Impact of intermittent fasting (5:2) on ketone body production in healthy female subjects

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Abstract

Intermittent fasting is a growing trend – used for weight loss and for increasing well-being. This nutrition strategy consists of fasting for short periods over the course of a day, or over the course of a whole week. During longer fasting periods, the main ketone body beta-hydroxybutyrate (βHB) plays an important role in energy supply. The 5:2 diet consists of eating normally on 5 days of the week and fasting for 2 non-consecutive days.

In this single-arm, non-controlled, interventional study, 19 healthy female subjects followed the 5:2 diet over a 7-day interventional period. 13 of the subjects completed the study.

Through the measurement of blood ketone (βHB) levels, it was demonstrated that there was a marked increase in ketone body levels in the blood during the aforementioned fasting period. During the second fasting day, adaptation was already observable. There was a reduction in βHB values and an increase in blood glucose concentration, together with a simultaneous reduction in the occurrence of unfavorable effects such as dizziness, shaking, tachycardia, and nausea.

Keywords: intermittent fasting, ketone bodies, beta-hydroxybutyrate, weight loss, prevention, energy restriction

Introduction

One of the greatest health policy challenges we currently face is the "obesity epidemic". Obesity is associated with various metabolic complications such as insulin resistance, dyslipidemia, hypertension, type 2 diabetes mellitus, and cardiovascular disease, all of which can be countered through weight loss. According to current recommendations, this can be achieved through moderate restriction of daily energy intake [1].

In recent years, there has been increasing discussion around periodic energy restriction in the form of intermittent fasting (IF) as an alternative nutrition strategy for weight management and management of metabolic dysfunctions [2–9]. Intermittent fasting involves a period of fasting that is repeated at regular intervals over the course of a certain amount of time – a day or a week [1].

In the case of time-restricted feeding (TRF), food intake is restricted to a defined time window during the day [10]. Here, the natural break from eating that occurs during sleep at night creates an overnight fasting (OF) period. Extending the OF period achieves the requirements for TRF [11].

The most well-known TRF method is the 16:8 method, in which the fasting period is 16 out of 24 hours, and eating is restricted to a period of 8 hours [10]. Alternate-day fasting (ADF) is fasting on every second day. Therefore, in the case of ADF, one day of fasting is immediately followed by one day of normal, unrestricted food intake. In the 5:2 method of IF, food intake is normal for five days of the week, and energy intake is drastically restricted on the remaining two days of the week (fasting) [10]. These diets were made famous through book

publications for the general market starting from the year 2013. The 5:2 Diet was made famous by Mosley ("The Fast Diet"), ADF was made famous by Varady ("The Every Other Day Diet"), and "The 2-day Diet" was made famous by Harvie [12–14].

The positive metabolic changes that occur in IF are attributed to the metabolic switch from mainly carbohydrate metabolism to mainly fat metabolism. Mobilization of free fatty acids from the adipose tissue increases. These fatty acids are partly used to form ketone bodies through ketogenesis. The ketone bodies can in turn be used directly by certain organs and can also be used by the brain as an alternative energy substrate instead of glucose after a period of adaptation.
Beta–hydroxybutyrate (βHB) is one of the main ketone bodies involved in energy supply [15, 16]. Since ketogenesis takes effect after only a short period of abstention from food, it is possible that the formation of ketone bodies also has a decisive impact on the positive effects of IF that have been demonstrated in studies. There is mounting evidence that βHB not only supplies energy, but also performs signaling functions, both on the cell surface and inside the cell, which affect factors such as gene expression, fat metabolism, neuronal function, and metabolic rate [17, 18]. These molecular signaling functions could have an impact on a range of human diseases such as type 2 diabetes mellitus and Alzheimer's dementia.

In order to better understand the metabolic situation in humans during short-term abstention from food, an interventional nutritional study was carried out to investigate the effect of IF on ketogenesis, using the 5:2 method as an example. The short-term change in βHB concentration in the capillary blood on repeated fasting days with complete energy restriction was chosen as the primary endpoint because this has not yet been investigated in studies on IF using the 5:2 Diet [3–6, 19–22].

Methodology

Study subjects
The study subjects (healthy subjects) were recruited through posters and through direct announcements in lecture halls at the Münster University of Applied Sciences. Positive responses were followed up with an online screening questionnaire to check eligibility according to the inclusion and exclusion criteria.
The inclusion criteria were age between 18 and 30 years, BMI within the normal range (18–25 kg/m²) and the exclusion of any pre-existing conditions such as metabolic disorders, serious illnesses, and psychiatric conditions including eating disorders. The exclusion criteria were defined as regular use of medication (with the exception of contraceptives), pregnancy or breastfeeding, inadequate health condition, special diets (vegan, low–carb, ketogenic), and excessive consumption of nicotine or alcohol.
Out of 41 potential subjects, 19 were able to be recruited for the study. Out of the 19 subjects who were enrolled, 13 completed the study (calculated drop-out rate = 32%). The subjects selected for the study were females with an average age of 21.5 ± 2.5 years, BMI 21.6 ± 1.6 kg/m². The reasons for study drop-out were time constraints (n = 3) or acute illness prior to the start of the intervention (n = 2). One subject discontinued her study participation on the first day of fasting due to feeling unwell (n = 1).

Ethical considerations
Prior to initiation of the study, the study was reviewed by the Ethics Committee of the Westphalia-Lippe Medical Association and the Westphalian Wilhelm University *[Ethikkommission der Ärztekammer Westfalen–Lippe and of Westfälische Wilhelms–Universität]* (2017-245-f–S). Checks were carried out to ensure that there was no dependent relationship between the subjects and the study staff. The subjects were only included in the study after being informed in detail about the study and after giving their written consent to participation (informed consent). During the study, there were no deviations from the study protocol that was submitted to the Ethics Committee.

Study design and study conduct
The subjects in this single–arm interventional study without a control group were instructed in how to carry out intermittent fasting according to the 5:2 method during the week of intervention. Prior to the start of the intervention, and after the subjects had been informed about how the study will be conducted and had signed the informed consent form, they were instructed in detail about the fasting method, including with regard to the devices that were to be used to measure the capillary blood parameters (βHB, glucose). Body weight was measured on the information day and after the entire intervention was complete, and height was measured once.
In accordance with the requirements of intermittent fasting, normal food intake was required for 5 days of the week, and complete abstinence from food was required for 2 days of the week. The fasting days had to be non-consecutive – they had to be separated by at least one non-fasting day. One important aspect was that the subjects were not allowed to eat anything after 8:00 p.m. on the day before a fasting day. In addition, the subjects were instructed to refrain from excessive exercise on the day before a fasting day

(e.g. jogging for longer than 30 minutes). On the fasting days, unrestricted consumption of unsweetened tea, water, and broth was allowed. Food intake was deliberately left unrestricted on the non-fasting days so that natural behavior after a day of strict fasting could be documented.

A 24-hour recall was carried out on the day after food intake to record the previous day's consumption. This was done either face-to-face or through an online interview via webcam. Self-measurement of the blood parameters (βHB, glucose) was carried out in the morning after getting up and in the evening before going to bed. Alcoholic beverages were to be avoided for the entire intervention week. For practical reasons, the total study population was randomized into two groups (double-blind), with no differences in study conduct.
◆ Figure 1 shows the course of the study.

24-hour dietary recall (24HR)
The 24HR records the subjects' consumption within the last 24 hours through targeted, repeated questions by the interviewer. The interviewers were all nutrition specialists (BSc or MSc in home and nutrition sciences). After the nutrition specialists had been given in-depth training, the interview was conducted in a standardized manner using a template (SOP). The protocols were evaluated using the EBISpro 2016 nutrition software. The daily energy requirement was calculated based on a PAL (physical activity level) of 1.6.

Capillary blood measurement
The Freestyle Precision Neo from Abbott (Witney, Oxon/UK) was used as the device for capillary blood measurement, along with the corresponding test strips for β-ketones and glucose (Abbott; Witney, Oxon/UK). Alcohol swabs were provided for pre-cleaning of the skin area.

Statistical evaluation
Prior to the study, a sample size calculation was performed based on the primary target parameter of βHB in the blood ($\mu1 = 0.2$; $\mu2 = 0.5$; $\beta = 0.05$; power = 0.9) using the GPower 3.1 program. The power analysis showed that the required sample size was 14 study subjects. In order to ensure statistical validity, the sample size was increased by 20% (expected drop-out rate) to 17 subjects. The statistical analysis was carried out using IBM SPSS Statistics 24 and Microsoft Excel 2016. In addition to descriptive statistical methods such as mean value, median and standard deviation, additional statistical inference methods were applied. Normal distribution was checked for using histogram analysis and established statistical tests (Shapiro-Wilk test, Kolmogorov-Smirnov test). In the case of normal distribution, the t-test was used for combined samples; in the case of non-normally distributed samples, the Wilcoxon signed-rank test was used to determine statistically significant differences.
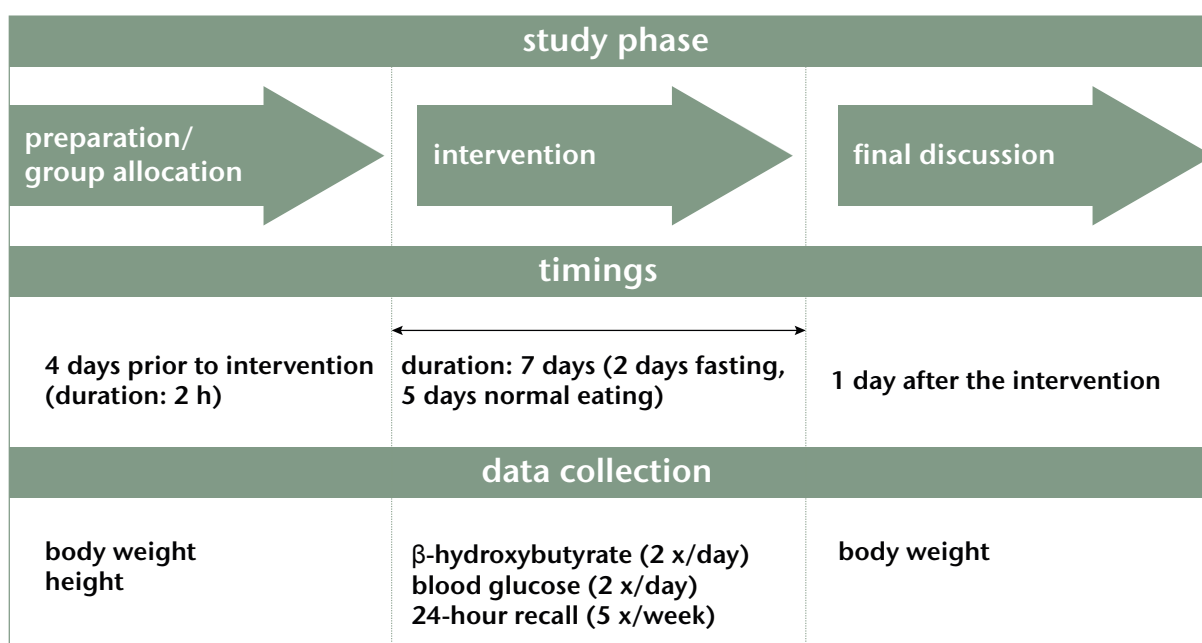

Fig. 1: **Diagram showing the course of the study with details of the phases, duration, and type of data collection**

Results

Duration of fasting and side effects

The duration of fasting on the two days of fasting was between 32 and 41.5 hours (37 ± 2.1 h), depending on the personal routine of the subjects. In one case, fasting was stopped early on the second day of fasting due to feeling unwell.

After the first day of fasting, 7 subjects reported mild to moderate side effects such as dizziness, shaking, tachycardia, headache, and nausea. The symptoms mostly occurred at night and on the morning after the fasting day. In addition, a strong feeling of hunger was more frequently reported on the first fasting day.

On the second fasting day, the subjects were already finding it easier to abstain from food, and the previously described physical symptoms did not reappear, except in one case. Three of the subjects experienced no problems during fasting days.

βHB measurement

The βHB values after overnight fasting were on average 0.14 ± 0.08 mmol/L on non-fasting days (NF), and 0.12 ± 0.09 mmol/L on fasting days (F; p = 0.195).

With the exception of the morning measurement, there were considerable differences between the measured values on the individual fasting days. On fasting day 1 (F1) the βHB concentration in the blood in the evening was 1.22 ± 0.74 mmol/L (min./max. = 0.4/2.9 mmol/L), and on the following morning it was 2.58 ± 1.34 mmol/L (min./max. = 0.4/4.3 mmol/L). The following fasting day, fasting day 2 (F2) showed significantly lower βHB values compared to F1 in the evening measurement (0.77 ± 0.33; min./max. = 0.2/1.4 mmol/L), and in the measurement on the following morning (1.14 ± 0.82; min./max. = 0.6/3.5 mmol/L). All measured increases in βHB on F1 and F2 were at a significant level in comparison to the morning fasting value (◆ Figure 2). Further significant differences were found in the evening measurement (p = 0.021) and the next morning measurement (p = 0.004) between the fasting days.

Glucose measurement

At the start of the fasting day, average blood glucose values of 85.0 ± 6.3 mg/dL were recorded. As with the measurement of ketone bodies, there was a difference between F1 and F2. In the evening of F1 (74.0 ± 7.2 mg/dL)
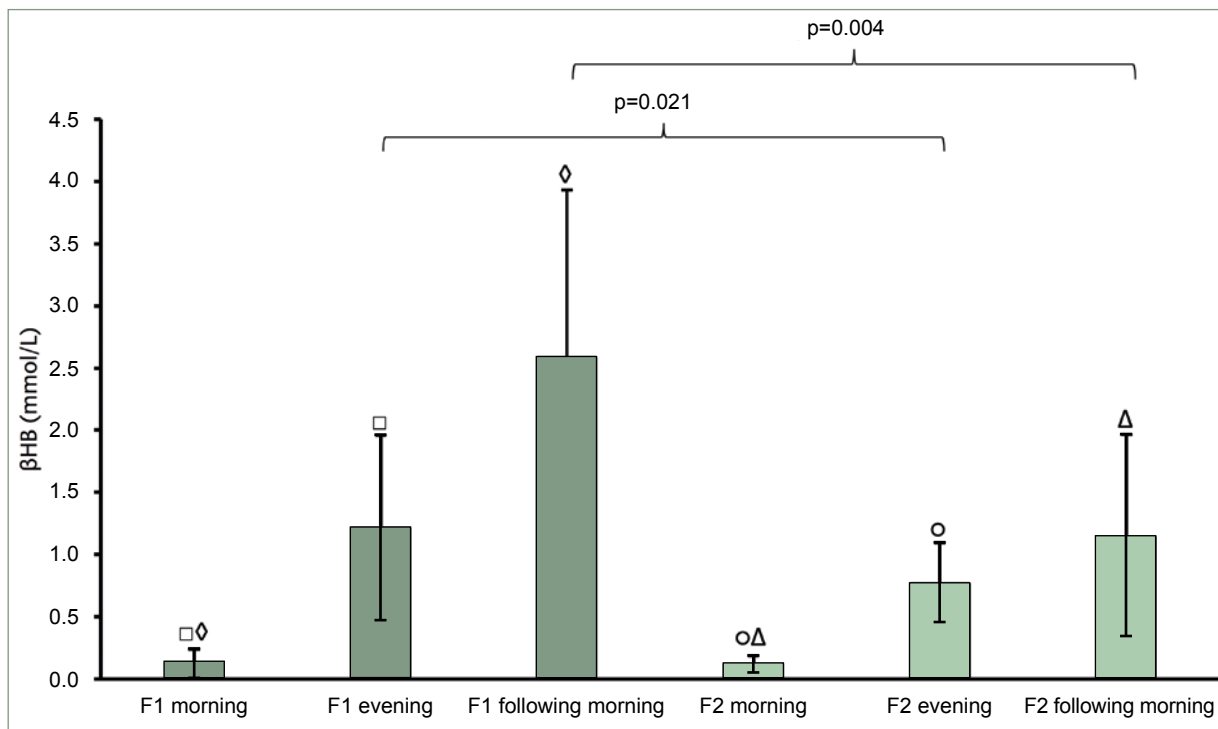

Fig. 2: **Average βHB concentrations (mmol/L) on the two fasting days (F1, F2) in the morning, in the evening, and on the morning after fasting**
□ F1 morning vs. F1 evening, p ≤ 0.001
◇ F1 morning vs. F1 following morning, p ≤ 0.001
○ F2 morning vs. F2 evening, p ≤ 0.001
∆ F2 morning vs. F2 following morning, p ≤ 0.001
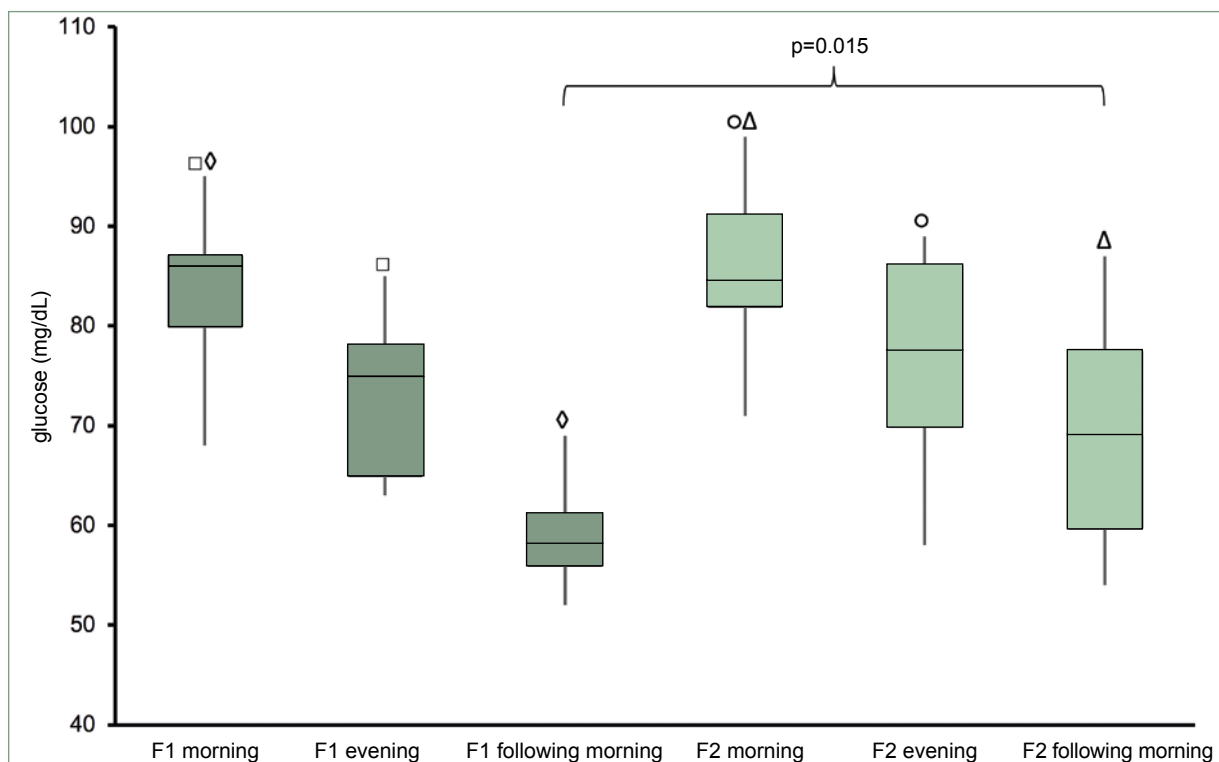βHB = β-hydroxybutyrate

Fig. 3: **Average blood glucose concentrations (mmol/L) on the two fasting days (F1, F2) in the morning, in the evening, and on the morning after fasting**
□ F1 morning vs. F1 evening, p = 0.001
◊ F1 morning vs. F1 following morning, p ≤ 0.001
○ F2 morning vs. F2 evening, p = 0.013
Δ F2 morning vs. F2 following morning, p = 0.001

the glucose concentration was slightly lower than on F2 (77 ± 9.6 mg/dL; p = 0.235). A significantly larger difference between F1 (59.0 ± 4.7 mg/dL) and F2 (69.0 ± 10.4 mg/dL; p = 0.015) was found the morning after the respective fasting day. A comparison of the morning measurement with the measurements from the evening and the following morning showed a significant reduction in blood glucose concentration on both fasting days (♦ Figure 3).

Body weight and energy intake
The calculated average energy requirement per day was 2,277 ± 76 kcal and actual intake was on average ~ 225 kcal (2,052 ± 312 kcal; p = 0.04) lower. The result was a weight loss of –0.8 ± 0.9 kg (p = 0.013) among the subjects during the 7-day intervention phase. In two cases, excess energy intake and an accompanying weight gain (of 0.2 and 1.5 kg respectively) was observed. Based on the 24HR, there was no strong increase in food intake after the fasting days. The overall evaluation of the 24-hour recalls showed a balanced in-

take of nutrients on the eating days, which was neither particularly low nor particularly high in carbohydrates or fat.

Discussion

The reported side effects occurred more frequently in the morning after F1, but either did not occur, or were very mild after F2. The blood glucose levels were significantly higher on F2 than on F1, but were still slightly lower than the values measured at the beginning of fasting (F1 in the morning, F2 in the morning). The reduced side effects could therefore be a result of the higher average blood glucose concentration, or a result of habituation.
It is known from the diabetes research that patients adapt to hypoglycemia [23, 24]. Furthermore, it was found that reactions to low blood glucose levels varied widely among individual subjects, which indicates that tolerance differs from person to person. One way to reduce side effects is to follow a 16:8 diet. However, this very likely leads to significantly lower ketone body values in the blood, in line with the measured value determined in this study after nightly fasting (~ 0.2 mmol/L). A further option is the use of the 5:2 Diet with 25% of normal energy intake being permitted on a fasting day.

The measured βHB values for overnight-fasting of 0.12 ± 0.09 mmol/L correspond to the values known in the literature, which vary between 0.07 and 0.27 mmol/L, depending on the study subjects selected [25, 26]. In addition to gender, weight, and especially the presence of metabolic diseases such as diabetes also play a role [15, 25]. These influences were greatly reduced through the targeted, uniform selection of the exclusively female study population.

Based on the premise that the physical condition of ketosis is present starting from a measured value of > 2 mmol/L, the data obtained shows that ketosis can be achieved at the start of the 5:2 diet (F1) in particular [27]. On the following fasting day (F2), such high values were observed only in isolated cases. The differences in βHB levels between individuals are known in the literature and they amount to approximately 30–50% [25, 28]. In the present study, deviations of 40–60% of the standard deviation were found.

> **Based on the data, it can be concluded that even short-term intermittent fasting can lead to an increase in ketogenesis, and even to the attainment of ketosis.**

It is interesting that there is a significant difference in βHB values between F1 and F2 – this points to rapid metabolic adaptation. According to the literature, a βHB concentration of 2–3 mmol/L is reached after 24–36 h [15]. The value on F2 falls far short of this. The reduced βHB concentration is associated with a simultaneous increase in blood glucose on F2. The increase in blood glucose concentration can lead to reduced production of ketone bodies, which explains the observation [29]. In order to better assess this effect, further studies on intermittent fasting and its impact on ketone body production are required.

In existing studies on intermittent fasting, there are hardly any mentions of the formation of ketone bodies [3–6, 9, 19]. Harvie et al. (2013) stated that in the groups that underwent intermittent fasting, there was a slight increase in the occurrence of short-term elevation of βHB levels in the blood after two days of fasting (max. 600 kcal per fasting day).

This paper does not provide the exact values [6]. Antoni et al. found βHB values of 0.56 ± 0.11 mmol/L in healthy, overweight or obese subjects after one day of complete energy restriction. Repeating the fasting state was not planned as part of the overall intervention [30]. A comparison of the results obtained showed a considerable difference, which could have been caused by the differences in weight (BMI < 25 vs. BMI > 25), age, nutritional behavior or differences in compliance. Further studies are required to better understand the effects on the formation of ketone bodies in different groups.

Weight loss was not planned as part of the scope of the intervention. The weight loss that occurred may have been due to the depletion of glycogen stores and the associated water loss and/or due to the energy deficit that was measured [15, 31, 32]. Due to the short intervention period of this study and its different focus, no statement can be made regarding the long-term effects of intermittent fasting on body weight. Studies with longer intervention periods and a primary focus on body weight indicate that continued weight loss takes place [3–6, 9, 19].

Limitations

The drop-out rate was 32% – markedly higher than the estimated rate of 20% that was calculated before the study. This effect is mainly attributable to the time of year in which the study took place (winter) and the limitations associated with this, such as the occurrence of colds. An additional factor is the lack of time that many people experience in the run-up to Christmas, which can lead to discontinuation of study participation, especially when there is no financial incentive.

Given the very large difference between the values, the shortfall in the sample size should be viewed as a non-critical limitation of the study. Due to the conservative calculation of the sample size, the expected results were exceeded. The calculated power (0.99) based on the measured values obtained exceeds the target and ensures the validity of the inductive statistical analysis.

The potential for factors that influence ketogenesis (such as a high-fat, low-carbohydrate diet or extensive exercise) to confound the results was minimized through the inclusion criteria and the instructions given regarding physical activity during the study [33, 34]. The uniformly female study population additionally reduced the confounding effect of gender differences (some studies report a higher rate of ketone body release in women) [32, 35, 36].

The 24HR method is not free of possible sources of error, so overreporting and underreporting by the participants is possible. Undereating and overeating are also known ways in which results may be confounded in this context. The deviation is in line with perceived desired behavior and mostly corresponds to the perceived expectations of the investigator.

The nutrient database itself is a further potential source of error because it may contain incorrect or incomplete data [37].

A standardized procedure was used to try to keep the sources of error during data collection to a minimum, but errors can never be completely ruled out. It should also be noted that the normal diet and dietary behavior of the subjects can only be inferred to a limited extent based on the short intervention period, which included two fasting days.

Although extensive training was given, the fact that the subjects performed the capillary blood sampling themselves may have led to incorrect use of the device or reading errors. The data stored in the measuring device was therefore subsequently compared to the standard protocols completed by a member of the study staff in order to minimize this source of error. Overall, the risk of measurement errors for the method used can be categorized as very low.

Conclusion

The parameters investigated demonstrate the basis of the effect that intermittent fasting (5:2) has on ketogenesis. On the fasting days, a clear increase was found in the level of βHB in the blood, and this was not found on non-fasting days, as expected. In order to gain a more detailed insight into the effects, the recording of data on hormones (glucagon, insulin), free fatty acids and/or filling of glycogen stores would be of interest. Further studies are required in order to better understand the effects of short-term intermittent fasting on metabolism and to interpret any possible positive effects.

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Conflict of Interest
The authors declare no conflict of interest.

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