

Ketocrinology

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Ketocrinology is the study of the relationship between ketosis, including ketogenic diet, and endocrine function of the body. This article introduces this novel concept, discusses its importance, lists the reasons for its neglect, and explores the wide clinical spectrum of the subject. The study of ketocrinology should be an integral part of the subject of endocrinology and metabolism. This will facilitate rational and evidence-based prescription of ketogenic diet, in an effective, safe, and well-tolerated manner.

Keywords

Acetoacetate, acetone, Atkin's diet, beta hydroxyl butyrate, ketone bodies, obesity, type 2 diabetes

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Ketogenic diet (KD), though over a century old,¹ has recently drawn attention to its multifaceted therapeutic potential. Modern use of KD can be traced back to 1911, when French physicians Gulep and Marie reported improvement in seizures in children and adults who were prescribed a fasting regimen.¹ Initially used for the management of childhood seizures, it is now being tried in a wide spectrum of specialties including neurology, oncology, nephrology, and dermatology.¹ A major clinical application of KD is in the management of the metabolic syndrome, including obesity and diabetes.^{2,3} Assessment of published literature, however, suggests that KD has not gained as much attention among endocrinologists as it has in neurology.⁴ This is unfortunate, as carbohydrate restriction has been used by experts in diabetes, such as Joslin, with reasonable results, 100 years ago.⁵

While ample publications are available in the nonscientific domain, very few reviews have been written on the topic from an endocrine perspective.^{6,7} Praise-worthy leadership has been provided by physiologists and bio scientists,⁸ and usage of KD is supported by data from well-conducted randomized controlled trials.⁹ A relative lack of focus on KD in endocrinology circles, however, has meant that the benefits of this therapy have not utilized their full potential. This is disturbing, considering the unabated pandemic of obesity, diabetes and metabolic dysfunction that the world grapples with today.

Definition

We aim to address this gap by creating the concept of "ketocrinology". We define ketocrinology as the study of the relationship between ketosis, including KD, and the endocrine function of the body. We draw from evidence in human and comparative endocrinology to suggest that ketocrinology should be an integral part of the study of endocrinology and metabolism. We hope that this concept is leveraged further to create rational guidance for effective and safe use of KD in endocrine disease. This in turn will facilitate the achievement of optimal endocrine and metabolic health.

Endocrine concerns—scientific explanations

Comparative endocrinology

Conventional endocrinology views ketosis as a Cassandra condition, i.e. a clinical state which is a harbinger of ketoacidosis and possible death. This has created an image of mistrust and dislike regarding KD in endocrine circles. This, however, is unwarranted.

Ketosis—physiological versus pathological

KD is actually a therapeutic diet, which can also be termed a macronutrient modulation strategy. Such modulation-induced ketosis is physiological, rather than pathological. The biochemist Hans Krebs differentiated between the physiological ketosis of very-low calorie diets and the pathological ketosis of diabetic ketoacidosis.⁹ The term "nutritional ketosis" is used to describe the physiological ketosis encountered in a keto diet.¹⁰

KD leads to lower levels of circulating glucose and insulin compared with people consuming a normal diet. The pH of blood remains normal (7.4) even in the face of elevated ketone body concentration (7–8 mmol/l versus 0.1–mmol/l). In diabetic ketoacidosis, on the other hand, glucose concentration is elevated, insulin is non-detectable, pH falls to acidotic level (<7.3), and ketone bodies rise above 25 mmol/l. Ketocrinology clearly differentiates between these two distinct ketotic states, and works to enhance utility of the physiological ketosis in various clinical situations.

Comparative ketocrinology

Another reason for the lack of acknowledgement of the potential benefits of KD is poor awareness of comparative endocrinology. In most mammals, the brain is not well developed and consumes <5% of basal metabolism. Thus, even during prolonged starvation, they do not need to become ketotic or become ketoverted (shift from carbohydrate-based metabolism to ketone-based metabolism). The minimal glucose requirements of the brain are met by gluconeogenesis from glycerol, which is stored in adipose tissue triglyceride depots.^{6,7} A classic example is seen in mammals that hibernate in winter or aestivate in summer.

Brain activity, or glucose requirement, is not related directly to brain size. A 40,000 kg whale has a 7.5 kg brain that consumes 5.25 mmol oxygen/minute. On the other hand, a 70 kg man has a 1.5 kg brain, which consumes 2.24 mmol oxygen/minute. It is thought that a sudden mutation, which occurred in *Homo sapiens* about 10,000 years ago, allowed humans to develop communication, including language and cognition. These energy-intensive processes made the brain evolve to use glucose. *Homo sapiens* would have needed a backup source of cerebral energy to tide over frequent famines and droughts.⁸ This energy was sourced from stored fat deposits—through ketone bodies. Such ketosis is physiological, adaptive, and pro-survival.

This phenomenon never occurred in other mammals; hence, there is no experimental animal model for "physiological ketosis". Ketosis, whenever encountered in animals, will be pathological. Also, ketosis in animal models will not be expected to lead to improvement in cognitive function. This implies that results of animal studies on carbohydrate metabolism and ketosis cannot be extrapolated to man. Therefore, one has to rely only on clinical data to assess the efficacy and safety of KD.

Need for scientific study design

Many human experiments and studies are based on designs that impose an extra ketogenic burden on a calorie-replete or carbohydrate-replete person.⁹ The term "exogenous ketones" is used to describe nutritional supplements that provide ketogenic precursors. These cannot be compared with KD, which promotes ketosis in a low-carbohydrate setting. Adding ketogenic precursors to a carbohydrate-rich diet will not lead to ketosis or ketonuria and will not facilitate preferential burning of fat for fuel. In fact, this will succeed only in adding fuel to the fire of obesity. This implies that ketocrinology should define KD and ketosis, and observe their effects in a scientific manner, using well-designed study frameworks.

Physiological rationale

The human child's brain consumes 40–50% of all basal metabolism; insulin deficiency or carbohydrate deficiency rapidly leads to ketosis. The same holds true in pregnant women, as the fetus works like a second metabolic brain, consuming an extra 100 g glucose daily near term. A similar situation

occurs in lactation, where glucose requirement rises, due to the need to convert it to lactose.⁹

In adults, however, the brain consumes only 20% of basal metabolism, with the amount coming to 100–120 g glucose/24 hours. Thus, there is a huge buffer (safety net) between physiological ketosis and pathological ketoacidosis in adults. Availability of triglycerides in adipose tissue acts as a backup for survival in situations of prolonged starvation or carbohydrate restriction. KD seeks to utilize this "excess" fuel in a parsimonious and physiological manner. This can be termed an extension of the Law of Endocrine Parsimony.

Ketocrinology and the glands

Lipids

Hypo caloric KD have been shown to have conflicting results on lipid profile.^{2,10} While some authors report beneficial effects on total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, others suggest a neutral impact. Most trials using normocaloric KD demonstrate no alteration in lipid profile. The benefits shown by some hypo caloric KD appear to be due to loss of body fat and carbohydrate restriction. Some KD variants, such as Mediterranean KD, contain high levels of antioxidants, which can also contribute to lipid health.

It has been suggested that KD should not be prescribed with concurrent statin therapy.¹¹ Statins inhibit the cholesterol pathway and prevent conversion of dietary cholesterol to testosterone.¹² This dose-related effect may lead to suboptimal clinical results by interfering with the increase in testosterone that is seen with high-cholesterol KD. The ketone bodies acetoacetic acid and R-3-hydroxy-butyric acid (BHB) inhibit several carbonic anhydrase isoforms involved in lipogenesis. The BHB fragment is also present in the molecules of atorvastatin, fluvastatin, and rosuvastatin. These drugs may exert a therapeutic effect by inhibiting lipogenesis through mitochondrial carbonic anhydrase inhibition.¹³

The pituitary

Pituitary extracts have long been shown to be ketogenic.¹⁴ We now understand that this may be part of the hyperglycemic effects of anterior pituitary hormones. No human studies have explored the effect of KD on hypothalamic activity. KD is associated with increased water drinking, which occurs due to increased secretion of fibroblast growth factor 21.¹⁵ However, animal studies suggest the possibility of ketoacid feedback on pituitary function.¹⁶

The thyroid

A high protein diet has been shown to stimulate thyroid hormone synthesis in rat models.¹⁷ On the other hand, a low protein diet, supplemented with essential amino acids, is able to restore thyroid secretion in uremic patients.¹⁸ There are no data regarding the influence of KD on thyroid function, or vice versa, in humans.

The parathyroid

Ketone administration has been shown to correct hyperparathyroidism, reverse renal osteodystrophy, and slow the progression of disease in chronic renal failure.^{19,20} The role of protein restriction in management of chronic kidney disease is controversial. There are studies that report the benefits of a high protein diet in this condition. However, the benefits of KD per se on renal impairment are yet to be studied in humans.

Diabetes

Most research on KD in endocrinology is related to type 2 diabetes. Both short- and long-term KD trials have demonstrated improvement in glycemic and metabolic parameters, including a reduction in insulin levels.²¹ Some researchers have been able to reduce glucose-lowering medication significantly in diabetes.²² The islet de-stress hypothesis is based upon the anatomical and functional viewpoint that the islets of Langerhans should be treated as a single endocrine gland, rather than a collection of different hormone secreting cells. It posits that KD reduces the stress on both alpha and beta cells, by reducing requirement and secretion of glucagon and insulin. Thus, it resets the bipolar insulin—glucagon fulcrum—at a lower, more physiological, level.²³ The antiepileptogenicity of KD is well documented; however, children with type 1 diabetes seem to have a greater incidence of seizures.²⁴

Obesity

KD is also used as a weight loss therapy.²⁵ Published data show excellent results in the short- and mid-term; however, long-term adherence is a challenge. The mechanisms of weight loss include reduction in calorie intake due to satiety mediated through general and protein-specific pathways; an increase in resting expenditure and postprandial thermogenesis; and an increase in lipolysis with a reduction of lipogenesis.²⁶

The adrenals

KD is characterized by increased sympathetic activity.²⁷ This is thought to be a contributory factor for the weight loss noted with this diet. High protein-fed animals have been demonstrated to have heavier adrenal glands than low protein-fed peers.²⁸ However, there are no published

human studies which explore the link between adrenal function and ketosis. The relationship between adrenal status and response to KD has not been studied either.

Testosterone

KD has been shown to increase total, but not free, testosterone, in college-aged, resistance-trained athletes. It is thought that this may be due to the increased cholesterol content, or the reduced fibre content, of KD. While testosterone is known to reduce body fat, the action of KD does not seem to be mediated through serum testosterone modulation. The increase of testosterone with KD can be thought to contribute to an anabolic effect, but this seems highly unlikely. Rather, it is the high protein composition of KD that leads to an anabolic or muscle-building effect.¹²

Polycystic ovary syndrome

The similarity in pathogenesis of polycystic ovary syndrome (PCOS) with type 2 diabetes and obesity has led to the use of KD in this condition. KD has been found helpful in correction of PCOS and in the management of acne as well.^{29,30} Case series, randomized controlled trials, and reviews suggest a role for KD in improving fertility in PCOS as well.^{31–33}

Conclusion

This communication introduces the concept of ketocrinology, which we define as study of the relationship between ketosis, including KD, and endocrine function of the body. Ketocrinology is relevant to every glandular function, including that of the pituitary, thyroid, parathyroid, islet of Langerhans, adrenal, testis, and ovary. The article explores the vast spectrum of this subject and calls for wide-ranging research in the field. □

1. Wheless JW. History of the ketogenic diet. *Epilepsia*. 2008;49:3–5.
2. Gupta L, Khandelwal D, Kalra S, et al. Ketogenic diet in endocrine disorders: Current perspectives. *J Postgrad Med*. 2017;63:242.
3. Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. *Front Psychol*. 2015;6:27.
4. Kossoff EH, Cervenka MC, Henry BJ, et al. A decade of the modified Atkins diet (2003–2013): Results, insights, and future directions. *Epilepsy Behav*. 2013;29:437–42.
5. Joslin EP. The treatment of diabetes mellitus. *Can Med Assoc J*. 1916;6:673–84.
6. Masino S (ed). *Ketogenic Diet and Metabolic Therapies. Expanded Roles in Health and Disease*. New York: Oxford University Press, 2017.
7. Westman EC, Feinman RD, Mavropoulos JC, et al. Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr*. 2007;86:276–84.
8. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. *JAMA*. 2018;319:215–7.
9. Cahill Jr GF, Veech RL. Ketoacids? Good medicine? *Trans Am Clin Climatol Assoc*. 2003;114:149.
10. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr*. 2013;67:789.
11. Santos HO. Ketogenic diet and testosterone increase: Is the increased cholesterol intake responsible? To what extent and under what circumstances can there be benefits? *Hormones* 2017;16:266–70.
12. Schooling CM, Yeung SL, Freeman G, Cowling BJ. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med*. 2013;11:57.
13. Parkkila S, Vullo D, Maresca A, et al. Serendipitous fragment-based drug discovery: ketogenic diet metabolites and statins effectively inhibit several carbonic anhydrases. *Chem Commun (Camb)*. 2012;48:3551–3.
14. Young FG. The pituitary gland and carbohydrate metabolism. *Endocrinology*. 1940;26:345–51.
15. Johnson RE, Passmore R, Sargent F. Multiple factors in experimental human ketosis. *Arch Int Med*. 1961;107:43–50.
16. Song P, Zechner C, Hernandez G, et al. The hormone FGF21 stimulates water drinking in response to ketogenic diet and alcohol. *Cell Metab*. 2018;27:1338–47.
17. Ibarz A, Costa R, Harrison AP, Power DM. Dietary keto-acid feed-back on pituitary activity in gilthead sea bream: Effects of oral doses of AKG. A proteomic approach. *Gen Comp Endocrinol*. 2010;169:284–92.
18. Jepson MM, Bates PC, Millward DJ. The role of insulin and thyroid hormones in the regulation of muscle growth and protein turnover in response to dietary protein in the rat. *Br J Nutr*. 1988;59:397–415.
19. Ciardella F, Morelli E, Caprioli R, et al. Restoration of thyroid secretion in uremic patients following a low protein low phosphorus diet supplemented with essential amino acids and keto analogues. *Contr Nephrol*. 1986;53:51–7.
20. Lindenau K, Kokot F, Fröhling PT. Suppression of parathyroid hormone by therapy with a mixture of keto analogues/amino acids in hemodialysis patients. *Nephron*. 1986;43:84–6.
21. Lafage MH, Combe C, Fournier A, Aparicio M. Ketodiet, physiological calcium intake and native vitamin D improve renal osteodystrophy. *Kidney Int*. 1992;42:1217–25.
22. Staverosky T. Ketogenic Weight Loss: The Lowering of Insulin Levels Is the Sleeping Giant in Patient Care. *J Med Pract Manage*. 2016;32:63.
23. Azar ST, Beydoun HM, Albadri MR. Benefits of ketogenic diet for management of type two diabetes: a review. *J Obes Eat Disord*. 2016;2:1–3.
24. Kalra S, Gupta Y. The insulin: glucagon ratio and the choice of glucose-lowering drugs. *Diabetes Therapy*. 2016;7:1–9.
25. Kalra S, Unnikrishnan AG, Gupta Y. Epileptogenicity of diabetes and antiepileptogenicity of ketogenic states: Clarity or confusion? *Indian J Endocrinol Metab*. 2016;20:583.
26. Paoli A. Ketogenic diet for obesity: friend or foe? *Int J Environ Res Public Health*. 2014;11:2092–107.
27. Owen BM, Ding X, Morgan DA, et al. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metab*. 2014;20:670–7.
28. Tepperman J, Engel FL, Long CN. Effect of high protein diets on size and activity of the adrenal cortex in the albino rat. *Endocrinology*. 1943;32:403–9.
29. Muscogiuri G, Palomba S, Laganà AS, Orio F. Current insights into inositol isoforms, mediterranean and ketogenic diets for polycystic ovary syndrome: From bench to bedside. *Curr Pharm Des*. 2016;22:5554–7.
30. Toniolo AP, Canato M, Bianco A, Fratter A. Therapeutic Potential of Ketogenic Diets. *Pharmacology*. 2012;25:111–7.
31. Alwahab UA, Pantalone KM, Burguera B. A ketogenic diet may restore fertility in women with polycystic ovary syndrome: a case series. *AAACE Clinical Case Reports* 2018;4:e427–31.
32. Mavropoulos JC, Yancy WS, Hepburn J, Westman EC. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab (Lond)*. 2005;2:35.
33. McGrice M, Porter J. The effect of low carbohydrate diets on fertility hormones and outcomes in overweight and obese women: a systematic review. *Nutrients*. 2017;9:204.