take into consideration patients with thyroid disorders or diabetes while prescribing KD.

***Keywords*---**thyroid releasing hormones (TRH), ketogenic diet, Physiology laboratory.

Introduction

The ketogenic diet (KD) follows a pattern of moderate protein, low carbohydrate intake, and high fat. KD, which is characterized by using fat as the body's main energy source instead of carbs, was first applied to treat children with refractory epilepsy (1). However, weight loss is currently the most prevalent reason for beginning a KD (2). It has been reported in the literature that more body mass is lost when KD is followed compared to high carbohydrate diet (3,4). By avoiding carbohydrates, the level of insulin hormone in the blood decreases, resulting in a higher rate of fat burning to provide energy when the body needs it (5). The increasing number of patients getting KD and previous experiences with KD have prompted researchers to study the metabolic effects of KD. The ketogenic diet seeks to simulate the metabolic consequences of fasting. It has been found that hunger inhibits anabolic activity through downregulating the hypothalamic-pituitary-thyroid axis. It is well-established that thyroid hormone level correlates directly with body mass and energy consumption (6). Nonetheless, the effects of the KD on thyroid function remain unknown. In one study ketosis was associated with higher levels of T4 but no change in T3 (7). Whereas in another study, ketosis was associated with lower levels of T3 (8). Numerous research on the KD have been undertaken on overweight/obese patients or individuals with insulin resistance, with varying outcomes. Thus, the evidence assessing the effects of the KD on Insulin and Thyroid levels in healthy persons is minimal. The purpose of this study was to assess the effect of KD on insulin and thyroid hormone levels in healthy participants.

Methodology

From January 2022 to June 2022, a single-arm, before-and-after (pre and post) comparison experimental intervention was undertaken at the Biochemistry Clinical trial room and Physiology laboratory IBMS, Khyber Medical University, Peshawar. The study enrolled normal, healthy adults with BMIs ranging from 20 to 29.9 kg/m2 and ages ranging from 25 to 45 years. Those with an age below 25 and above 45, a body mass index (BMI) above 30 kg/m2, impaired liver and renal functions, kidney stones, pregnant and lactating females, diabetes mellitus, fatty acid metabolism illness, immunocompromised diseases, high blood pressure, cardiac diseases, obesity, a history of impaired renal function, smoking, and alcohol consumption were excluded. Sample size was 46, this was calculated through an open epi sample size calculator. Assuming the power of 80%, confidence interval of 95% and by taking the mean difference between PRE and POST of matched pairs of 0.216(10%), the exact sample size was 38, however,

considering 20% dropouts, we enrolled 46 individuals. Non-probability convenience sampling method was used.
Ethical clearance was obtained from the Khyber Medical University. Verbal and written consent was taken from the participants, and they were informed of the professional secrecy maintained in this voluntary study. A detail questionnaire containing demographic data, 24 hours dietary recall, daily caloric intake was distributed. Physical examination including height and weight and history of hypertension, diabetes, liver disease, fat metabolic disorders and pregnancy and lactation were taken. A 24- hour dietary recall of two days i.e., 2 days prior to the screening day was obtained from each participant by the researcher in the form of an interview. Venous blood samples (10 mL) were drawn from the antecubital vein in the morning after 10-12 hours overnight fast using the aseptic technique. Assessment of thyroid and insulin hormone levels was done using the Elisa technique according to the manufacturer's instructions.

After completion of health questionnaires, blood profiling and anthropometric measurements, ketogenic diet boxes were provided to the participants for breakfast, lunch and dinner which were continued for four weeks in the form of lunch boxes. Nutritional counselling of all participants was done in which changes in lifestyle adaptations, changing food priorities, diet recipes and any possible side effects were discussed. A caloric intake logbook was kept keeping a daily record of the estimated quantity of food consumed by the participants. On the 29th day of the intervention, participants were again invited to the clinical trial room of Khyber medical university and blood samples were collected for estimating insulin and thyroid hormone levels. For data analysis, SPSS v.26 was used. Mean and standard deviation were used to describe continuously measured variables, and frequency and percentages were used for categorically measured variables. Pearson's correlation test was applied to assess correlations between metric variables and the independent t-test. One-way ANOVA tests were used to determine statistical significance for mean differences across the levels of binary and categorical variables of more than two levels. The alpha significance level was considered at 0.05.

Results

In this study total of 45 participants were recruited in which females were 30 (66.7%), and males were 15 (33.3%). The mean age of the participants was 29.8±5.28 years with a range from 24 to 45 years. The mean energy level was highest on day 1st (13170±2966.2) and least on day 29th (8322.7±2143.3), which was statistically significant (P<0.001). Similarly, for kilocalories, the mean level was highest on day 1st (3176.8±720.22) and least on day 29th (2011.8±519.52). The statistical difference was found between 24-hours recall versus day 1st. it was also found between day 1st versus day 29th (P<0.001). The mean level of fat was higher on day 1st (292.95±74.431) than 29th day (183.06±53.171) statistically significant (P<0.001). Similarly, the mean protein level was higher on day 1st than 29th day statistically significant (P<0.001). A significant difference was found for carbohydrates on day 1st versus day 29th with the highest mean on day 1st (26.907±10.37) and was least on day 29th (17.026±10.502) **(Table 1)**

Table 1: Comparison of dietary agents at various time points

Variable	24-hour dietary recall (24H)	1st day (D1)	29th day (D29)	P-Value for comparison		
				24H vs D1	D1 vs D29	24H vs D29
Energy (kJ)	8705.5±4406.3	13170±2966.2	8322.7±2143.3	<0.001	<0.001	0.844
Energy (Kcal)	2078.1±1058.1	3176.8±720.22	2011.8±519.52	<0.001	<0.001	.916
Fat (gm)	102.54±78.124	292.95±74.431	183.06±53.171	<0.001	<0.001	<0.001
Protein (gm)	79.887±37.968	127.93±101.2	74.552±26.79	0.001	<0.001	0.916
Carbohydrate (gm)	222.19±98.92	26.907±10.37	17.026±10.502	<0.001	.691	<0.001
Starch (gm)	153.68±79.94	7.928±8.152	6.443±9.34	<0.001	0.987	<0.001
Dietary Fiber (gm)	18.141±11.71	13.124±4.09	8.602±5.019	0.006	0.016	<0.001
Cholesterol (mg)	341.44±246.95	1000.5±243.32	646.17±270.33	<0.001	<0.001	<0.001

Fasting blood sugar reduced from day 1(91.78 ±8.257mg/dl) to day 29 (85.73 ±9.319 mg/dl). (P=0.006). Similarly, FBS similar results were for glucose ketone index. Ketone level was lowest on day 1 (0.133 ±0.199) then day 29(1.378 ±1.119). Body mass index was higher on day 1 (26.2 ±2.619) than day 29(24.82 ±2.435) statistically significant (P=0.029). **(Table 2)**

Table 2: Comparison of multiple parameters on day 1, and day 29

Variable	Day 1 (D1)	Day 29 (D29)	P value
Fasting blood sugar (mg/dl)	91.78 ±8.257	85.73 ±9.319	0 .006
Ketone level (mmol/L)	0.133 ±0.199	1.378 ±1.119	<0.001
Glucose ketone index	42.21 ±16.58	8.747 ±10.14	<0.001
Weight (kg)	73.59 ±10.36	69.72 ±9.497	0.157
Body mass index (kg/m²)	26.2 ±2.619	24.82 ±2.435	0 .029
Body fat (%age)	34.19 ±6.248	31.79 ±7.202	0.228
Water mass (kg)	46.11 ±3.792	47.7 ±4.279	0 .162
Basic metabolic rate	1442 ±196.7	1409 ±185.2	0 .982
Muscle mass (kg)	45.62 ±8.535	44.85 ±8.298	0.898
Visceral mass (kg)	7.689 ±2.745	7.313 ±2.85	0.999
Bone mass (kg)	2.698 ±0.3	2.638 ±0.295	0.599
Protein	15.62 ±2.483	16.34 ±2.912	0.436

The mean value of TSH, T3 and insulin statistically decrease from day 1 to day 29 (P<0.05). The mean TSH, T3 and insulin were 1.109±1.054, 1.23±0.240 and 12.21 (9.76-15.29) on day 1 respectively and day 29 were 0.90±0.799, 1.02±0.23 and 6.65 (5.59-7.90) respectively. But the value of T4 increase from day 1 (6.26±0.8301) to day 29 (7.70±0.931) statistically. However, there was no significant difference for TRH on day 1 (36.71 (24.64-54.71)) and day 29 (36.21 (24.76-52.95)). **(Table 3)**

Table 3: Comparison of TSH, T_3, T_4, TRH and insulin between before and after ketogenic diet

Parameter	Day 1	Day 29	P-Value*
	Mean ± SD	Mean ± SD	
Insulin# (µIU/mL)	12.21 (9.76-15.29)	6.65 (5.59-7.90)	<0.001
TRH# (ng/L)	36.71 (24.64-54.71)	36.21 (24.76-52.95)	0.895
TSH (µIU/mL)	1.109±1.054	0.90±0.799	0.005
T3 (ng/mL)	1.23±0.240	1.02±0.237	<0.001
T4 (µg/dl)	6.26±0.8301	7.70±0.931	<0.001

Discussions

This study was aimed to find out the effect of a 4-week ketogenic diet on levels of Insulin, TSH, T3, T4 and TRH in healthy adult individuals. This was a mechanistic study. The study showed a significant reduction in TSH, T3, TRH and Insulin after 4 weeks of ketogenic diet (KD). In contrast, T4 levels were significantly increased at the end of the trial. The ketogenic diet (KD) provided to the participants consisted of 75% fat, 20-25% protein and less than 5% carb. KD is used nowadays for weight reduction and widely studied in literature. Most of the studies are on the obese or overweight individuals. Here in this study, we explored the effects of KD on normal or overweight subject. The mechanism of KD is to shift the metabolism of the body from carbohydrate predominant energy expenditure state to a fat burning state. Taking fewer carbs and high protein and fats in the diet are considered a healthy way to decrease weight. Because by reduced intake of sugar and starch the level of insulin hormone drops in blood, which is considered an anabolic hormone in the body. As one of the functions of insulin is to store fats thus when the levels of insulin drop it will result in high burning of stored fats during times of energy need of the body (9).

ketogenic diet (KD) causes a decrease in levels of insulin along with a surge in circulating glucagon. Glucose is the stimulant of insulin release; it directly enters the Beta cells of pancreas and produces ATP, leading to calcium influx and releases insulin. But when carbohydrate is restricted the stimulus for beta cell finishes with low or diminished insulin release. This causes liver glycogen usage along with the disintegration of stored triglycerides from adipose tissue and fat from food is consumed as a primary source of fuel by the body (10). Physiological ketosis occurs when a person is in fasting state and during KD. The common ketones are β-hydroxy-butyrate and acetoacetate. These ketones circulate from

liver to muscles and other tissues in order for them to function normally. Ketone bodies production can be dangerous for diabetic patients with hyperglycemia because the decreased level of insulin in the body leads to the production of more ketone bodies from fat cells, this continuous cycle causes the situation known as Diabetic Keto-Acidosis in which increase production of ketones raise the pH level of blood and may cause diabetic coma or even death (11). However, the physiological ketosis due to the ketogenic diet has normoglycemia and beneficial for weight loss and also used for glycemic control.

Our study found that the use of KD can significantly decrease insulin levels after a one-month duration. A study showed that the use of KD for 1.5 months can decrease the level of glucose and insulin. These results are similar to our findings. Similarly, there was a decrease in insulin levels in other studies after the use of KD as well (12, 13). The role of KD in the reduction of insulin level can be due to increased glucagon formation (14). The human pancreas releases both insulin and glucagon in a balanced way causing homeostasis. If one hormone is high the other will be low to keep the balance of glucose metabolism at an optimal level (15).

Two studies reported that KD cannot affect insulin statistically (16, 17). *Wilson et al.* (16) conducted a study on 25 college-aged men and checked the effects of the use of KD for 11 weeks on body composition and hormonal profile. Their results showed that KD does not affect insulin levels. The variation in results can be attributed to the genetic level of the participants. A study reported that change in TSH level after KD use was not significant, T3 decrease and T4 increase statistically. (18) These results are consistent with our study as far T3 and T4 results are concerned. Other previous studies also reported that T3 level decrease after the use of KD (19, 20).

A study was conducted on the effects of KD on TRH, T3 and T4 in healthy adult for 8 days. They found that only T3 reduces after using a ketogenic diet (21). This study supports our results for T3 and TRH. Another study was conducted on the effects of the modified ketogenic diet on thyroid function in 120 adult patients with epilepsy. They reported that after three months use of modified KD can decrease the T3 level statistically (22). This study supports our findings with one difference that our study is on healthy adults production and it was expected to raise the thyroid hormones and TRH. In contrast, we find normal levels of TRH which suggests the changes at cellular levels did not affect the central axis of TRH secretion. This raises an important point that the changes in metabolism in KD might occur at the mitochondrial level which are responsible for raised BMR and weight loss.

Conclusion

It is concluded that KD leads to increase in the T4 levels and decline in insulin, TSH and T3 levels. Furthermore, it also leads to significant reduction in the anthropometric measurements including weight, body mass index, after 4 weeks of intervention.

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