Effects of modified Atkins diet on thyroid function in adult patients with pharmacoresistant epilepsy

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A B S T R A C T
Introduction: The use of ketogenic diet as a supplement to antiseizure medication (ASM) in refractory epilepsy has increased in the past decades. This high-fat, low-carbohydrate diet mimics the metabolic state of fasting and is generally well-tolerated. However, the long-term adverse effects of the diet are unclear.

The purpose of this study was to investigate whether the modified Atkins diet (MAD), a variant of the ketogenic diet, may have an impact on thyroid hormone levels.

Methods: We assessed thyroid function by measuring thyroid stimulation hormone (TSH), fT4, T3, fT3, and rT3 before diet start (baseline) and after 12 weeks on the diet in 53 adult patients with drug-resistant epilepsy. Further, we examined the correlation between the changes in thyroid function during dietary treatment and type of (i) change in seizure frequency, (ii) drugs in use, and (iii) degree of ketosis.

Results: After 12 weeks on the diet, we found a significant reduction in T3 and fT3 values (13.4% and 10.6%, respectively) and a significant increase in fT4 values (12.1%) compared with baseline. In addition, there was an insignificant increase in TSH and rT3. These changes were similar in women and men, and there was no correlation to drugs in use (enzyme-inducing vs. nonenzyme-inducing drugs), changes in seizure frequency, or level of ketosis.

Conclusion: This study indicates that dietary treatment for epilepsy may bring about a modest fall in thyroid hormone levels. This could be relevant for those patients with low thyroid hormones and those treated with ASMs known to lower thyroid hormone levels. A cumulative effect of ASMs, low basal thyroid hormone levels, and ketogenic diet may therefore be of clinical importance in the case of thyroid hormones when treating patients with MAD.

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1. Introduction
Ketogenic diet is a high-fat, low-carbohydrate diet that has gained increasing attention the past decades as treatment for drug-resistant epilepsy. Children with severe epilepsy have shown to benefit from such dietary treatment [1]. In recent years, ketogenic diets are being increasingly used also in adult patients with drug-resistant epilepsy [2]. An updated review reported that 66 adult patients on such diets experienced on average a 35% seizure reduction [3]. We recently completed a randomized controlled study on the effect of modified Atkins diet (MAD, a variant of the ketogenic diet) in adults with drug-resistant focal epilepsy and found that significantly more patients in the intervention group compared with the controls achieved >25% reduction in seizures, when analyzed as on treatment [4]. Ketone bodies are produced in the liver under certain physiological conditions such as fasting or starvation, and also when eating a ketogenic diet, which was originally designed to mimic the metabolism during fasting [5]. In these situations, ketone bodies become the main source of energy for the brain instead of carbohydrates. Moreover, introduction of a ketogenic diet requires radical dietary changes that cause metabolic changes throughout the body [3].

During fasting, alterations of thyroid hormones may occur [6]. Both studies in animals and humans show reduced levels of thyroid hormones during fasting or starvation. The reason for this is unclear.
Moreover, thyroid hormones have also been shown to affect neuronal excitability thereby having an impact on seizure susceptibility [7]. A possible change in thyroid hormones could therefore have a clinical consequence on seizure frequency.

Concerns have been raised about the long-term effects of the ketogenic diet. For example, an increased risk of unfavorable profile of blood lipids, impaired bone health, gastrointestinal disturbances, weight loss, and kidney stones have been recognized [2,3]. To our knowledge, a diet-induced effect similar to fasting has yet to be explored in the case of endocrine functions in adult patients. For example, it is unknown if the diet has a similar effect on thyroid hormones as confirmed during fasting.

It has been shown that especially enzyme-inducing antiseizure medications (EIASMs) and also noninducing antiseizure medications (NEIASMs) have an influence on endocrine functions, including the thyroid gland [8–11].

Two studies on this topic have been carried out, both in children. Kose et al. have analyzed the effect of ketogenic diet on thyroid function in 120 children, and in 16.7% of them, hypothyroidism was diagnosed [12]. Elevated thyroid stimulation hormone (TSH) values at baseline and female gender were found to be risk factors. Another study based on 28 children with severe epilepsy and using a ketogenic diet for a mean of about two years did not find any significant diet-induced changes in thyroid hormone levels [13].

Because of the lack of studies focusing on ketogenic diets and thyroid hormones in adults with epilepsy, the aim of the current study was to investigate whether consumption of MAD by adults with drug-resistant epilepsy has an impact on thyroid function measured by different thyroid hormones.

2. Material and methods

2.1. Patients

A total of 53 adults with drug-resistant focal or generalized epilepsies were recruited from a tertiary referral epilepsy center and enrolled from March 2011 to March 2017 and merged from two studies by Kverneland et al. [4,14]. The aim of the first study was to examine the efficacy and tolerability of the MAD for 12 weeks in adult patients with drug-resistant focal epilepsy. The aim of the second study was to evaluate the efficacy and tolerability of the MAD in adults with drug-resistant generalized epilepsy in a prospective study. All 53 patients used MAD for 12 weeks.

Briefly, screening and inclusion were performed by two senior neurologists and a clinical nutritionist. For both studies, the inclusion criteria were (i) age >16 years, (ii) having tried at least three antiseizure medications (ASMs), including current treatment, and (iii) having a body mass index >18.5 kg/m². The medication was kept unchanged, and oral contraceptive medications or other hormone therapies that could affect thyroid function or other hormone levels were not used during the whole study period.

The ASMs were categorized into EIASMs and NEIASMs (Table 1). The patients had to have at least three countable seizures per month at inclusion, and the seizures had to be countable either by the patient or relatives/caregivers. After inclusion, all patients completed 12 weeks’ baseline period before they started with the MAD for the following 12 weeks. All seizures were recorded in diaries and analyzed by the study team at each hospital visit. The patients (and/or their caregivers) also had to be motivated for adhering to the diet and confident in preparing meals.

Exclusion criteria were pregnancy, use of a ketogenic diet the previous year, change of ASMs, psychogenic nonepileptic seizures, status epilepticus the previous 6 months, surgery or implantation of vagus nerve stimulator the last 12 months, or having psychosocial or physical comorbidities that contraindicated use of the diet. The study was approved by the Regional Committee for Medical and Health Research Ethics in South East of Norway (number 2010/2326). Written informed consent was obtained from all participants.

2.2. Laboratory tests and hormone analyses

The diet allowed an intake of maximum 16 g of carbohydrates daily. Adherence to the diet was checked by measuring blood ketones after an overnight fast during short hospital stays after 4 and 12 weeks on the diet. During the hospital stays, the extent of blood ketosis was measured by the concentration of the ketone body β-hydroxybutyrate based on a finger-prick blood sample in the morning using Precision Xtra Blood Ketone Test Strips (Abbott, Alameda, CA, USA).

Thyroid function was assessed by measuring TSH, thyroxine (fT4), triiodothyronine (T3), free triiodothyronine (FT3), and rT3 (reverse triiodothyronine) before diet start (baseline) and after 12 weeks on the diet in venous blood collected between 8 and 10 am after an overnight fast. The samples were stored at −80 °C for 6 to 76 months. All samples were analyzed together in one batch. Thyroid stimulation hormone (intra-assay coefficient of variation (CV): 2% at 3.8 mIU/l, detection limit: 0.03 mIU/l), FT4 (CV: 4% at 11 pmol/l, detection limit: 3 pmol/l), and T3 (CV: 4% at 1.8 nmol/l, detection limit: 0.5 nmol/l) were analyzed using noncompetitive immunofluorometric assays (DELFIA, Wallac Oy, Finland); FT3 (CV: 4% at 5.2 pmol/l, detection limit: 1.5 pmol/l) was measured by an electrochemoluminescence assay (Roche Diagnostics, Manheim, Germany) technique, and rT3 (CV: 5% at 0.36 nmol/l, detection limit: 0.04 nmol/l) was measured by a competitive radio immunoassay (ZenTech, Angleur, Belgium). All analyses were performed at the Hormone Laboratory, Oslo University Hospital, Oslo, Norway, and they were all accredited according to ISO 17025.

2.3. Statistics

Normally distributed data were analyzed using parametric methods, and not normally distributed data were analyzed using nonparametric methods. Normality tests included both histograms and Q-Q plots.

Thyroid hormone levels were analyzed and compared with baseline after 12 weeks on the diet using a paired samples Student’s t-test. Subanalysis was performed to analyze for possible sex differences.

Seizure frequency was recorded at baseline and during the 12 weeks’ study period on a weekly basis. From week 5 to week 12, the seizure frequency was recorded as a mean value for these weeks together. The differences in mean seizure frequency between baseline and week 5–12 were then calculated.

A linear regression analysis was performed to examine possible associations between the difference in seizure frequency and the difference in thyroid hormone levels (i.e., TSH, FT4, FT3, T3, and rT3) between baseline and week 12 (i.e., the mean weekly seizure frequency from week 5 to week 12). We also examined if the levels of thyroid

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Table 1
Antiseizure medication used by the participants.

| Enzyme-inducing ASMs n = 13 | Nonenzyme-inducing ASMs n = 40 |
|-----------------------------|--------------------------------|
| Phenytoin n = 4             | Zonisamide n = 4                |
| Phenytoin n = 2             | Levetiracetam n = 14            |
| Carbamazepine n = 7         | Valproate n = 15                |
|                            | Topiramate n = 8*               |
|                            | Oxcarbazepine n = 16*          |
|                            | Clonazepam n = 8               |
|                            | Lamotrigine n = 16             |
|                            | Lacosamide n = 6               |
|                            | Polygabalin n = 2              |
|                            | Clonazepam n = 2               |

ASMs = antiseizure medications.

* Partly enzyme-inducing ASMs.
hormones at baseline and after 12 weeks were associated with the difference in seizure frequency.

Antiseizure medications may reduce thyroid hormone levels, especially the EIASMs [8–10]. Thyroid hormone levels were therefore analyzed separately according to the type of ASM (EIASMs or NEIASMs) the patients used (Table 1) applying a Student’s t-test. The patients who were treated with EIASMs together with NEIASMs were categorized in the EIASM group.

We used linear regression models to examine if there was any association between the extents of ketosis (measured as the blood concentration of β-hydroxybutyrate) after 12 weeks on MAD and the differences in thyroid hormone levels between baseline and at week 12.

Significance was assumed for p < 0.05. All analyses were performed using SPSS Statistics v 25.

3. Results

3.1. Patient characteristics

Thirty-three women and 20 men were included in the study. Forty-seven of the patients had focal epilepsy, whereas six had generalized epilepsy. Mean age was 37.9 (16.0–65.0) years at baseline. The patients had been diagnosed with epilepsy for a mean of 25 (5–58) years earlier. All patients except three had been treated with ASM for N10 (range: 5–58) years. The mean (range) number of currently used ASMs was 2.1 (1–3), and the patients had used a mean (range) of 8 (3–18) ASMs at the time of inclusion. Of the 47 with focal epilepsy, 8 had undergone surgery for epilepsy. Twenty patients had vagus nerve stimulator implanted (19 patients with focal epilepsy and one with generalized epilepsy). Mean body weight at baseline and after 12 weeks were, respectively, 78.8 (95% Confidence interval (CI): 73.4–84.1) kg and 74.2 (95% CI: 69.4–78.9) kg. There was a mean weight loss of 4.6 (95% CI: 3.3–5.3) kg (p < 0.01).

3.2. Thyroid hormones

At baseline, none of the patients had abnormal thyroid hormone levels. The changes in thyroid hormone values after 12 weeks on MAD are shown in Table 2. There was a significant reduction in T3 and fT3 values and a significant increase in fT4 values from baseline for all patients as shown in Fig. 1. Moreover, there was a nonsignificant tendency towards increased TSH and rT3 values. We found that both fT3 and T3 decreased significantly in both female and male patients, whereas fT4 increased significantly in men only.

3.3. Seizure frequency

The mean (range) seizure frequency at baseline was 15.7 (0.08–268.0) per week, while the mean (range) weekly seizure frequency in weeks 5 to 12 was 12.4 (0.38–162.8). Because of the wide variety in seizure frequency, we also calculated median seizure frequency that was 3.5 per week at baseline, and 2.8 per week in weeks 5 to 12. Using a linear regression model, we found no significant association between the difference in seizure frequency and the differences in thyroid hormone levels from baseline to 12 weeks. The corresponding correlation coefficients were low and nonsignificant (0.13 for TSH, 0.09 for fT4, 0.30 for fT3, 0.10 for T3, and 0.05 for rT3).

### Table 2

Thyroid hormone levels at baseline and after 12 weeks on modified Atkins diet.

|                | Baseline Mean (SD) | 12 weeks Mean (SD) | p-Value | % change |
|----------------|--------------------|--------------------|---------|----------|
| TSH (0.2–4.5 mIU/l)a |                    |                    |         |          |
| All (n 53)     | 2.10 (1.03)        | 2.31 (1.10)        | 0.10    | 10.0     |
| Women (n 33)   | 2.03 (0.96)        | 2.26 (0.87)        | 0.18    | 11.3     |
| Men (n 20)     | 2.22 (1.15)        | 2.39 (1.41)        | 0.37    | 7.7      |
| fT4 (8.2–22 pmol/l)a |                |                    |         |          |
| All (n 53)     | 13.43 (3.09)       | 15.05 (2.66)       | 0.004   | 12.1     |
| Women (n 33)   | 13.55 (2.40)       | 14.57 (2.75)       | 0.15    | 7.5      |
| Men (n 20)     | 13.24 (4.06)       | 15.84 (2.36)       | 0.04    | 19.6     |
| fT3 (2.8–7.0 nmol/l)a |               |                    |         |          |
| All (n = 53)   | 4.63 (0.84)        | 4.14 (0.71)        | <0.01   | −10.6    |
| Women (n = 28) | 4.50 (0.88)        | 4.10 (0.74)        | 0.004   | −9.0     |
| Men (n = 17)   | 4.83 (0.76)        | 4.22 (0.66)        | 0.001   | −11.0    |
| T3 (1.2–2.5 nmol/l)a |             |                    |         |          |
| All (n = 45)   | 2.17 (0.49)        | 1.88 (0.46)        | 0.01    | −13.4    |
| Women (n = 28) | 2.18 (0.54)        | 1.92 (0.52)        | <0.01   | −12.0    |
| Men (n = 17)   | 2.16 (0.43)        | 1.82 (0.32)        | <0.01   | −15.7    |
| rT3 (0.14–0.54 nmol/l)a |         |                    |         |          |
| All (n = 53)   | 0.29 (0.11)        | 0.30 (0.10)        | 0.66    | 3.5      |
| Women (n = 33) | 0.28 (0.11)        | 0.27 (0.09)        | 0.45    | 3.6      |
| Men (n = 20)   | 0.31 (0.12)        | 0.34 (0.11)        | 0.70    | 9.7      |

The data are analyzed with Student’s t-test with mean, SD, and p-value. a Reference values of the Hormone Laboratory, Oslo University Hospital.

Fig. 1. Box plots with thyroid function assessed as T3, fT3, and fT4 at baseline and after 12 weeks on modified Atkins diet. *p < 0.05.
We analyzed if there were any associations between the levels of the different thyroid hormones at baseline and after 12 weeks compared with seizure difference (between baseline and weeks 5–12). We found no associations as shown in Fig. 2.

3.4. Enzyme-inducing ASMs vs. nonenzyme-inducing ASMs

The patients used different combinations of ASMs, and some patients used both EIASMs and NEIASMs. No patients used monotherapy. Those using NEIASMs had a significant decrease in fT3 and T3 values and an increase in fT4 values (Table 3), whereas those using EIASMs had a significant decrease in fT3 and T3 values, but only a nonsignificant (p = 0.08) increase in fT4.

We also analyzed the group (n = 19) using NEIASMs after removing the data from those who used the partly enzyme-inducing drugs oxcarbazepine and topiramate (see Table 1) to examine if this had an impact on the results. However, this analysis did not alter the results for the patients using NEIASMs.

3.5. Ketosis

The extent of ketosis, measured as β-hydroxybutyrate, could be analyzed in 46/53 (87%) because of insufficient material in some samples. After 12 weeks on MAD, all patients except five achieved ketosis, i.e., β-hydroxybutyrate > 0.3 mmol/l. The mean (range) β-hydroxybutyrate concentration was 1.15 (0.00–4.20) mmol/l.

The differences in thyroid hormone levels between baseline and at 12 weeks were analyzed with linear regression to examine if there was any correlation with the corresponding difference in the levels of β-hydroxybutyrate. No statistically significant associations were found, and the corresponding correlation coefficients were low and nonsignificant (0.33 for TSH, 0.12 for fT4, 0.18 for fT3, 0.08 for T3, and 0.09 for rT3).

Fig. 2. Scatter plots with thyroid function parameters measured at baseline and after 12 weeks on modified Atkins diet compared with changes in seizure frequency.
3.6. Liver and kidney function

Liver and kidney function were measured respectively as Aspartate transaminase (AST), Alanine transaminase (ALT), and creatinine at baseline and after 12 weeks. Mean AST level at baseline was 19.33 (95% CI: 17.5–21.2) U/l compared with 20.1 (95% CI: 17.9–22.3) U/l after 12 weeks (p = 0.48). Mean ALT levels were 25.3 (95% CI: 21.4–29.2) U/l and 25.6 (95% CI: 22.1–29.1) U/l, respectively (p = 0.84). For creatinine, mean levels were 72.9 (95% CI: 68.7–77.0) mmol/l at baseline, and 70.2 (95% CI: 65.6–74.8) mmol/l after 12 weeks (p = 0.07).

4. Discussion

4.1. Main findings

The main finding in this study of adult patients with severe and pharmacoresistant epilepsy was a significant reduction in T3 and rT3 values and an increase in fT4 values after treatment with MAD. Moreover, TSH and rT3 values were both increased, although not statistically significant.

Although the ketogenic diets aim at mimicking a fasting state, our findings do not resemble what is observed in fasting conditions. In such conditions, the net result is decreased TSH release by the anterior pituitary gland, decreased thyroidal secretion of thyroid hormones, and decreased peripheral conversion of T4, resulting in decreased serum levels of T3 and increased rT3 levels [6]. These changes are believed to represent an adaptive mechanism that can be regarded as beneficial. Similar changes are reported in nonthyroidal illness syndrome (NTIS), also named “sick euthyroid syndrome” or “low T3 syndrome”. This syndrome is recognized in acute stressful situations like myocardial infarction, surgery, and other critical illnesses with a decrease of T3 and T4 values, and an increase in rT3 values. In these situations, TSH stays normal or is slightly reduced [15]. The normal negative feedback system can apparently not explain all the changes in NTIS. The mechanisms behind the alterations seen in NTIS or fasting are not well established.

Our findings may suggest that the peripheral conversion of fT4 to rT3 can be altered when using MAD. In our study, TSH and rT3 were nonsignificantly increased. This trend cannot be taken as support of the assumption that hypothalamus or pituitary is involved. On the contrary, a possible increase in the TSH values supports and strengthens the hypothesis of a peripherally located mechanism of action. The nonsignificant increase in rT3 could be explained by increased degradation from fT4 as a regulatory mechanism.

Both the liver and kidneys are involved in peripheral thyroid hormone metabolism. The activation of thyroid hormone is regulated by the iodothyronine deiodinases types I, II, and III (D1, D2, and D3, respectively) [16]. It is known that abnormalities in deiodinase activity are important in a number of clinical settings, one being critical illness. These enzymes are expressed differently in different tissues, i.e., D1 in peripheral tissues like liver and kidney and D2 in Central nervous system (CNS) and pituitary gland. A possible mechanism for the decrease in fT3 and T3 values observed in our study is reduced conversion from fT4 because of an abnormality in deiodinase activity. Since D1 is expressed in liver and kidneys, and D2 is expressed in CNS, it is possible that D1 is affected since TSH is not decreased as would be expected if D2 was involved. Liver and kidney function was analyzed as AST, ALAT, and creatinine at baseline and after 12 weeks. There were no significant changes during the study period for any of the analyses concerning liver and kidney function.

The weight loss of mean 4.6 (95% CI: 3.3–5.3) kg was regarded as a modest weight reduction not to be considered of relevance for thyroid hormone levels [17].

4.2. Seizure frequency

Diseases affecting the thyroid gland are known to have an impact on seizure threshold [18,19]. In this study, we were not able to find a correlation between the change in thyroid hormone levels and change in seizure frequency during the 12-week study period. This is to be expected as the hormonal changes were relatively modest, and the hormone levels stayed within the reference range. In patients with epilepsy, we know that even minor changes of hormone levels within the reference range can be of importance for the occurrence of seizures [19]. In a clinical setting, it was therefore interesting to analyze if the change of thyroid hormone levels after 12 weeks on MAD is correlated to a change in seizure frequency; however, we did not find such a correlation.

4.3. Antiseizure medications

Antiseizure medications can have an impact on endocrine functions, including the thyroid hormones. In particular, carbamazepine, a strong enzyme-inducing drug, may reduce fT4 values. These changes may be reversed when the drug is withdrawn [20]. Pharmacokinetic interactions between MAD and ASMs have been shown [21].

In our study, we could not find reliable differences between the two categories of drugs regarding their impact on thyroid hormones during the MAD treatment. Both categories were associated with a significant decrease in fT3 and T3 during the 12-week diet, which is in line with a recent report [8]. Those using NEIASMs had a significant increase in fT4 during the study period, and the increase was similar in those patients treated with EIAsMs although not statistically significant. Thyroid stimulation hormone and rT3 were nonsignificantly increased. As our patients had used ASMs for a long time before entering the study and their thyroid hormones were within normal limits at baseline, it is fair to assume that the changes we found in thyroid hormone values were diet-induced and not drug-induced.

4.4. Ketosis

Assuming that the changes in thyroid hormone levels were diet-induced, we would expect that the extent of changes would increase with increasing level of the ketone body [β-hydroxybutyrate]. However, we did not find such a correlation.
4.5. Limitations

We acknowledge that our study has several limitations. Ideally, there should have been a control group in the study and the number of participants should have been higher. Our study population is also skewed against difficult-to-treat epilepsies. However, despite these restrictions, we believe that major effects of the diet on thyroid functions should nevertheless have been revealed.

5. Conclusion

To conclude, this study indicates that treatment with MAD for epilepsy may bring about a fall in thyroid hormone levels. Although the clinical significance of such a fall is unclear, we suggest that clinicians should monitor thyroid hormone levels while treating adult patients with MAD. Especially, this could be relevant for those patients with low thyroid hormones (even within reference ranges) treated with ASMs that may lower thyroid hormones. A cumulative effect of ASMs, low basal thyroid hormone levels, and a ketogenic diet may therefore be of importance in case of thyroid hormones when treating patients with epilepsy with MAD.

Declaration of conflicting interest

Ellen Molteberg received a payment from Nutricia for a lecture held in December 2019. The other authors declare no conflict of interest.

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5. Conclusion

To conclude, this study indicates that treatment with MAD for epilepsy may bring about a fall in thyroid hormone levels. Although the clinical significance of such a fall is unclear, we suggest that clinicians should monitor thyroid hormone levels while treating adult patients with MAD. Especially, this could be relevant for those patients with low thyroid hormones (even within reference ranges) treated with ASMs that may lower thyroid hormones. A cumulative effect of ASMs, low basal thyroid hormone levels, and a ketogenic diet may therefore be of importance in case of thyroid hormones when treating patients with epilepsy with MAD.

Declaration of conflicting interest

Ellen Molteberg received a payment from Nutricia for a lecture held in December 2019. The other authors declare no conflict of interest.

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