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Review

Effects of Ketone Bodies on the Brain

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ABSTRACT

Ketone bodies, which are formed by liver mitochondria from acetyl coenzyme A, serve as an alternate fuel source for cells. They can be delivered exogenously as well as endogenously produced in the liver. Ketone bodies have a variety of impacts on the brain. They provide an alternate fuel source for the brain is one of the reasons that they have a positive influence on neurological disorders such as Alzheimer's and Parkinson's disease. Another reason ketone bodies are beneficial to the brain is their neuroprotective effect. The neuroprotective effect is the impact that prevents neuronal damage from occurring. Ketoacidosis is the excessive concentration of ketone bodies in the blood, which causes increased acidity. One of the harms caused by ketone bodies to the brain is that ketoacidosis results in death by altering the critical blood pH level. Exogenous ketone bodies should be supplied in a regulated way for these reasons. In this review, the effects of ketone bodies on the brain were discussed.

Keywords: Brain, ketoacidosis, ketone bodies, neuroprotective effect

Ketone bodies are small lipid-derived molecules that provide circulatory energy to tissues during times of hunger or prolonged exercise. More than 80% of the stored energy in the human body is found as fatty acids in adipose tissue. Muscle and liver glycogen stores are depleted first during starvation.[1] Then, the fatty acids are recruited from the adipocytes and transferred to the liver to be converted into ketone bodies. The ketone bodies are subsequently distributed through the circulation to metabolically active tissues like muscle and the brain, where they are metabolized to acetyl coenzyme A (acetyl-CoA) and utilized as a glucose-sparing energy source.[2] Acetoacetate, acetone, and beta-hydroxybutyrate (β-hydroxybutyrate) are the components of ketone bodies.[3] Acetoacetate is a precursor to acetone and β-hydroxybutyrate. The most frequent ketone body in circulation is β-hydroxybutyrate.[2]

Ketone bodies are involved in several metabolic processes, including fatty acid β-oxidation, the tricarboxylic acid cycle (TCA), gluconeogenesis, *de novo* lipogenesis (DNL), and sterol biosynthesis. In humans, ketone body metabolism is utilized to nourish the brain during times of nutritional deficiency.

Ketones contribute significantly to overall energy metabolism by acting as energy fuels for extrahepatic tissues such as the brain, heart, or skeletal muscle in a variety of physiological conditions such as body oxidation, hunger, the neonatal period, post-exercise, pregnancy, and low-carbohydrate diets. Total circulatory ketone body concentrations in healthy adult humans typically oscillate between 100 and 250 μM, increase to 1 mm≥ after prolonged exercise or 24 hours of fasting, and can accumulate up to 20 mm in conditions such as ketosis, ketonuria, diabetic ketoacidosis.[4,5]

Ketone bodies have essential functions in mammalian cell metabolism, homeostasis, and signaling under a range of physiological and pathological situations, according to researchers. They are also key signaling agents, drivers of protein post-translational modification (PTM), and modulators of inflammation and oxidative stress.[4,6]

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KETOGENESIS

Ketogenesis is a chain of reactions that results in the formation of ketone bodies.[7] When glycogen supplies are severely depleted or the concentration of fatty acids rises, the production of ketone bodies increases. When glucose is not readily accessible, the brain turns to ketone bodies as its primary source of energy. The reason behind this is, in contrast to other bodily organs, the brain has a strict minimum demand for glucose. The decrease in hepatic glycogen concentration and the glucagon-insulin ratio are among the factors that stimulate ketogenesis. Low insulin results in an increase in free fatty acids that are transported to the mitochondria, enhancing the formation of ketone bodies.[8]

Ketogenesis requires mitochondrial β-oxidation of fatty acids.[9] Carnitine palmitoyltransferase (CPT-1) introduces fatty acids into the mitochondria, where they are broken down into acetyl-CoA by β-oxidation. The enzyme thiolase converts two acetyl-CoA molecules to acetoacetyl coenzyme A (acetoacetyl-CoA). Following that, acetoacetyl-CoA is transformed into hydroxymethylglutaryl-coenzyme A (HMG-CoA). HMG-CoA is also converted to acetoacetate. Non-enzymatic decarboxylation converts acetoacetate to acetone or β-hydroxybutyrate and ketone bodies are formed. When ketone bodies increase, free fatty acids decrease, and ketogenesis is suppressed so that ketone bodies do not accumulate dangerously in the blood, resulting in ketoacidosis.[8] Ketolysis, on the contrary, is the inverse process of ketogenesis. It is a series of processes that take place to replenish the energy of ketone bodies. It occurs in nearly every cell.[10]

Hyperketonemia

Irregularities in the level of carbohydrates in plasma induce variable degrees of hyperketonemia.[11] While the post-meal plasma concentration [KC] is <0.1 mM, ketone body concentrations more than 0.2 mM are considered hyperketonemia.[3]

EFFECTS OF KETONE BODIES ON BRAIN

The human brain is a structure with highly developed skills such as comprehending, feeling, and reasoning, as well as a high energy need. Although the brain accounts for only 2% of body weight, the energy it uses at rest accounts for 20% of overall energy consumption.[12,13] Neurons consume 70-80% of the brain's energy, while glial cells consume the rest.[14]

The concentration of ketones in the blood influences their usage in the brain.[15] When glucose becomes scarce, ketones provide an alternate source of energy for the brain.[16] The utilization of ketone bodies in the adult brain is considerably reduced during satiety.[17] However, adults utilize ketone bodies during extended hunger, such as fasting.[18,19] During the development stage, ketones are regarded as one of the basic energy sources of the brain, meeting 70% of the energy needed.[20]

Metabolic and Signaling Roles of Ketone Bodies

Ketones appear to be dependent on ketosis for the appropriate development and operation of a healthy neonatal brain since they are a source of energy and precursors for fatty acids and cholesterol, which make up the majority of the brain's dry matter.[3,21,22] Therefore, continual ketone production is normal in newborns to some extent. Blood β-hydroxybutyrate (BHB) levels in healthy newborns rise to roughly 0.5-2 mM within 12 hours of birth and remain elevated for at least a week.[23] Many human infant tissues, particularly the brain, have significant amounts of ketone absorption and oxidation. In the perfused premature baby brain, for example, the molar consumption of BHB is approximately 50% more than that of glucose.[24] Preclinical research in other model species, particularly nursing mice, supports the relevance of ketone bodies in brain development.[3,20,25] The damage to brain cells caused by hypoxia is known as hypoxic-ischemic encephalopathy (HIE). Since the newborn brain is designed to accept and utilize ketone bodies, maintaining enough ketosis in post-HIE newborns has the potential to ameliorate many of the brain's degenerative processes. In addition, because the endogenous ketogenesis mechanism takes many hours to occur, endogenous ketosis cannot achieve high blood ketone levels during the 6-hour latent period of HIE brain damage. This suggests that exogenous ketones can be administered to preserve cellular function during the latent and secondary phases of damage. Exogenous ketones may potentially contribute to long-term healing processes due to their possible neurotrophic effects and role as synthetic precursors.[26,27] Exogenous ketones, including ketogenic medium-chain fatty acids (MCFAs), ketone mineral salts, BHB, or the ketone bodies acetoacetate (AcAc), are typically found as ketone bodies, liquids containing ketone precursors, or soluble powders. Ketone bodies, which can be derived from both endogenous and exogenous

sources, are processed uniformly within the body. While there are certain limits to using exogenous ketones, the majority of these constraints are less likely to cause issues in babies getting active therapy for HIE in an intensive care setting.[26] While the evidence supporting the neuroprotective benefits of ketone bodies for newborn brain damage is still in its early stages, an important working group has reported neuroprotection resulting from the injection of exogenous ketone bodies in a range of adult brain injury animal models. The study in question contains numerous Alzheimer's disease (AD) models, as well as stroke, Parkinson's disease (PD), and traumatic brain injury (TBI).[6,26] Alzheimer's disease is a neurological disorder that causes memory loss and cognitive impairment.[28-30] The main features of AD pathology include the accumulation of amyloid-beta (Aβ) plaques followed by the formation of neurofibrillary tangles (NFTs).[31,32] Microglia enhance Aβ and tau clearance in response to Aβ aggregation, providing physical barriers to shield neurons from neurotoxic plaque but also causing neuroinflammation, which damages neurons.[28]

The ketogenic diet is a high-fat, low-carbohydrate diet regimen that stimulates the breakdown of fatty acids and ketogenic amino acids; this diet is a process that results in the production of ketone bodies that can be further metabolized for energy production. Blood β-hydroxybutyrate, one of the three ketone bodies, has been found at considerably reduced levels in the blood of AD patients.[28,33]

According to a study, a ketogenic diet can promote changes in synaptic morphology and function involving ionic channels or synaptic vesicular loop mechanisms, hence increasing motor performance. As a result, the ketogenic diet is linked to disorders defined by these processes. Several motor dysfunction disorders, such as epilepsy, metabolic disorders, cancers, autism, depression, migraine, narcolepsy, PD, and AD, can sample these diseases. Motor dysfunction can also be called motor learning disabilities. It is a developmental coordination disorder.[34]

With BHB therapy, reduced cortical plaque development was found in the mouse model of AD, resulting in lower cortical plaque volume and less prominent microgliosis. In this circumstance, increasing the amount of BHB is a potential approach for AD.[28] BHB therapy resulted in decreased plaque development in mice, according to the studies. Blood β-hydroxybutyrate must be able to pass the blood-brain barrier to be used as a treatment agent for AD. Endothelial cells in blood vessels in the brain convey monocarboxylate carriers, which mediate ketone body transport via crossing the blood-brain barrier.[35,36] Many clinical trials are presently ongoing as a result of the recent surge in interest in the use of ketosis as a treatment or adjuvant in a variety of neurological disorders. These include studying the metabolism of exogenous ketones in healthy human adults, as well as the feasibility and efficacy of ketosis in treating AD and PD, as well as adult stroke and cardiac arrest.[26]

The β-oxidation of fatty acids during ketogenesis might be harmful.[37] While increased oxygen consumption for fatty acid oxidation leads to dysfunctional adenosine triphosphate (ATP) synthesis, it also raises the likelihood that the environment of neurons in the brain parenchyma will become hypoxic, where the oxygen pressure is not uniform and is relatively low.[8] Simultaneously, the utilization of ketone bodies in neurons, as well as their inclination toward glycolysis, might result in a drop in nicotinamide adenine dinucleotide phosphate (NADPH), increased oxidative stress, and cell death.[38] Depending on the circumstances, pregnant women with diabetes should avoid ketoacidosis because of the risk of low intelligence quotient (IQ) in their children.[39]

Although ketone bodies are used as an energy source, their accumulation has several negative consequences, including diabetic ketoacidosis, brain damage, and hypoxia. Ketoacidosis is the presence of high doses of ketone bodies in the blood. Ketoacidosis is associated with a high mortality and morbidity rate.[40] Patients with ketoacidosis had infectious conditions such as vomiting, malnutrition, and gastroenteritis. Decompensation is described as a decline in the heart's working power; the frequency and length of episodes influence morbidity. Morbidity and mortality can be avoided with efficient treatment and measures implemented in the presence of the catabolic process as a result of the patient's diagnosis.[41]

KETOSIS

Ketosis is defined as a rise in ketone levels in the blood for a variety of causes. This rise might be due to either physiological ketosis or pathological ketosis.[16,42]

Physiological Ketosis

The level of ketone bodies in the blood increases during physiological ketosis, although this increase does not reach harmful levels.

a. Hunger: In the case of fasting or hunger, ketogenesis is initiated to maintain energy balance and continuity throughout the body, particularly to supply fuel to the brain.[43]

b. The ketogenic diet: Fat-rich diets induce a rise in the number of ketone bodies in the blood. The ketogenic diet has not become widely used, since it raises the risk of systemic problems such as growth retardation, nephrolithiasis, and hyperlipidemia.[44]

c. Age and energy demand: Newborn babies' ketone bodies are increased by high-fat milk.[45] In children, the amount of blood ketone bodies and age are inversely associated. The amount of blood ketone bodies declines with aging.[46] High blood ketone body concentrations are also common in pregnant women. They become more susceptible to ketoacidosis as a result.[47]

Pathological Ketosis

Pathologic ketosis is a state of dangerously elevated ketone bodies in the blood brought on by anomalies in ketone metabolism, which alters the pH of the blood.[16,42]

a. Impaired ketolysis pathway: People with a deficit in a ketolysis-related enzyme and those with congenital anomalies in ketogenesis have issues with blood ketone body levels.[16]

b. Alcoholic ketoacidosis: Alcoholic ketoacidosis is a condition caused by excessive ethanol consumption. Excessive alcohol intake promotes ethanol oxidation, which raises the number of ketones in the blood, resulting in ketoacidosis.[48]

c. Diabetic ketoacidosis: Ketogenesis is reported to be enhanced in diabetic individuals due to insulin deficiency. It is the most significant factor responsible for the increase in pathological ketosis.[49] Oxidative damage has been found in the brains of diabetic ketoacidosis patients.[50,51] Cerebral edema, hemorrhagic stroke, intracerebral complications, and neurological impairment are all possible causes of diabetic ketoacidosis.[52-54]

In conclusion, acetyl-CoA, the usual result of fatty acid oxidation in the liver, is converted into ketones, which are acidic molecules. When blood glucose levels fall, endogenously generated ketone bodies in the liver are transferred to the brain and utilized as fuel. They offer a considerable portion of the required energy in situations such as extended fasting and hunger. Ketone bodies can also be administered exogenously. In case of excessive administration or a genetic defect in ketogenesis enzymes, ketone bodies accumulate in people's blood and cause ketoacidosis. Fasting or hunger causes a rise in blood ketone levels, however, this is not on a harmful level and does not result in ketoacidosis. On the other hand, ketone bodies are one of the brain's primary energy sources during development. Ketone bodies have shown neuroprotective effects, leading to potential advancements in diseases characterized by motor dysfunction, such as AD and PD. That is why individuals suffering from neurological diseases are encouraged to follow a ketogenic diet. According to the findings of this review, ketone bodies are advantageous to the brain; however, too much accumulation in the blood is hazardous.

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REFERENCES

1. Topal E, Aydemir K, Çağlar Ö, Arda B, Kayabaşı O, Yıldız M, et al. Fatty Liver Disease: Diagnosis and Treatment. JEB Med Sci 2021;2:343-57.
2. Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends Endocrinol Metab. 2014 Jan;25:42-52.
3. Robinson AM, Williamson DH. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol Rev. 1980 Jan;60:143-87.
4. Puchalska P, Crawford PA. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. Cell Metab. 2017 Feb 7;25:262-84.
5. Wang L, Chen P, Xiao W. β-hydroxybutyrate as an Anti-Aging Metabolite. Nutrients. 2021 Sep 28;13:3420.
6. Masi D, Spoltore ME, Rossetti R, Watanabe M, Tozzi R, Caputi A, et al. The Influence of Ketone Bodies on Circadian Processes Regarding Appetite, Sleep and Hormone Release: A Systematic Review of the Literature. Nutrients. 2022 Mar 28;14:1410.
7. Foster DW, McGarry JD. The regulation of ketogenesis. Ciba Found Symp. 1982;87:120-31.
8. McGarry JD, Foster DW. Hormonal control of ketogenesis. Biochemical considerations. Arch Intern Med. 1977 Apr;137:495-501.
9. Foster DW. Malonyl-CoA: the regulator of fatty acid synthesis and oxidation. J Clin Invest. 2012 Jun;122:1958-9.
10. Grabacka M, Pierzchalska M, Dean M, Reiss K. Regulation of Ketone Body Metabolism and the Role of PPARα. Int J Mol Sci. 2016 Dec 13;17:2093.
11. Evans M, Cogan KE, Egan B. Metabolism of ketone bodies during exercise and training: physiological

basis for exogenous supplementation. J Physiol. 2017 May 1;595:2857-71.
12. Pan Y. Nutrients, Cognitive Function, and Brain Aging: What We Have Learned from Dogs. Med Sci (Basel). 2021 Nov 18;9:72.
13. Igwe O, Sone M, Matveychuk D, Baker GB, Dursun SM. A review of effects of calorie restriction and fasting with potential relevance to depression. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Dec 20;111:110206.
14. Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. Neuron. 2012 Sep 6;75:762-77.
15. Brocchi A, Rebelos E, Dardano A, Mantuano M, Daniele G. Effects of Intermittent Fasting on Brain Metabolism. Nutrients. 2022 Mar 17;14:1275.
16. Kanikarla-Marie P, Jain SK. Hyperketonemia and ketosis increase the risk of complications in type 1 diabetes. Free Radic Biol Med. 2016 Jun;95:268-77.
17. Edmond J. Energy metabolism in developing brain cells. Can J Physiol Pharmacol. 1992;70 Suppl:S118-29.
18. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF Jr. Brain metabolism during fasting. J Clin Invest. 1967 Oct;46:1589-95.
19. Nehlig A, Pereira de Vasconcelos A. Glucose and ketone body utilization by the brain of neonatal rats. Prog Neurobiol. 1993 Feb;40:163-221.
20. Nehlig A. Brain uptake and metabolism of ketone bodies in animal models. Prostaglandins Leukot Essent Fatty Acids. 2004 Mar;70:265-75.
21. Patel MS, Johnson CA, Rajan R, Owen OE. The metabolism of ketone bodies in developing human brain: development of ketone-body-utilizing enzymes and ketone bodies as precursors for lipid synthesis. J Neurochem. 1975 Dec;25:905-8.
22. Tracey TJ, Steyn FJ, Wolvetang EJ, Ngo ST. Neuronal Lipid Metabolism: Multiple Pathways Driving Functional Outcomes in Health and Disease. Front Mol Neurosci. 2018 Jan23;11:10.
23. Melichar V, Drahota Z, Hahn P. Ketone bodies in the blood of full term newborns, premature and dysmature infants and infants of diabetic mothers. Biol Neonat. 1967;11:23-8.
24. Adam PA, Räihä N, Rahiala EL, Kekomäki M. Oxidation of glucose and D-B-OH-butyrate by the early human fetal brain. Acta Paediatr Scand. 1975 Jan;64:17-24.
25. Cremer JE. Substrate utilization and brain development. J Cereb Blood Flow Metab. 1982Dec;2:394-407.
26. Wood TR, Stubbs BJ, Juul SE. Exogenous Ketone Bodies as Promising Neuroprotective Agents for Developmental Brain Injury. Dev Neurosci. 2018;40:451-62.
27. Ko A, Kwon HE, Kim HD. Updates on the ketogenic diet therapy for pediatric epilepsy. Biomed J. 2022 Feb;45:19-26.
28. Shippy DC, Wilhelm C, Viharkumar PA, Raife TJ, Ulland TK. β-Hydroxybutyrate inhibits inflammasome activation to attenuate Alzheimer's disease pathology. J Neuroinflammation. 2020 Sep 21;17:280.
29. Cevik B, Solmaz V, Yigitturk G, Cavusoğlu T, Peker G, Erbas O. Neuroprotective effects of erythropoietin on Alzheimer's dementia model in rats. Adv Clin Exp Med. 2017 Jan-Feb;26(1):23-29.
30. Erbaş O, Solmaz V, Aksoy D. Inhibitor effect of dexketoprofen in rat model of pentylenetetrazol-induced seizures. Neurol Res. 2015;37:1096-101.
31. İpek Konaklı M, Erbaş O. Alzheimer's Disease and Animal Models. JEB Med Sci 2020;1:107-12.
32. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015 Mar;31:196-201.
33. Hersant H, Grossberg G. The Ketogenic Diet and Alzheimer's Disease. J Nutr Health Aging. 2022;26:606-14.
34. Veyrat-Durebex C, Reynier P, Procaccio V, Hergesheimer R, Corcia P, Andres CR, et al. How Can a Ketogenic Diet Improve Motor Function? Front Mol Neurosci. 2018 Jan 26;11:15
35. Pierre K, Pellerin L, Debernardi R, Riederer BM, Magistretti PJ. Cell-specific localization of monocarboxylate transporters, MCT1 and MCT2, in the adult mouse brain revealed by double immunohistochemical labeling and confocal microscopy. Neuroscience. 2000;100:617-27.
36. Bergersen L, Rafiki A, Ottersen OP. Immunogold cytochemistry identifies specialized membrane domains for monocarboxylate transport in the central nervous system. NeurochemRes. 2002 Feb;27:89-96.
37. Schönfeld P, Reiser G. Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain. J Cereb Blood Flow Metab. 2013 Oct;33:1493-9.
38. Herrero-Mendez A, Almeida A, Fernández E, Maestre C, Moncada S, Bolaños JP. The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. Nat Cell Biol. 2009 Jun;11:747-52.
39. Rizzo T, Metzger BE, Burns WJ, Burns K. Correlations between antepartum maternal metabolism and intelligence of offspring. N Engl J Med. 1991 Sep 26;325:911-6.
40. Bilici M, Tavil B, Dogru O, Davutoglu M, Bosnak M. Diabetic ketoasidosis is associated with prothrombotic tendency in children. Pediatr Hematol Oncol. 2011 Aug;28:418-24.
41. Bashir B, Fahmy AA, Raza F, Banerjee M. Non-diabetic ketoacidosis: a case series and literature review. Postgrad Med J. 2021 Oct;97:667-71.
42. Anderson JC, Mattar SG, Greenway FL, Lindquist RJ. Measuring ketone bodies for the monitoring of pathologic and therapeutic ketosis. Obes Sci Pract. 2021 May 4;7:646-56.
43. Altayyar M, Nasser JA, Thomopoulos D, Bruneau M Jr. The Implication of Physiological Ketosis on The Cognitive Brain: A Narrative Review. Nutrients. 2022 Jan 25;14:513.
44. Kwiterovich PO Jr, Vining EP, Pyzik P, Skolasky R Jr,

Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA. 2003 Aug 20;290:912-20.

45. Ward Platt M, Deshpande S. Metabolic adaptation at birth. Semin Fetal Neonatal Med. 2005 Aug;10:341-50.
46. Saudubray JM, Marsac C, Limal JM, Dumurgier E, Charpentier C, Ogier H, et al. Variation in plasma ketone bodies during a 24-hour fast in normal and in hypoglycemic children: relationship to age. J Pediatr. 1981 Jun;98:904-8.
47. Paterson P, Sheath J, Taft P, Wood C. Maternal and foetal ketone concentrations in plasma and urine. Lancet. 1967 Apr 22;1:862-5.
48. Long B, Lentz S, Gottlieb M. Alcoholic Ketoacidosis: Etiologies, Evaluation, and Management. J Emerg Med. 2021 Dec;61:658-65.
49. Grinblat L, Pacheco Bolaños LF, Stoppani AO. Decreased rate of ketone-body oxidation and decreased activity of D-3-hydroxybutyrate dehydrogenase and succinyl-CoA:3-oxo-acid CoA-transferase in heart mitochondria of diabetic rats. Biochem J. 1986 Nov 15;240:49-56.
50. Hoffman WH, Siedlak SL, Wang Y, Castellani RJ, Smith MA. Oxidative damage is present in the fatal brain edema of diabetic ketoacidosis. Brain Res. 2011 Jan 19;1369:194-202.
51. Uyanikgil Y, Özkeşkek K, Çavuşoğlu T, Solmaz V, Tümer MK, Erbas O. Positive effects of ceftriaxone on pentylenetetrazol-induced convulsion model in rats. Int J Neurosci. 2016;126:70-5.
52. Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. Stroke Res Treat. 2011 Feb 22;2011:219706.
53. Wolfsdorf J, Glaser N, Sperling MA; American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. Diabetes Care. 2006 May;29:1150-9.
54. Teymur H, Tiftikcioglu YO, Cavusoglu T, Tiftikcioglu BI, Erbas O, Yigitturk G, Uyanikgil Y. Effect of platelet-rich plasma on reconstruction with nerve autografts. Kaohsiung J Med Sci. 2017 Feb;33:69-77.