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Dietary supplements based on the ketone body β-hydroxybutyrate

Market analysis and evaluation of ingredients of supplements used in the USA

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Abstract

The use of β-hydroxybutyrate (βHB) as a supplement to the everyday diet is a new development in the lifestyle supplement market. In the USA, the market is growing and the composition of the products varies greatly. The supplements are mainly postulated to be useful for providing energy, for weight loss, for increasing athletic performance, improving mental performance, and increasing the level of ketone bodies in the blood. Using βHB supplements in the form of a salt has the unfavorable effect of increasing intake of sodium, potassium, calcium, and magnesium. Depending on the salt composition used, it is possible for these supplements to cause the reference values to be exceeded by up to five times. Based on the currently available research, side effects cannot be ruled out. The available research currently supports the appetite-reducing effect of ketone bodies. Further research is required to confirm their effectiveness with regard to the other publicized areas of application, such as targeted fat loss, weight loss, and increased performance (cognitive and physiological). However, exogenous intake of ketone bodies could be advantageous in the clinical field, for example in supporting a medically necessary ketogenic diet and making it easier to follow.

Keywords: β-hydroxybutyrate, ketone bodies, supplements, market analysis, ketogenic diet

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Introduction

The original founder of the low-carb diet is William Banting, who published his "Letter on Corpulence, Addressed to the Public" in 1865. In this letter, he criticized the increasing obesity of the population. In his view, the cause was certain foods such as bread, butter, milk, potatoes, sugar, and beer. The resulting meat-, fish-, and alcohol-heavy diet bears little resemblance to modern habits [1]. In the 1970s, Dr. Atkins' book launched a new trend in low-carb, high-fat diets (LCHF or HFLC) [2]. The first two books sold 12 million copies and achieved cult status [3].

In more recent years, there has been a continuous growth in low-carb diets. The health merits of various versions of the diet with different fat, protein, and carbohydrate contents are the subject of much discussion. Some versions are diets that closely correspond to a ketogenic diet and contain less than 50 g of carbohydrate per day (very low-carb, high-fat – VLCHF) [4, 5]. In the U.S. News Diet Rankings, the Atkins, Eco-Atkins and Keto diets were shortlisted by 24 experts for the categories of best overall diet, best for weight loss, and best for rapid weight loss. The rating was generally better for the Atkins-based diets. In the category for rapid weight loss, the ketogenic diet (kD) even came 13th. On the other hand, the kD only achieved 39th place in the overall assessment [6–8].

In stark contrast to this trend, the kD is highly relevant in the field of nutritional therapy. The positive effects of the traditional kD were described in epilepsy patients as early as 1921, and it is still practiced in a similar form today [9, 10]. In addition to drug-resistant epilepsy, the classic indications for the kD also include some rare metabolic diseases such as pyruvate dehydrogenase (PDH) deficiency and GLUT1 deficiency. Its use in other metabolic diseases such as glycogenosis (Type III, V, and VII) and complex 1 mitochondrial respiratory chain deficiency is also a current subject of discussion [11, 12].

The kD is based on the formation of ketone bodies from acetyl-CoA, which is formed by the breakdown of fatty acids. In this context, ketone bodies means acetoacetate (AcAc), β-hydroxybutyrate (βHB), and acetone, although acetone does not play a significant role in terms of providing energy [13, 14].
There are three ways to trigger ketosis – meaning an increase in the level of ketone bodies in the blood. These are fasting (hunger), exercise, or a very high-fat diet with simultaneous reduction of carbohydrate intake [15–17]. In all three cases, the glucose deficit and the stimulation of lipolysis trigger the production of an alternative source of energy, which is particularly important for the brain. This alternative source of energy is the ketone bodies, and especially βHB , which is the most abundant among them [18]. In order to significantly increase the level of ketone bodies in the blood (> 2 mmol/L), 60–90% of daily energy intake (E%; Low Glycemic Index Treatment [LGIT] vs. classic kD 4:1) need to come from fat [19]. Generally, it is assumed that in adults, a carbohydrate intake of over 50 g per day will not produce ketosis, or will only do so to a very limited extent [20]. The fact that this diet is so different from a normal balanced diet leads to problems with compliance, which in turn leads to treatment discontinuation [21, 22].

Back in the 1980s, exogenous intake of ketone bodies had already caught the attention of the field of sports medicine [23, 24]. Later on, possible medical applications started to be discussed and compassionate use treatments were carried out using sodium βHB in various rare metabolic diseases, such as Multiple Acyl-CoA-Dehydrogenase Deficiency (MADD), PDH deficiency, and hyperinsulinism [25–27]. Among the benefits described were the supporting and compliance-increasing effects of concomitant treatment with exogenous ketone body products while on a ketogenic diet [26]. In recent years, several publications on ketone body salts have been published in the wellness and lifestyle sector. In these publications, the main focus is on sports applications and the health benefits of opting for a ketogenic diet or choosing to supplement with ketone bodies themselves [28–30]. It should be noted here that a ketotic metabolic state was a normal condition for the vast majority of human history ("movement guaranteed, food intake uncertain"), and it only began to disappear over the last 200 years due to increasing sugar consumption, higher energy intake and changes in lifestyle ("movement uncertain, food intake guaranteed") [31, 32]. The use of ketone bodies as nutritional supplements is a new and interesting development on the global market.

Increasing general and scientific interest in the kD has led to new areas of application being opened up. In addition to the classic applications of weight loss and performance enhancement, there is also much discussion about positive effects when used in cancer or neurodegenerative diseases (dementia, Alzheimer's, etc.) [33]. In terms of trend diets using ketone bodies or the kD, the appetite-reducing effect is one of the most commonly cited advantages [34].

The kD appears to have great market potential. At present, there is no data on the size of the market for the kD and related products. Alongside the supplements mentioned above, during the kD, it is also possible to self-track by measuring general vital parameters, blood values (βHB, glucose), and the concentration of acetone in the exhaled air [35, 36].

The following article will provide an overview of the ketone body supplements based on βHB salts available on the US market, and will then weigh up the risks and benefits. At present, no such evaluation is available – none that can provide an overview of the market situation, its development, and the extent of the current "keto trend".

Methodology

To compile the dataset, the largest online mail order company, Amazon.com, was searched for products falling under the keywords "hydroxybutyrate" and "beta hydroxybutyrate". All of the products displayed that belonged to the category of foodstuffs in the broadest sense were viewed and listed. The data collection period was four weeks and ended on 20 February 2018. In order to ensure that the data was entered correctly, data entry was done by two people. In the case of several pack sizes, the medium-sized pack was listed. Different flavors or formulations with different ingredients (e.g. with or without caffeine) were entered into the dataset as separate products.
The following information was gathered and used for the evaluation: the product name, manufacturer, quantity, price, serving size, ingredients (macro and micronutrients, βHB), additives, other ingredients (sweeteners, plant extracts, etc.), consumer ratings and the main advertising statements.
For the statistical calculation, descriptive statistical methods (mean value, median, standard deviation) were carried out using the programs Microsoft Excel 2016 and IBM SPSS Statistics 24. For nominal data, such as advertising statements, the number of them was determined and compared with the total quantity of products.

N = 86	Price ($)	Price per portion ($)	Pack size (g)	Portion size (g)	Portions per day
Mean	50.24	2.99	316.7	17.3	2.8
Median	49.95	2.80	240.0	15.0	3.0
SD	23.12	1.52	154.8	7.2	0.4
Min.–Max.	12.95–154.97	0.40–9.96	57.3–825.0	1.0–59.0	2.0–3.0

Tab. 1: **Price, pack size, and recommended daily portion amount of the recorded βHB salt products**
Mean, median, standard deviation [SD], minimum [min.], maximum [max.]

Results

Products, flavors and presentation

A total of 86 products based on the ketone body βHB made by 49 different manufacturers were identified. The majority of these (94.2%) came in powder form, to be used for making a drink. The remaining products were a liquid, a capsule formulation, two bars, and a spray for spraying directly into the mouth.

The manufacturers varied widely in terms of the selection of flavors they offered. There were 40 different flavorings in total, from classic flavorings such as orange to variations such as cucumber and melon, blue raspberry or tropical frost. Some products used no flavorings or additives whatsoever, and offered pure βHB salt.

One aspect that stood out in terms of product design was the gendering of the products. Some of them clearly targeted a particular gender (male/female), using a corresponding selection of flavorings (e.g. pink lemonade). The Amazon ranking system of 1 to 5 stars (5 stars = highest possible rating), showed good customer satisfaction and high popularity with an average of 4.0 ± 0.7 stars (median: 4.0; min./max.: 1–5) and 199 ± 390 overall ratings (median: 38; min./max.: 1–1.543).

Pack size and price

The average pack size of the products was 316.7 ± 154.8 g. The wide variation in the size of the packaging units is due to the fact that some products came in the form of large packs, and some came as formulations in sachet portions. One pack had a price of $50.24 ± 23.12 (median: $49.95), corresponding to $2.99 ± 1.52 (median: $2.80) per serving or $0.22 ± 0.27 per gram of final product. The most expensive supplement found had a price of $154.97 for a pack size of 663 g. One portion as recommended by the manufacturer corresponds to 17.3 ± 7.2 g of the ready-to-eat mixture, distributed over 2.8 ± 0.4 portions per day (◆ Table 1).

Composition of the products

The most abundant ingredient in terms of volume was βHB, which was present in the form of a racemate, i.e. a mixture of the D and L forms of βHB. The information on the packaging referred to the total salt content, which means this information included the cations that were present. The average quantity of βHB salt present in the products was 11.4 ± 2.7 g. In 50% of cases, a combination of Na-, Ca- and Mg-βHB was used. The next most common combination was a mixture of four HB salts (Na, Ca, Mg, K), which accounted for 18.6% of cases, and then a mixture of Na- and Ca-βHB, which accounted for 9.3% of the total number of products. All other possible combinations and formulations using individual salts were less well represented (1.16–5.8%).

Including the use of individual salts, there were 10 different combinations of βHB salts. The most commonly used salt, sodium salt (91.9%) was used with 860.3 ± 358.5 mg sodium per portion on average, and the second most common element, calcium, was used with an average quantity of 824.1 ± 348.6 mg per portion. The high standard deviations and corresponding minimum–maximum val-

N = 86	Sodium (mg/portion)	Potassium (mg/portion)	Calcium (mg/portion)	Magnesium (mg/portion)	βHB (g/portion)	Energy (kcal/portion)
Number of products (n)	79	31	73	61	79	66
Percentage	91.9	36.1	84.9	70.9	91.9	76.7
Mean	860.3	501.7	824.1	198.6	11.4	40.2
Median	908.0	99.0	850.0	170.0	11.7	37.5
SD	358.5	871.0	348.6	137.2	2.7	27.2
Min.–Max.	0–1 611.0	0–3 800.0	0–1 635.0	0–722.0	0.1–15.0	0–140.0

Tab. 2: **Overview of the composition of ketone body supplements per portion (serving size) using the number of products**
Percentage, mean, median, standard deviation [SD], minimum [min.], maximum [max.]

ues demonstrated the flexibility of the formulations (βTable 2).
In almost all products, the energy per portion came mainly from βHB itself and was 40.2 ± 27.2 kcal/portion. In a few exceptional cases, there was a higher total energy content (max. 140 kcal), which was mainly due to the addition of fats such as medium-chain triglycerides (MCT).

The extrapolation to a three times daily intake of the products yielded a daily intake of 2,580.9 mg Na, 1,505.1 mg K, 2,472.3 mg Ca and 595.8 mg Mg for the mean value. Using the maximum determined values in the calculation yielded an even higher cation load (◆ Table 3). Comparing these values with the D-A-CH reference values and the Tolerable Upper Intake Level (UL) of the Institute of Medicine (IOM) showed that, except in the case of the mean value of K, the recommended values were markedly exceeded. This deviation from the recommendations was particularly noticeable when considering the possible maximum values of minerals. In the case of alkali metals (Na, K) the intake would be three times higher, and in the case of alkaline earth metals (Mg, Ca) as much as five times higher (β Table 3). Regular intake is therefore associated with a risk of electrolyte disorders and of developing metabolic alkalosis.

In terms of the other ingredients, most of the mixtures had a simple composition, made up of flavorings, stevia, citric acid, or other additive acids. These were therefore also the additives most commonly found in the products. The sweeteners used showed a clear trend towards natural alternatives such as stevia (70.9%) and monk fruit (9.3%). Even the thaumatin that was used (3.5%) came mostly from natural sources. Acesulfame potassium salt was used in only one product. In addition to the use of sugar alcohols as an additive (5.8%) (erythritol for instance), sucralose (2.3%) was also used as a sweetener.
Dyes or anti-caking agents were not present in > 70% of the salt mixtures and thickeners were only used in isolated cases (10.5%). Supplementary amino acids, vitamins, MCTs, or caffeine were contained in 15–20% of the products. The use of these substances was mostly based on customer demand, i.e. aimed at targeted use by athletes or use in the wellness/fitness sector. All other ingredients, such as dietary fiber or L-carnitine, were present in a maximum of 10.5% of products (◆ Figure 1).

Manufacturers' advertising statements

The evaluation of the main advertising statements from the manufacturers showed a clear trend. Advertising focused mainly on the provision of energy through βHB intake (70.9%), and this was closely followed by statements about weight loss and fat loss (67.4%). An increase in mental and cognitive performance was also frequently mentioned as a benefit of intake (50.0%).
Advantages in terms of the implementation of a ketogenic diet, such as rapid ketosis and an increase in levels of ketone bodies in the blood, indicated the direct advantage of the products. These statements were usually supported by a label such as "keto friendly" to illustrate the benefit of intake while on a kD. Approximately 35% of the products evaluated referred to an increase in performance and endurance while doing sports or workouts (◆ Figure 2). For all of the supplements, there was a notice (usually in small print), stating that the statements had not been reviewed by the Food and Drug Administration (FDA).

Discussion

Current research, uptake, and sport

Within the current trend, there are many products and product innovations based on βHB salts. The rapidly developing market is focused primarily around lucrative areas of application, such as obesity, sport, or mental performance. However, the selection of

N = 86	Sodium	Potassium	Calcium	Magnesium
Mean (mg/day)[a]	2580.9	1505.1	2472.3	595.8
Maximum (mg/day)[b]	4833.0	11400.0	4905.0	2166.0
D-A-CH-reference values[b] (mg/Tag)	1500.0	4000.0	1000.0	400.0
Tolerable Upper Intake Level (UL), IOM[c] (mg/day)	2300.0	4700.0	2500.0	350.0

Tab. 3: **Table showing the intake of minerals (Na, K, Ca, Mg) in the case of three times daily intake of the corresponding βHB salt, compared to the D-A-CH reference values and the UL of the Institute of Medicine (IOM) in mg/day**
[a] Calculation based on three times daily intake of the product
[b] Adults > 19 years
Mg = use of the maximum available level (male, 19–25 years)
Na, K = adequate intake
Ca, Mg = recommended intake
[c] Adults (19–50 years); no UL available for K, here the Adequate Intake (AI) was used

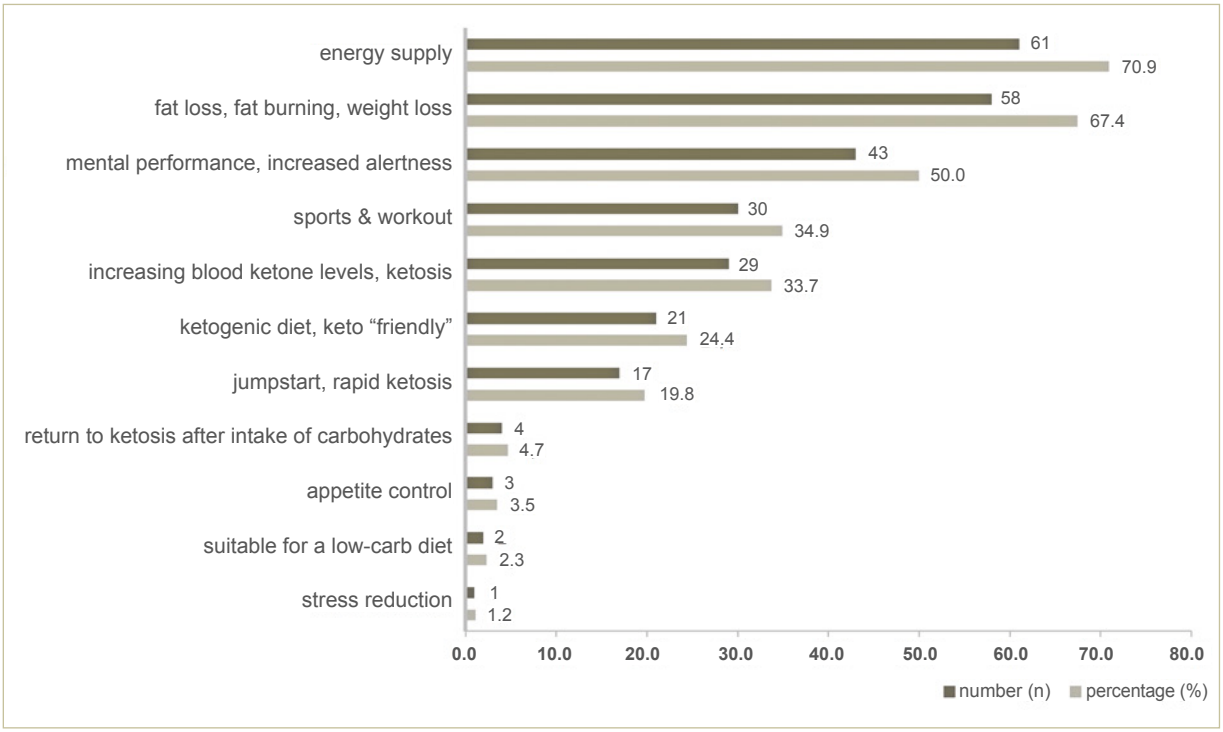

Fig. 1: **Overview of the main advertising statements of the manufacturers of βHB salt supplements**
Graph showing the number of times each was mentioned (multiple mentions possible) and percentage out of all products

studies available is rather disappointing. Human studies often concentrate on the area of sport or metabolic utilization after a single dose or one-day intake of a βHB salt dissolved in water. In all cases, an increase in blood levels of D-βHB was found in healthy, normal-weight study subjects or athletes [28–30]. For an intake of 282 mg/kg of a ketone body salt based on Na-K-βHB, a maximum increase to 1.0 ± 0.1 mmol/L βHB in the blood within approx. 1.5 hours was determined [30]. In further studies with 300 mg/kg and 11.7 g as the total portion, maximum values from 0.6 to approx. 0.8 mmol/L βHB were determined [28, 29]. According to the data, exogenous intake of ketone bodies can increase the D-βHB level in the blood, thus allowing a supply of energy. An increase in performance in sport could not be demonstrated for βHB salts. On the contrary, a decrease in performance was observed, although there was increased fat oxidation [29, 28]. There are no long-term studies in healthy volunteers available.

Rare metabolic diseases

The only field in which there has been long-term experience with the intake of ketone body salt (Na-βHB) is the field of rare metabolic diseases. The use of exogenous ketone bodies is an important form of treatment, especially in the case of MADD, in which the breakdown of fatty acids is completely defective.

A clear improvement in health and/or improvement of disease-related accompanying symptoms, such as leukodystrophy (= progressive degeneration of the white matter of the nervous system), has been reported in various case reports. In this field, up to 2.6 g of the sodium salt per kg of body weight was used. The longest published period of administration is three years and no individual case description refers to possible side effects [25, 37, 38].

The same applies for an individual medical treatment in two patients with hyperinsulinism, in which up to 4 g/kg body weight per day was used. No adverse effects were documented here either [27]. However, in the authors' own experience, disturbances in the electrolyte and acid-base balance can be expected starting from a daily dose of 1 g of ketone body salt per kg body weight.

Ketone body salts are also of medical interest for diseases that require a ketogenic diet. The fact that they can be used as a supplement or as a supporting aid for a diet, or to increase ketosis through exogenous intake of ketone bodies is of interest. In the case of PDH deficiency, it has already been demonstrated that the use of ketone body salts can achieve a clinical improvement of the initial situation, while at the same time simplifying the kD [26].

Mental and cognitive performance

The mental and cognitive performance enhancement aspect mainly originates in research on neurodegenerative diseases. It has been

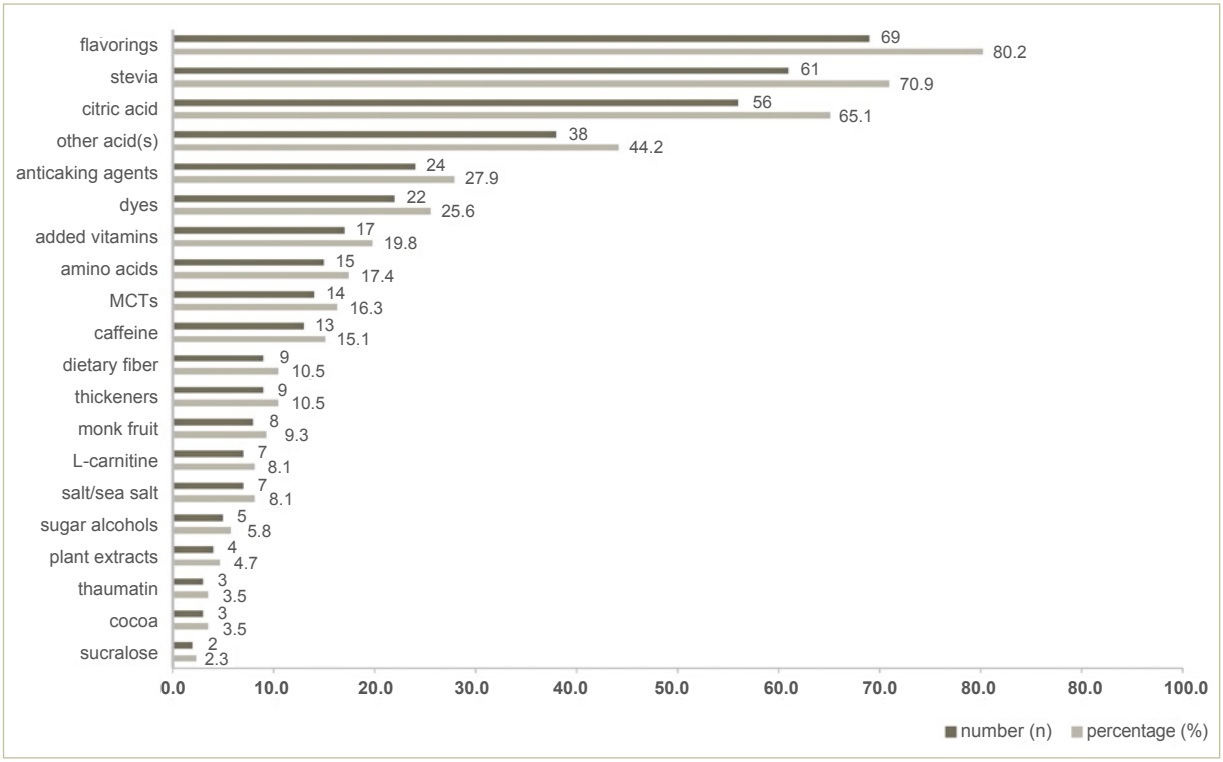

Fig. 2: **Table showing the number and percentage of products with other ingredients in addition to the main ingredient βHB salt**
MCT = medium chain trigycerides

shown that an increase in ketone body levels in the blood caused by MCTs or a ketone supplement can contribute to an improvement in cognition [39, 40]. Further controlled studies with the respective substances must be carried out in order to confirm efficacy in this area of application.

Obesity

The use of a kD and the effect of ketone bodies in the case of overweight and obesity is highly controversial. Depending on the evaluation in question, the kD was either found to have a clear advantage for weight loss, or no difference was found compared to other diets [4, 5]. However, the current consensus is that kD reduces appetite and that users feel less hungry compared to carbohydrate-based normal diets. Ketosis is considered to be a possible explanation for this [34].

Critical mineral content

When using βHB salts, a particularly critical consideration is the high cation load, i.e. the absorption of minerals (Na, K, Mg, Ca), which in some cases markedly exceeds the established reference values (see comparison with reference values ◆ Table 3). As the supplements are used in addition to the diet, it can be assumed that the daily intake of minerals is significantly higher.

A markedly increased Na intake is associated with a variety of problems, such as increased blood pressure, cardiovascular diseases, and effects on the calcium balance in the body. The negative effects of excessive salt consumption are well known today and extremely high intake is not recommended [41–43]. In the case of increased calcium intake in particular, one of the long-term consequences can be an increased risk of kidney stones [41, 44]. An increased calcium intake can also lead to gastrointestinal side effects such as diarrhea, and it is also suspected that it may be associated with increased cardiovascular risks [45, 46].

Discussion is ongoing as to whether the two divalent alkaline earth metals Ca and Mg work against each other as antagonists. The mutual inhibition of absorption that is the subject of the discussion has the potential to cause mineral deficiencies and should not be ignored [47]. Mg alone can cause diarrhea in high doses. A toxic effect with hypotension and muscle weakness is only possible if the specified limits are exceeded to an extreme extent (e.g. by 10 times) [48].

The effect of higher (or in this case, very high) doses of potassium is not clear. However, positive aspects such as blood pressure reduction and improved control of the glucose balance, i.e. reduction of the risk of type 2 diabetes mellitus, are fre-

quently reported for an adequate or slightly increased supplementation of potassium [49, 50]. Continuous supplementation of 2–3 g potassium per day showed no effect on the heart rate [51]. The occurrence of hyperkalemia (> 5 mmol/L) is unusual in healthy adults due to good renal excretion, even at higher intakes. In individuals with kidney problems, increased intake is a critical factor and should therefore be avoided [52].

Racemate

An additional limiting factor of the salt mixtures is the use of the racemate. Only the D-form can be sufficiently metabolized by the human body. The L-βHB is the non-physiological form and is therefore not produced by the body itself. Some animal tests have indicated that L-βHB can be converted into active ketone bodies (D-βHB) and fatty acids, but only to a very limited extent [53, 54]. In humans, a significantly lower rate of metabolization and significantly higher renal excretion of L-βHB was observed after taking a racemic βHB salt [30]. Based on the available research, it must be assumed that the conversion of L-βHB is minimal.

According to current knowledge, increased intake does not represent any particular advantage, but rather a disadvantage, because 50% of the ingested product cannot be effectively used by the organism. However, the actual normal value for human is still unclear and requires further investigations into the utilization of the L-enantiomer.

Second generation: Ester compounds

As early as spring 2018, the "second generation" of ketone body supplements appeared on the US market. The trend is moving towards salt-free ester compounds, which still refer to the main ketone body βHB [55].

Investigations into the safety and tolerability of the ester showed gastrointestinal side effects such as diarrhea, nausea and vomiting only at a very high dose of 2.1 g/kg [56]. The ester tastes bitter and the taste needs to be masked in order for the product to be accepted by consumers.

When directly compared with a ketone body salt, the combination of βHB and 1,3-butanediol leads to a significantly higher increase in D-βHB in the blood (1.0 ± 0.1 vs. 2.8 ± 0.2 mmol/L). This is mainly due to the enantiomerically pure formulation of the ester, i.e. the use of the pure D-form.

Despite the absence of accompanying salts, there were no clear differences in electrolyte levels after a single dose. The only difference was in the acid-base balance. The salts led to an increase in the pH value, the esters to a reduction. It was also possible to achieve ketosis by using a ketone ester alongside normal food. Overall, the ester led to a higher and more stable increase in D-βHB levels in the blood [30].

This emerging alternative offers some advantages over the βHB salts and could compete well on the market. Based on the information above as a whole, gastrointestinal side effects, in particular diarrhea, are to be expected in the case of excessive intake of ketone body salts.

Dosage form and price

The dosage form, in particular the dosage form of a drink, is comprehensible and is in part attributable to the fact that it is easy to optimize the taste of a drink, and due to the fact that the product is diluted by dissolving it in water. Some ketone body salts themselves have an unpleasant salty or bitter taste, which needs to be masked by flavorings, sweeteners and acids. The reason behind the often very simple composition of the products at present could be due to the rapid entry to market. Formulations such as the spray make little sense in practice in light of the rather high intake level of βHB required. In future mixtures in particular, an increase in additives is to be expected, as this will be needed to ensure differentiation from the competition.

The market volume of the products is unclear at present. Overall, the price of the products appears to be stable and high, leading to high costs of approx. $80–160/month in the case of a once daily intake, depending on the supplement chosen. In the case of recommended three times daily use, costs of above $200 per month (range ~ $80–500/month) are quickly reached.

Limitations

The market analysis is subject to certain limitations. Due to the fact that this is a constantly growing market and due to the many online avenues through which dietary supplements can be procured, it is not possible to provide a complete overview. In particular, products that are only sold via the manufacturer's own online store are not included in this overview. It should be assumed that the actual range of βHB supplements available on the market is much larger. Furthermore, the information provided by the manufacturers regarding the ingredients has not been checked extensively (e.g. through laboratory analyses), and therefore errors cannot be ruled out.

In some cases, the declarations were illegible or poorly displayed, and therefore it is possible that there may have been some under-reporting in the ingredient data. Entry of incorrect data was reduced through the use of the four-eyes principle.

Conclusion

In summary, dietary supplements based on the ketone body β-hydroxybutyrate represent an interesting development. A new development

of the market and the associated research is providing much new information about ketone bodies. However, βHB should be used with caution because the side effects, such as gastrointestinal symptoms, can only be assessed to a limited extent at present. In particular, no statements can be made regarding the potential long-term effects. An overall evaluation of the individual advertising statements (such as those regarding use in neurodegenerative diseases and weight reduction), shows that further research is needed in many areas before the possible effects of βHB can be said to be proven.

The appetite-reducing effects have been confirmed in the last few years. In terms of use in the medical sector, the development of this areas as a whole may open up new options for nutritional therapy, and it therefore merits further investigation. Use as an addition to the kD is an interesting aspect that could significantly simplify and improve the everyday nutritional composition of the diet, e.g. by using smaller amounts of fat in the kD.

Conflict of interest
The authors declare no conflict of interest.

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