



trumacro™ Ketogenic BHB

D,L-Beta-Hydroxybutyrate Mineral Salt Blend

PRODUCT INFORMATION

trumacro™ Ketogenic BHB Unflavored, 500g bulk powder

trumacro™ Ketogenic BHB Orange Flavor, 500g bulk powder

Manufactured in the U.S.A. in a cGMP facility for Disruptive Nutrition, LLC, Durham, North Carolina, U.S.A. www.trumacro.com.

DISPENSE BY PRESCRIPTION OR PHYSICIAN ORDER

trumacro™ Ketogenic BHB is a medical food for the dietary management of a patient requiring a source of ketone bodies, such as certain inborn errors of metabolism and genetic disorders (fatty acid oxidation disorders; glycogen storage disease type III; 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency; congenital hyperinsulinism). Not intended to be used as a sole source of nutrition. trumacro™ Ketogenic BHB is to be used under the supervision of a licensed health care practitioner.

DESCRIPTION AND MEDICAL FOOD STATUS

trumacro™ Ketogenic BHB is a medical food containing a mixture of *D,L*-Beta-Hydroxybutyrate mineral salts. trumacro™ Ketogenic BHB is used for the clinical dietary management of patients requiring a source of ketone bodies such as certain inborn errors of metabolism and other genetic disorders. trumacro™ Ketogenic BHB is to be used only under medical supervision. trumacro™ Ketogenic BHB has been developed, labeled and should be used in accordance with the statutory and the Food and Drug Administration's (FDA's) regulatory definition of Medical Foods. The Orphan Drug Act of 1988 defines a medical food as "a food which is formulated to be consumed or administered enterally (or orally) under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation,"[1]. Medical foods are specially formulated foods intended for the dietary management of certain medical conditions with distinctive nutritional requirements, which cannot be managed by altering a normal diet. Medical foods must be used under the supervision of a licensed health care practitioner.

trumacro™ Ketogenic BHB is a ready to use powder providing a concentrated source of the ketone body beta-hydroxybutyrate. Ketone bodies, including beta-hydroxybutyrate, are naturally occurring metabolites used as fuel in the body for muscle, heart, and brain. The benefits of using trumacro™ Ketogenic BHB include a balanced mineral profile, variable dosing, mixability with water and foods, palatability (flavored), elevated nutritional ketosis, and the provision of an alternative energy source to carbohydrates, proteins, and fat.

INGREDIENTS

All ingredients in trumacro™ Ketogenic BHB are Generally Recognized as Safe (GRAS) as defined under the Food and Drug Administration guidance [2]. Ingredients are considered GRAS either because their safety had been established by a long history of use in food; or by virtue of the nature of the substances, their conditions of use, and the information generally available to scientists.

Macronutrient Profile

trumacro™ Ketogenic BHB does not contain fat or protein. trumacro™ Ketogenic BHB unflavored contains no carbohydrates, but there is a small amount in the trumacro™ Ketogenic BHB Orange Flavor (<3g per 100g). The formulations provide fuel in the form of beta-hydroxybutyrate, a naturally occurring ketone body used by muscle, brain and heart. Each gram of pure *D,L*-Beta-Hydroxybutyrate provides 2 kcal of energy, which correlates to 1.5 kcal per gram of unflavored trumacro™ Ketogenic BHB, and 1.1 kcal per gram of flavored trumacro™ Ketogenic BHB.

D,L-Beta-Hydroxybutyrate

trumacro™ Ketogenic BHB contains mineral salt forms of the biologically important ketone body, beta-hydroxybutyrate. trumacro™ uses a racemic mixture, *D,L*-beta-hydroxybutyrate. trumacro™ uses a blend of mineral salts (sodium, calcium, and magnesium) in order to deliver the maximum amount of beta-hydroxybutyrate while minimizing the total content of any one mineral. These minerals are crucial electrolytes and may be important when a ketogenic diet is used in conjunction with trumacro™ Ketogenic BHB.

Potassium Citrate

Kidney stones are a potential side effect of the ketogenic diet in children. Consuming citrates has been shown to reduce the likelihood of stone formation. trumacro™ Ketogenic BHB Unflavored contains potassium citrate at 75 mEq per 100g. trumacro™ Ketogenic BHB Orange contains 60 mEq per 100g.

Silicon Dioxide

Silicon dioxide is used in small amounts to prevent clumping of trumacro™ Ketogenic BHB due to the humid conditions that can occur during home use.

Flavoring

Ketogenic BHB Unflavored does not contain any ingredients intended to flavor or mask the flavor of the individual ingredients. Therefore, trumacro™ Ketogenic BHB Unflavored is not recommended for oral consumption, but can be used for enteral nutrition. trumacro™ Ketogenic BHB Orange contains natural flavors and is recommended for oral feeding. These flavors contribute less than 3g of carbohydrates per 100g of formula.

Sweeteners

trumacro™ Ketogenic BHB Unflavored does not contain any ingredients intended to sweeten or mask the flavor of the individual ingredients. Therefore, trumacro™ Ketogenic BHB Unflavored is not recommended for oral consumption, but can be used for enteral nutrition. trumacro™ Ketogenic BHB Orange contains the sugar alternative, stevia extract, and is recommended for oral feeding.

Colors

trumacro™ Ketogenic BHB Unflavored and trumacro™ Ketogenic BHB Orange do not contain any ingredients intended to color the formulations.

NUTRITION FACTS AND COMPLETE INGREDIENT LISTING

trumacro™ Ketogenic BHB, Unflavored	trumacro™ Ketogenic BHB, Orange
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Nutrition Facts	
500 grams per container	
Nutrients	Per 100 grams
Calories	220
Total Fat	0g
Saturated Fat	0g
Trans Fat	0g
Cholesterol	0mg
Sodium	7480mg
Total Carbohydrates	0g
Dietary Fiber	0g
Total Sugars	0g
Includes 0g of added sugars	0g
Protein	0g
Calcium	3740mg
Potassium	3160mg
Magnesium	1040mg
goBHB® Free D,L-Beta-Hydroxybutyrate	66g

Nutrition Facts	
500 grams per container	
Nutrients	Per 100 grams
Calories	200
Total Fat	0g
Saturated Fat	0g
Trans Fat	0g
Cholesterol	0mg
Sodium	6370mg
Total Carbohydrates	3.0g
Dietary Fiber	0g
Total Sugars	0g
Includes 0g of added sugars	0g
Protein	0g
Calcium	3170mg
Potassium	2670mg
Magnesium	890mg
goBHB® Free D,L-Beta-Hydroxybutyrate	56g

Ingredients: sodium *D,L*-beta-hydroxybutyrate, calcium *D,L*-beta-hydroxybutyrate, magnesium *D,L*-beta-hydroxybutyrate, tripotassium citrate, silicon dioxide.

Ingredients: sodium *D,L*-beta-hydroxybutyrate, calcium *D,L*-beta-hydroxybutyrate, magnesium *D,L*-beta-hydroxybutyrate, tripotassium citrate, citric acid, malic acid, natural flavors, silicon dioxide, stevia extract.

CLINICAL EXPERIENCE

D,L-beta-hydroxybutyrate sodium salt has been used clinically in both healthy subjects and patient populations since the 1980s in an effort to understand both fat and ketone body metabolism [3-16]. More recently, *D,L*-beta-hydroxybutyrate sodium, calcium, and magnesium salts have been granted GRAS status and are ingredients in many consumer products and dietary supplements. Beta-hydroxybutyrate salts are safe both for occasional and long-term use and rapidly induce ketosis upon ingestion. Inborn errors of metabolism in particular may benefit from the addition of beta-hydroxybutyrate to nutritional protocols.

Conditions Shown to respond to ketone body therapy

- Fatty Acid Oxidation Disorders
 - Carnitine-acylcarnitine translocase (CACT) deficiency [17]
 - Multiple Acyl Co A Dehydrogenase Deficiency (MADD)/Glutaric Aciduria Type II (GATII) [18-23]
- Glycogen Storage Disease Type III (GSD III) [24-25]
- 3-Hydroxy-3-methylglutaryl-Coenzyme A Lyase Deficiency (HMG CoA Lyase Deficiency) [26]
- Congenital Hyperinsulinism (CHI) [27-30]

SERVING SIZE DETERMINATION

trumacro™ Ketogenic BHB is to be used under medical supervision. The health care practitioner will need to consider patient body weight, medical conditions, medications, and dietary intake when determining the amount of formula to consume each day, as well as how often.

Full nutrition information can be incorporated into a dietary plan using the Keto Diet Calculator app available at the Charlie Foundation website: <https://www.ketodietcalculator.org>. The formula can be weighed out for each serving, or the common household measure equivalent can be used, based on HCP recommendation. All measures are “leveled” i.e. “one level teaspoon.” The equivalents are shown below:

Formula in Grams	Household Measure
0.35	1/8 teaspoon
0.7	1/4 teaspoon
1.4	1/2 teaspoon
2.8	1 teaspoon
5.6	2 teaspoons
9	1 tablespoon
35	1/4 cup
70	1/2 cup
140	1 cup

The charts on the following pages can be used to determine the amount of *D,L*-beta-hydroxybutyrate consumed per day based on desired target consumption and patient body weight. For example, if the HCP determines that the patient should consume 500mg of *D,L*-beta-hydroxybutyrate per kg of body weight per day, and the patient weighs 40kg, then 30g of trumacro™ Ketogenic BHB Unflavored should be consumed. If it is determined that three servings spread across the day is desired, then this would correlate to about 10g per serving, or approximately one tablespoon. Similarly, calculations can be made if the Orange Flavor product is preferred.

Product administration guidelines based on patient body weight

QUICK REFERENCE GUIDE FOR GRAMS OF KETOGENIC BHB UNFLAVORED FORMULA PER DAY

		<i>Grams of free BHB per kilogram body weight per day</i>									
		<i>0.1</i>	<i>0.2</i>	<i>0.3</i>	<i>0.4</i>	<i>0.5</i>	<i>0.6</i>	<i>0.7</i>	<i>0.8</i>	<i>0.9</i>	<i>1</i>
<i>Body weight in kilograms</i>	<i>5</i>	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.1	6.8	7.6
	<i>10</i>	1.5	3.0	4.5	6.1	7.6	9.1	10.6	12.1	13.6	15.2
	<i>15</i>	2.3	4.5	6.8	9.1	11.4	13.6	15.9	18.2	20.5	22.7
	<i>20</i>	3.0	6.1	9.1	12.1	15.2	18.2	21.2	24.2	27.3	30.3
	<i>25</i>	3.8	7.6	11.4	15.2	18.9	22.7	26.5	30.3	34.1	37.9
	<i>30</i>	4.5	9.1	13.6	18.2	22.7	27.3	31.8	36.4	40.9	45.5
	<i>35</i>	5.3	10.6	15.9	21.2	26.5	31.8	37.1	42.4	47.7	53.0
	<i>40</i>	6.1	12.1	18.2	24.2	30.3	36.4	42.4	48.5	54.5	60.6
	<i>45</i>	6.8	13.6	20.5	27.3	34.1	40.9	47.7	54.5	61.4	68.2
	<i>50</i>	7.6	15.2	22.7	30.3	37.9	45.5	53.0	60.6	68.2	75.8
	<i>55</i>	8.3	16.7	25.0	33.3	41.7	50.0	58.3	66.7	75.0	83.3
	<i>60</i>	9.1	18.2	27.3	36.4	45.5	54.5	63.6	72.7	81.8	90.9
	<i>65</i>	9.8	19.7	29.5	39.4	49.2	59.1	68.9	78.8	88.6	98.5
	<i>70</i>	10.6	21.2	31.8	42.4	53.0	63.6	74.2	84.8	95.5	106.1
<i>75</i>	11.4	22.7	34.1	45.5	56.8	68.2	79.5	90.9	102.3	113.6	
<i>80</i>	12.1	24.2	36.4	48.5	60.6	72.7	84.8	97.0	109.1	121.2	

Calculation to determine the amount of formula per day for any given body weight and desired BHB delivery:

$$\text{Grams of formula per day} = \frac{(\text{grams/kg/day of free BHB desired}) \times (\text{kg body weight}) \times 100\text{g of formula}}{\text{Grams of free BHB in formula}}$$

For example $\frac{(0.1\text{g/kg/day BHB})(20\text{kg})(100\text{g})}{66\text{g}} = 3.0\text{g of unflavored formula per day}$

QUICK REFERENCE GUIDE FOR GRAMS OF KETOGENIC BHB ORANGE FORMULA PER DAY

		Grams of free BHB per kilogram body weight per day									
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Body weight in kilograms	3	0.5357	1.1	1.6	2.1	2.7	3.2	3.8	4.3	4.8	5.4
	4	0.7	1.4	2.1	2.9	3.6	4.3	5.0	5.7	6.4	7.1
	5	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.1	8.0	8.9
	10	1.8	3.6	5.4	7.1	8.9	10.7	12.5	14.3	16.1	17.9
	15	2.7	5.4	8.0	10.7	13.4	16.1	18.8	21.4	24.1	26.8
	20	3.6	7.1	10.7	14.3	17.9	21.4	25.0	28.6	32.1	35.7
	25	4.5	8.9	13.4	17.9	22.3	26.8	31.3	35.7	40.2	44.6
	30	5.4	10.7	16.1	21.4	26.8	32.1	37.5	42.9	48.2	53.6
	35	6.3	12.5	18.8	25.0	31.3	37.5	43.8	50.0	56.3	62.5
	40	7.1	14.3	21.4	28.6	35.7	42.9	50.0	57.1	64.3	71.4
	45	8.0	16.1	24.1	32.1	40.2	48.2	56.3	64.3	72.3	80.4
	50	8.9	17.9	26.8	35.7	44.6	53.6	62.5	71.4	80.4	89.3
	55	9.8	19.6	29.5	39.3	49.1	58.9	68.8	78.6	88.4	98.2
	60	10.7	21.4	32.1	42.9	53.6	64.3	75.0	85.7	96.4	107.1
	65	11.6	23.2	34.8	46.4	58.0	69.6	81.3	92.9	104.5	116.1
	70	12.5	25.0	37.5	50.0	62.5	75.0	87.5	100.0	112.5	125.0
	75	13.4	26.8	40.2	53.6	67.0	80.4	93.8	107.1	120.5	133.9
80	14.3	28.6	42.9	57.1	71.4	85.7	100.0	114.3	128.6	142.9	
85	15.2	30.4	45.5	60.7	75.9	91.1	106.3	121.4	136.6	151.8	
90	16.1	32.1	48.2	64.3	80.4	96.4	112.5	128.6	144.6	160.7	

Calculation to determine the amount of formula per day for a given body weight and desired BHB delivery:

$$\text{Grams of formula per day} = \frac{(\text{grams/kg/day of free BHB desired}) \times (\text{kg body weight}) \times 100\text{g of formula}}{\text{Grams of free BHB in formula}}$$

For example $\frac{(0.1\text{g/kg/day BHB})(20\text{kg})(100\text{g})}{56\text{g}} = 3.6\text{g}$ of orange flavored formula per day

PHARMACOKINETICS

Beta-hydroxybutyrate mineral salts when dissolved in an aqueous environment dissociate into free beta hydroxybutyric acid and the corresponding mineral ion, both of which are rapidly absorbed by the small intestine. When consumed as a single ingredient, beta-hydroxybutyrate blood levels rise rapidly and peak between 30-90 minutes, declining back to baseline by 3 hours post ingestion [31]. The degree and duration of ketosis are directly related to the amount consumed and is affected by basal dietary habits, whether or not the subject is fed or fasted when ingesting the material, and genetic predisposition. Blood ketone levels typically increase by about 0.5-1 mMol [31]. Beta-hydroxybutyrate blood levels will slowly decline back to basal levels by about four hours. Concurrently, urine acetoacetate levels will start to rise by 30 minutes post ingestion and taper off slowly by 3-4 hours. There is the potential for blood glucose to dip slightly depending on background dietary habits, and whether or not the subject is fed or fasted when ingesting the material. Therefore, close monitoring is important if a patient is susceptible to hypoglycemia.

PRECAUTIONS and CONTRAINDICATIONS

trumacro™ Ketogenic BHB contains significant amounts of the electrolytes sodium, calcium, magnesium, and potassium, and therefore, should only be used under medical supervision. trumacro™ Ketogenic BHB may not be suitable for individuals that are sodium sensitive. There are certain conditions in which a ketogenic diet may be contraindicated, and therefore, the use of ketone-containing formulations may also be contraindicated, such as:

- Beta-oxidation defects
- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase I or II deficiency
- Carnitine translocase deficiency
- Porphyrria
- Pyruvate carboxylase deficiency
- Long-chain 3-hydroxyacyl-CoA deficiency
- Medium-chain 3-hydroxyacyl-CoA deficiency
- Long-chain acyl dehydrogenase deficiency
- Medium-chain acyl dehydrogenase deficiency
- Short-chain acyl dehydrogenase deficiency
- Long-chain 3-hydroxyacyl-CoA deficiency

SPECIAL POPULATIONS

Ketogenic BHB is appropriate for consumption by patients requiring a dietary source of beta-hydroxybutyrate. trumacro™ Ketogenic BHB unflavored is suitable for use with a gastronomy tube or nasogastric tube, but not palatable for oral feeding. trumacro™ Ketogenic BHB Orange Flavored is suitable for oral feeding. Always check with your physician for proper use recommendations.

ADMINISTRATION

Use as directed by your physician. Must be administered under medical supervision only. Dry powder should be stored in a cool, dry place. Powder can be mixed in water where it readily dissolves, or mixed with food. Once reconstituted, any unused mixture should be refrigerated and consumed within 24 hours.

HOW SUPPLIED

trumacro™ Ketogenic BHB is supplied as a bulk powder, 500 grams per container. Store in a cool, dry place.

ADVERSE REACTIONS

There are no known incremental adverse reactions for the use of trumacro™ Ketogenic BHB as a part of dietary intervention. Consumption of *D,L*-Beta-Hydroxybutyrate mineral salts are well tolerated. Reported side effects include gastrointestinal discomfort, dehydration, metabolic alkalosis, and renal stone formation [20-21]. Close medical supervision is required.

DRUG INTERACTIONS

trumacro™ Ketogenic BHB, when used as a medical food for supplemental nutrition, may impact how some drugs are metabolized. All medications should be discussed with a physician or pharmacist. Medical supervision by a physician is required.

REFERENCES

- [1] Section 415 of the FD&C Act (21 U.S.C. 350d)
- [2] Code of Federal Regulations CFR title 21 170.30(b)
- [3] Amiel SA, Archibald HR, Chusney G, Williams AJ, Gale EA. Ketone infusion lowers hormonal responses to hypoglycaemia: evidence for acute cerebral utilization of a non-glucose fuel. *Clin Sci (Lond)*. 1991 Aug;81(2):189-94. PubMed PMID: 1653662.
- [4] Chioléro R, Mavrocordatos P, Burnier P, Cayeux MC, Schindler C, Jéquier E, Tappy L. Effects of infused sodium acetate, sodium lactate, and sodium beta-hydroxybutyrate on energy expenditure and substrate oxidation rates in lean humans. *Am J Clin Nutr*. 1993 Nov;58(5):608-13. PubMed PMID: 8237864.
- [5] Christensen CK, Schmitz O, Pedersen EB, Alberti KG, Mogensen CE. Effect of 3-hydroxybutyrate infusion on urinary protein excretion in healthy man. *Scand J Clin Lab Invest*. 1986 May;46(3):239-43. PubMed PMID: 3520791.
- [6] Féry F, Plat L, Melot C, Balasse EO. Role of fat-derived substrates in the regulation of gluconeogenesis during fasting. *Am J Physiol*. 1996 May;270(5 Pt 1):E822-30. PubMed PMID: 8967471.
- [7] Fischer T, Och U, Klawon I, Och T, Grüneberg M, Fobker M, Bordewick-Dell U, Marquardt T. Effect of a Sodium and Calcium DL-β-Hydroxybutyrate Salt in Healthy Adults. *J Nutr Metab*. 2018 Apr 12;2018:9812806. doi: 10.1155/2018/9812806. eCollection 2018. PubMed PMID: 29850235.
- [8] Frølund L, Kehlet H, Christensen NJ, Alberti KG. Effect of ketone body infusion on plasma catecholamine and substrate concentrations during acute hypoglycemia in man. *J Clin Endocrinol Metab*. 1980 Mar;50(3):557-9. PubMed PMID: 6987257.
- [9] Gormsen LC, Svart M, Thomsen HH, Søndergaard E, Vendelbo MH, Christensen N, Tolbod LP, Harms HJ, Nielsen R, Wiggers H, Jessen N, Hansen J, Bøtker HE, Møller N. Ketone Body Infusion With 3-Hydroxybutyrate Reduces Myocardial Glucose Uptake and Increases Blood Flow in Humans: A Positron Emission Tomography Study. *J Am Heart Assoc*. 2017 Feb 27;6(3). PubMed PMID: 28242634.
- [10] Lestan B, Walden K, Schmaltz S, Sychala J, Fox IH. beta-Hydroxybutyrate decreases adenosine triphosphate degradation products in human subjects. *J Lab Clin Med*. 1994 Aug;124(2):199-209. PubMed PMID: 8051483.
- [11] Mikkelsen KH, Seifert T, Secher NH, Grøndal T, van Hall G. Systemic, cerebral and skeletal muscle ketone body and energy metabolism during acute hyper-D-β-hydroxybutyratemia in post-absorptive healthy males. *J Clin Endocrinol Metab*. 2015 Feb;100(2):636-43. PubMed PMID: 25415176.

- [12] Nair KS, Welle SL, Halliday D, Campbell RG. Effect of beta-hydroxybutyrate on whole-body leucine kinetics and fractional mixed skeletal muscle protein synthesis in humans. *J Clin Invest.* 1988 Jul;82(1):198-205. PubMed PMID: 3392207.
- [13] Pan JW, de Graaf RA, Petersen KF, Shulman GI, Hetherington HP, Rothman DL. [2,4-13 C]-beta-Hydroxybutyrate metabolism in human brain. *J Cereb Blood Flow Metab.* 2002 Jul;22(7):890-8. PubMed PMID: 12142574.
- [14] Pan JW, Telang FW, Lee JH, de Graaf RA, Rothman DL, Stein DT, Hetherington HP. Measurement of beta-hydroxybutyrate in acute hyperketonemia in human brain. *J Neurochem.* 2001 Nov;79(3):539-44. PubMed PMID: 11701757.
- [15] Svart M, Gormsen LC, Hansen J, Zeidler D, Gejl M, Vang K, Aanerud J, Moeller N. Regional cerebral effects of ketone body infusion with 3-hydroxybutyrate In humans: Reduced glucose uptake, unchanged oxygen consumption and increased blood flow by positron emission tomography. A randomized, controlled trial. *PLoS One.* 2018 Feb 28;13(2):e0190556. doi: 10.1371/journal.pone.0190556. eCollection 2018. PubMed PMID: 29489818.
- [16] Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. *Diabetes.* 1994 Nov;43(11):1311-7. PubMed PMID: 7926305.
- [17] Dalkeith T, Ellaway CJ, Thompson S, Dennison B, Matar W, Wilcken B, Bhattacharya K. The use of 3-hydroxybutyrate in patients with fat oxidation disorders (CACT). *J Inher Metab Dis.* 2013. 36 (Suppl 2):S91–S342
- [18] Saral NY, Aksungar FB, Aktuglu-Zeybek C, Coskun J, Demirelce O, Serteser M. Glutaric acidemia type II patient with thalassemia minor and novel electron transfer flavoprotein-A gene mutations: A case report and review of literature. *World J Clin Cases.* 2018 Nov 26;6(14):786-790. doi: 10.12998/wjcc.v6.i14.786. PubMed PMID: 30510944.
- [19] Bonham JR, Tanner MS, Pollitt RJ, Manning NJ, Olphin SE, Dwoning M, Robertson L, Pourfarzam M, Bartlett K. Oral sodium 3-hydroxybutyrate, a novel adjunct to treatment for multiple acyl CoA dehydrogenase deficiency. *J Inher Metab Dis.* 22. 1999. Suppl.1.
- [20] Fischer T, Och U, Marquardt T. Long-term ketone body therapy of severe multiple acyl-CoA dehydrogenase deficiency: A case report. *Nutrition.* 2019 Apr;60:122-128. PubMed PMID: 30557775.
- [21] Gautschi M, Weisstanner C, Slotboom J, Nava E, Zürcher T, Nuoffer JM. Highly efficient ketone body treatment in multiple acyl-CoA dehydrogenase deficiency-related leukodystrophy. *Pediatr Res.* 2015 Jan;77(1-1):91-8. PubMed PMID: 25289702.
- [22] Van Hove JL, Grünwald S, Jaeken J, Demaerel P, Declercq PE, Bourdoux P, Niezen-Koning K, Deanfeld JE, Leonard JV. *D,L*-3-hydroxybutyrate treatment of multiple acyl-CoA dehydrogenase deficiency (MADD). *Lancet.* 2003 Apr 26;361(9367):1433-5. PubMed PMID: 12727399.
- [23] Van Rijt WJ, Heiner-Fokkema MR, du Marchie Sarvaas GJ, Waterham HR, Blokpoel RG, van Spronsen FJ, Derks TG. Favorable outcome after physiologic dose of sodium-*D,L*-3-hydroxybutyrate in severe MADD. *Pediatrics.* 2014 Oct;134(4):e1224-8. PubMed PMID: 25246622.
- [24] Bhattacharya K. Investigation and management of the hepatic glycogen storage diseases. *Transl Pediatr.* 2015 Jul;4(3):240-8. Review. PubMed PMID: 26835382.
- [25] Valayannopoulos V, Bajolle F, Arnoux JB, Dubois S, Sannier N, Baussan C, Petit F, Labrune P, Rabier D, Ottolenghi C, Vassault A, Broissand C, Bonnet D, de Lonlay P. Successful treatment of severe

- cardiomyopathy in glycogen storage disease type III With *D,L*-3-hydroxybutyrate, ketogenic and high-protein diet. *Pediatr Res.* 2011 Dec;70(6):638-41. PubMed PMID: 21857385.
- [26]Bhattacharya K, Ho G, Dalkeith T, Dennison B, Thompson S, Christodoulou J. Improvement in severe HMG co-lyase deficiency with fat restriction and 3-hydroxybutyrate therapy. *J Inherit Metab Dis* (2010) 33 (Suppl 1):S1–S197.
- [27]Bougnères PF, Ferré P, Chaussain JL, Job JC. Glucose metabolism in hyperinsulinemic infants: the effects of fasting and sodium DL-beta-hydroxybutyrate on glucose production and utilization rates. *J Clin Endocrinol Metab.* 1983 Nov;57(5):1054-60. PubMed PMID: 6352723.
- [28]Hussain K, Eaton S, Clayton P. Exogenous administered DL- sodium beta-hydroxybutyrate (beta-OHB) can cross the blood brain barrier. *Pediatr Res.*2003 May;53(5):865; author reply 865-6. PubMed PMID: 12715792.
- [29]Plecko B, Stoeckler-Ipsiroglu S, Schober E, Harrer G, Mlynarik V, Gruber S, Moser E, Moeslinger D, Silgoner H, Ipsiroglu O. Oral beta-hydroxybutyrate supplementation in two patients with hyperinsulinemic hypoglycemia: monitoring of beta-hydroxybutyrate levels in blood and cerebrospinal fluid, and in the brain by in vivo magnetic resonance spectroscopy. *Pediatr Res.* 2002 Aug;52(2):301-6. PubMed PMID: 12149510.
- [30]Webber J, Simpson E, Parkin H, Macdonald IA. Metabolic effects of acute hyperketonaemia in man before and during an hyperinsulinaemic euglycaemic clamp. *Clin Sci (Lond).* 1994 Jun;86(6):677-87. PubMed PMID: 8062504.
- [31]Evans M, Patchett E, Nally R, Kearns R, Larney M, Egan B. Effect of acute ingestion of β -hydroxybutyrate salts on the response to graded exercise in trained cyclists, *European Journal of Sport Science*, 2018 DOI:10.1080/17461391.2017.1421711.