Evidence on chronic ketosis in traditional Arctic populations

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Introduction

Two alternate hypotheses about human adaptation to nutritional ketosis are contrasted by the supposition of the first that ketosis is foremost an adaptation to cope with periods of starvation, and therefore would be stressful if prolonged, whereas the second considers long-term ketosis natural and safe due to presumed adaptation to extended periods of negligible carbohydrate availability. If there were concrete evidence of a traditional population whose members were usually in ketosis, this would support the second hypothesis by providing a precedent. American Arctic populations traditionally followed a diet that might be expected to be ketogenic due to low levels of carbohydrate intake. Therefore, historical reports finding a lack of ketosis have been surprising. Moreover, some evidence suggests that these populations have a genetic mutation preventing significant ketogenesis. Because an adaptation that can reduce ketogenesis occurred specifically in an environment known to be perpetually low in carbohydrates and which would therefore otherwise result in chronic ketosis, some writers have proposed that this proves chronic ketosis is sufficiently detrimental to health that evolution selects against ketogenesis (Ballantyne 2017, Masterjohn 2017, Chuter 2019). However, the evidence on which this argument rests has important limitations that impact the conclusions. In this brief review, I describe these limitations and conclude that there is insufficient evidence to rule out chronic ketosis in Arctic populations, and provide alternative explanations for the findings consistent with the second hypothesis.

There are two lines of evidence suggesting that Arctic Peoples were not in ketosis. The first comes from experiments over the last century in which ketosis was measured as negative in indigenous Alaskans and Greenlanders. As detailed below, although ketosis was not detected in many of the following cases, the results may be explained by the diet including significant carbohydrates, or the testing methods being insufficiently sensitive. These points hinge on the definition of "in ketosis". I will follow Guerci et al. (2003) and Gibson et al. (2015) in using a serum β-hydroxybutyrate (BOHB) of 0.5 mM as the threshold of ketosis although, lower values have been used (See e.g. Mitchell et al. 1995 who use 0.2 mM).

Evidence from ketone testing

In searching the literature, I found five studies reporting on four experiments measuring ketosis in natives of the North American Arctic between 1928 and 1972. Two studies in Baffin Island measured urine BOHB over several days of fasting in a total of seven subjects (Heinbecker 1928, 1931). They found urinary ketosis in all subjects, but only after the first day of fasting had elapsed. With the exception of two subjects, who were

nursing mothers, one of whom was also pregnant, the level of ketosis was lower than expected for fasting. These subjects were on a traditional diet composed of only animal foods. A third experiment was conducted in 1949 on Southampton Island (Sinclair 1953) and measured urine acetoacetate (AcAc), and again found ketosis only in the fasted condition. Finally, a fourth study, reported in both Ho et al. (1972) and Feldman et al. (1975) found no ketosis in native people of Point Hope, AK even after nearly a day of fasting (fasting ranged from 16-26 hours). If we expected them to already be in ketosis from their diets, this would be surprising. However, the diets were not traditional and included an average carbohydrate intake of 150-280g of carbohydrate a day, which would not be expected to induce ketosis. So, this study cannot inform us about the question at hand, whether they would be in ketosis on their traditional diets, and it is not considered further.

The lack of ketones found in the urine of fed individuals in the first three studies could be interpreted as indicating they were not in fact, in ketosis, as claimed in the aforementioned writings. However, there is another interpretation consistent with these findings. Two factors could result in negative ketone measurements, even if ketosis was present.

First, levels of urinary ketones associated with fasting are not normally expected in people metabolically adjusted to nutritional ketosis. This adjustment is called keto-adaptation, and can take 4-6 weeks (Volek and Phinney 2011). It is well known now, and was known to some even when the later of those studies were conducted, that after some time on a ketogenic diet, urinary ketones subside. For example, In subjects studied by McClellan and DuBois (1930) the ketonuria diminished after several months on a carbohydrate-free diet. Rodahl et al. (1954) cite observations attributed to Peters and Van Slyke in 1946 who said that in their camp, an Eskimo who had been eating regular high carb rations, had ketonuria to the same high degree as the non-Eskimo men in the camp when given a ketogenic diet. They thus suggest that the lower ketonuria reported by others was due to metabolic adjustment.

This reported phenomenon of reduced or absent urinary ketones in keto-adapted individuals may be explained by 1) as ketosis develops, the ratio of AcAc to BOHB decreases (Owen 1974, Balasse 1979, Neal et al. 2009), sinces more AcAc is converted into BOHB (Volek and Phinney 2012) and 2) that AcAc is excreted proportionately to blood levels (Passmore 1961). So, if keto-adaptation has occurred, but the overall level of AcAc + BOHB is lower than what would be found in fasting, then urinary AcAc may be expected to fall below detectable levels, as discussed below. A second possible contributor to the keto-adaptation effect comes from the problem of using a single variable to characterize a multivariate system. The production and use of ketone bodies each have variable rates. That means it is possible that production and use could both increase, even while detected levels decrease, provided that the

DOI: 10.15310/2334-3591.1101

increase in use exceeds the increase in production. Ideally, we could use a measure of the actual use of ketone bodies as fuel, for example respiratory quotient (RQ). Studies including RQ measurements have been reported in Greenland (Krogh and Krogh 1915) and in both Heinbecker's above-mentioned Baffin Island studies. Krogh and Krogh measured RQ, but the diet in their experiments was high in carbohydrates, including bread, sugar, and dried fruits. The average daily caloric and carbohydrate intake was 2366 kCal and 430 g, respectively. Therefore, it is neither surprising nor informative that RQ levels were consistently high, ranging from 0.75, on the lowest calorie and carbohydrate days, to 1.11. In Heinbecker's fasting studies, RQ levels averaged 0.70 after one day of fasting. However, I found no studies with measurements prior to fasting on a traditional diet.

The second factor is that urinary measurements were not developed to detect the milder levels of ketosis found in fed people on maintenance calories as compared to fasting or ketoacidosis. The nitroprusside method used to detect urine AcAc by Sinclair above will still today often give a negative result when serum BOHB is below 1.0. Harano et al. (1984) report that 39 children with serum BOHB ranging from 0.1 to 4.0 mM registered no ketonuria. Seven of these, or 18%, had serum BOHB of at least 0.5 mM. Even keto-acidosis, which can entail much higher levels of BOHB, is sometimes not detected as ketonuria (Stojanovic 2011). For example, Bektas et al. (2004) found a ketonuria sensitivity of only 66%, although others have reported sensitivity in the 95-98% range (Schwab 1999, Hendey 1997, Arora 2011).

Considering that even weight stable keto-adapted athletes have been reported with an average BOHB level of only 0.6 mM (Volek 2016), it seems reasonable to assume that a population in chronic ketosis not associated with weight loss would also have levels this low. In this case it would be unremarkable if ketosis were not measured in the urine of these populations, even if present. Urinary BOHB as used by Heinbecker in his studies may be even more susceptible to false negative error, because unlike AcAc, which is excreted linearly with respect to serum concentrations, BOHB excretion rises more exponentially (Passmore 1961), and therefore it's possible it would not appear at all in the urine at mild, keto-adapted non-fasting serum levels, even though it would appear in the higher levels associated with fasting. In a 1969 review of ketonuria tests, Bradley states that there are no practical urine tests for BOHB (Bradley 1969). This appears to remain the case today.

Evidence from genetics

A second reason cited by the aforementioned authors that Arctic populations were not chronically in ketosis comes from a prevalent genetic variant of CPT1A known as the Arctic variant. The CPT1A enzyme is required for transporting fatty acids into liver mitochondria for oxidation and is thus on the critical path for hepatic ketogenesis

(Zammit 2011). The variant, found in Arctic populations worldwide (Collins et al. 2010, Gessner et al. 2011, Clemente et al. 2014), has been found to reduce CPT1A activity from 2-54% (average 22%) (Collins et al. 2010). Clinically, this has resulted in fasting intolerance in some young children who are homozygous for the variant. (Gillingham et al. 2011). Not only do they present as hypoketotic when fasted, but hypoglycemic as well, because gluconeogenesis is reliant on hepatic fatty acid oxidation (Tutwiler and Dellevigne 1979, Longo et al. 2006) via glucagon (Briant et al. 2018). Unless the environment was consistently abundant in food, this suggests there must have been a strong selective advantage to the variant to overcome its risk of homozygosity. Moreover, it raises the question of how the affected would have provided fuel to the brain without exogenous glucose if both ketogenesis and gluconeogenesis are compromised.

However, the effect of the variant may depend on dietary factors. The dietary context in the Arctic was not only low in carbohydrate, but it was relatively high in protein, and very high in fat (Krogh and Krogh 1915, Heinbecker 1928 and 1931, Sinclair 1953). Specifically, because primary foods included sea mammals such as seals, and cold water fish, it was extraordinarily high in long-chain polyunsaturated fatty acids (PUFAs) (Bang 1980). PUFAs are much more ketogenic than more saturated fatty acids. Cunnane summarises the evidence for ketogenic capacity of fatty acids as α-linolenate >linoleate >oleate >palmitate >stearate (Cunnane 2004). Fuehrlein et al. (2004) found a ketogenic diet of mixed PUFAs to result in BOHB levels more than twice as high as one composed of saturated fatty acids in human subjects. Ide et al. (2000) measured CPT1A activity in rat hepatocytes in response to different dietary fat sources: palm oil, safflower oil, perilla oil, and fish oil. The higher the level of polyunsaturates in the diet, the more fatty acid oxidation and the more CPT1 activity. In particular, hepatocytes from those consuming fish oil, high in DHA and EPA, had 61% higher CPT1 enzyme activity than those consuming the palm oil. A diet high in PUFAs would also be expected to increase PPAR-α transcription factor (Echevarria et al. 2016), CPT1A gene expression (van Schothorst et al. 2009, Kaplinskyi et al. 2009, Radler et al. 2011), and mitochondrial number (Flachs et al. 2005), each of which could compensate for lowered CPT1A activity in ways that would not be evident in fibroblast studies not using PUFAs, nor in affected children eating non-traditional diets (Koeller 2018).

In light of the strong possibility that traditional diets reduced the impact of the Arctic variant on fat metabolism, we can speculate on independent advantages of the variant that would have been allowed without full compromise of ketogenic capacity. One potential advantage that has been proposed comes from a second effect of the variant. Besides its reduction of CPT1A activity, the variant also reduces sensitivity of CPT1A to malonyl-CoA (Brown et al. 2001). Malonyl-CoA is a product of glucose (and thus protein) metabolism on the path of de novo lipogenesis. Normally, CPT1A activity is sensitive to malonyl-CoA and reduced in its presence, but this sensitivity is attenuated

in those with the Arctic variant (Brown et al. 2001), with the result that a higher tolerance of protein intake should be expected before ketogenesis would be halted. Some researchers have suggested that this potential protein tolerance may have been the selective advantage of the variant (Greenberg et al. 2009). Moreover, the effect may be most advantageous in the heterozygous case, since the reduction in fatty acid oxidation behaves more recessively, and the reduction in malonyl-CoA sensitivity behaves more dominantly (Koeller 2018).

Conclusions

Given that the PUFA content of traditional Arctic diets may compensate for the genetic reduction of CPT1A activity, and that the absence of urinary ketones found in early studies in North America may reflect fat adaptation and limitations in testing technology, current speculation about the lack of a ketogenic state in traditionally living Arctic peoples cannot be considered settled. Further studies of carriers of this gene variant in the appropriate context are warranted. If further studies confirm that Arctic populations avoid ketosis on traditional diets, this would not necessarily eliminate the hypothesis that long-term ketosis is safe for other populations, nor even that there were none. On the other hand, if ketogenesis is rescued by the appropriate dietary context, this casts doubt on the hypothesis that chronic ketosis is detrimental, because we would have a demonstrated precedent.

References

Arora, S., Henderson, S.O., Long, T., & Menchine, M. (2011). Diagnostic Accuracy of Point-of-Care Testing for Diabetic Ketoacidosis at Emergency-Department Triage. *Diabetes care*.

Ballantyne, Sarah (2017). “Paleo Principles: The Science Behind the Paleo Template, Step-by-Step Guides, Meal Plans, and 200+ Healthy & Delicious Recipes for Real Life.” Victory Belt Publishing.

Balasse, E.O. (1979). Kinetics of ketone body metabolism in fasting humans. *Metabolism: clinical and experimental, 28 1*, 41-50.

Bang, H., Dyerberg, J., & Sinclair, H.M. (1980). The composition of the Eskimo food in north western Greenland. *The American journal of clinical nutrition, 33 12*, 2657-61.

Bektaș, F., Eray, O., Sari, R., & Akbas, H.S. (2004). Point of care blood ketone testing of diabetic patients in the emergency department. *Endocrine research, 30 3*, 395-402 .

Bradley, G. M. and E. S. Benson (1969). Examination of the urine. In Todd-Sanford: *Clinical Diagnosis by Laboratory Methods* (14th ed.), I. Davidsohn and J. B. Henry, eds., chapter 3, P. 65. Philadelphia: Saunders.

Briant, L.J., Dodd, M.S., Chibalina, M.V., Rorsman, N.J., Johnson, P.R., Carmeliet, P., Rorsman, P., & Knudsen, J.G. (2018). CPT1a-Dependent Long-Chain Fatty Acid Oxidation Contributes to Maintaining Glucagon Secretion from Pancreatic Islets. *Cell reports, 23 11*, 3300-3311 .

Brown, N.F., Mullur, R.S., Subramanian, I., Esser, V., Bennett, M.J., Saudubray, J.M., Feigenbaum, A.S., Kobari, J.A., Macleod, P.M., McGarry, J., & Cohen, J.C. (2001). Molecular characterization of L-CPT I deficiency in six patients: insights into function of the native enzyme. *Journal of lipid research, 42 7*, 1134-42 .

Chuter, R (2019 Jan 17) *Is the Ketogenic Diet Natural for Humans?* Retrieved from https://nutritionstudies.org/is-the-ketogenic-diet-natural-for-humans/

Clemente, F.J., Cardona, A., Inchley, C.E., Peter, B.M., Jacobs, G.S., Pagani, L., Lawson, D.J., Antao, T., Vicente, M., Mitt, M., DeGiorgio, M., Faltyskova, Z., Xue, Y., Ayub, Q., Szpak, M., Mägi, R., Eriksson, A., Manica, A., Raghavan, M., Rasmussen, M.L., Rasmussen, S., Willerslev, E., Vidal-Puig, A., Tyler-Smith, C., Villems, R., Nielsen, R., Metspalu, M., Malyarchuk, B.A., Derenko, M.V., & Kivisild, T. (2014). A Selective Sweep on a Deleterious Mutation in CPT1A in Arctic Populations. *American journal of human genetics, 95 5*, 584-589 .

Collins, S.A., Sinclair, G.B., McIntosh, S.F., Bamforth, F., Thompson, R., Sobol, I., Osborne, G.M., Corriveau, A., Santos, M.D., Hanley, B., Greenberg, C.R., Vallance, H.D., & Arbour, L. (2010). Carnitine palmitoyltransferase 1A (CPT1A) P479L prevalence in live newborns in Yukon, Northwest Territories, and Nunavut. *Molecular genetics and metabolism, 101 2-3*, 200-4 .

Cunnane, S.C. (2004). Metabolism of polyunsaturated fatty acids and ketogenesis: an emerging connection. *Prostaglandins, leukotrienes, and essential fatty acids, 70 3*, 237-41 .

Echeverría, F., Ortiz, M., Valenzuela, R., & Videla, L.A. (2016). Long-chain polyunsaturated fatty acids regulation of PPARs, signaling: Relationship to tissue development and aging. *Prostaglandins, leukotrienes, and essential fatty acids, 114*, 28-34 .

Feldman, S.A., Rubenstein, A.H., K-J, H., Taylor, C.B., Lewis, L.A., & Mikkelson, B. (1975). Carbohydrate and lipid metabolism in the Alaskan Arctic Eskimo. *The American journal of clinical nutrition, 28 6*, 588-94 .

Flachs, P., Horakova, O., Brauner, P., Rossmeisl, M., Pecina, P., Hal, N.L., Růžičková, J., Sponarová, J., Drahota, Z., Vlček, Č., Keijer, J., Houštěk, J., & Kopecký, J. (2005). Polyunsaturated fatty acids of marine origin upregulate mitochondrial biogenesis and induce β -oxidation in white fat. *Diabetologia, 48*, 2365-2375.

Fuehrlein, B.S., Rutenberg, M.S., Silver, J.N., Warren, M.W., Theriaque, D.W., Duncan, G., Stacpoole, P.W., & Brantly, M.L. (2004). Differential metabolic effects of saturated versus polyunsaturated fats in ketogenic diets. *The Journal of clinical endocrinology and metabolism, 89 4*, 1641-5 .

Gessner, B.D., Gillingham, M.B., Johnson, M.A., Richards, C.S., Lambert, W.E., Sesser, D.E., Rien, L.C., Hermerath, C.A., Skeels, M.R., Birch, S.M., Harding, C.O., Wood, T., & Koeller, D.M. (2011). Prevalence and distribution of the c.1436C→T sequence variant of carnitine palmitoyltransferase 1A among Alaska Native infants. *The Journal of pediatrics, 158 1*, 124-9 .

Gibson, A.A., Lee, C.M., Ayre, J.M., Franklin, J., Markovic, T.P., Caterson, I.D., & Sainsbury, A. (2015). Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity, 16 1*, 64-76.

Gillingham, M.B., Hirschfeld, M., Lowe, S., Matern, D., Shoemaker, J.D., Lambert, W.E., & Koeller, D.M. (2011). Impaired fasting tolerance among Alaska native children with a common carnitine palmitoyltransferase 1A sequence variant. *Molecular genetics and metabolism, 104 3*, 261-4 .

Greenberg, C.R., Dilling, L.A., Thompson, G.R., Seargeant, L.E., Haworth, J.C., Phillips, S.S., Chan, A., Vallance, H.D., Waters, P.J., Sinclair, G.B., Lillquist, Y.P., Wanders, R.J., & Olpin, S.E. (2009). The paradox of the carnitine palmitoyltransferase type Ia P479L variant in Canadian Aboriginal populations. *Molecular genetics and metabolism, 96 4*, 201-7 .

Guerci, B., Benichou, M., Floriot, M., Bohme, P., Fougnot, S., Franck, P., & Drouin, P. (2003). Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. *Diabetes care, 26 4*, 1137-41 .

Harano, Y., Suzuki, M., Kojima, H., Kashiwagi, A., Hidaka, H., & Shigeta, Y. (1984). Development of paper-strip test for 3-hydroxybutyrate and its clinical application. *Diabetes care, 7 5*, 481-5 .

Heinbecker, Peter (1928). Studies on the Metabolism of Eskimos. *Journal of Biological Chemistry*.

Heinbecker, Peter (1931). Further Studies on the Metabolism of Eskimos. *Journal of Biological Chemistry.*

Hendey, G.W., Schwab, T., & Soliz, T. (1997). Urine Ketone Dip Test as a Screen for Ketonemia in Diabetic Ketoacidosis and Ketosis in the Emergency Department. *Annals of emergency medicine, 29 6*, 735-8 .

Ho, K.J., Mikkelson, B., Lewis, L.A., Feldman, S.A., & Taylor, C.B. (1972). Alaskan Arctic Eskimo: responses to a customary high fat diet. *The American journal of clinical nutrition, 25 8*, 737-45.

Ide, T., Kobayashi, H., Ashakumary, L., Rouyer, I.A., Takahashi, Y., Aoyama, T., Hashimoto, T., & Mizugaki, M. (2000). Comparative effects of perilla and fish oils on the activity and gene expression of fatty acid oxidation enzymes in rat liver. *Biochimica et biophysica acta, 1485 1*, 23-35.

Kaplins'kyĭ, S.P., Shysh, A.M., Nahibin, V.S., Dosenko, V., Klimashevs'kyĭ, V.M., & Moibenko, O.O. (2009). [Omega-3 polyunsaturated fatty acids stimulate the expression of PPAR target genes]. *Fiziolohichnyi zhurnal, 55 2*, 37-43 .

Koeller, D. (2018). Personal communication.

Krogh, A. and Krogh, M. (1915). A study of the diet and metabolism of eskimos undertaken in 1908 on an expedition to greenland. *Meddelelser om Grønland*., 51.

Longo, N., Filippo, C.A., & Pasquali, M. (2006). Disorders of carnitine transport and the carnitine cycle. *American journal of medical genetics. Part C, Seminars in medical genetics, 142C 2*, 77-85 .

Masterjohn, C. (2016, Oct 26) *Inuit genetics show us why evolution does not want us in constant ketosis.*Retrieved from https://chrismasterjohnphd.com/2017/10/26/inuit-genetics-show-us-evolution-not-want-us-constant-ketosis-mwm-2-37/.

McClellan, S and Eugene F. Du Bois. (1930) Prolonged Meat Diets with a Study Function and Ketosis. *The Journal of Biological Chemistry*, 87, 651-668.

Mitchell, G.A., Kassovska-Bratinova, S., Boukaftane, Y., Robert, M.F., Wang, S.-., Ashmarina, L., Lambert, M., Lapierre, P., & Potier, E. (1995). Medical aspects of ketone body metabolism. *Clinical and investigative medicine. Medecine clinique et experimentale, 18 3*, 193-216.

Neal, E.G., Chaffe, H.M., Schwartz, R.H., Lawson, M.S., Edwards, N.J., Fitzsimmons, G., Whitney, A., & Cross, J.H. (2009). A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia, 50 5*, 1109-17 .

Owen, O. E. (1974). Ketone bodies as a fuel for the brain during starvation. *Biochemistry and Molecular Biology Education*, 33(4):246-251.

Passmore, R. (1961). On ketosis. *The Lancet*, 277(7182):839-843.

Radler, U., Stangl, H., Lechner, S., Lienbacher, G., Krepp, R., Zeller, E., Brachinger, M., Eller-Berndl, D., Fischer, A., Anzur, C., Schoerg, G., Mascher, D.G., Laschan, C., Anderwald, C.H., & Lohninger, A. (2011). A combination of (ω-3) polyunsaturated fatty acids, polyphenols and L-carnitine reduces the plasma lipid levels and increases the expression of genes involved in fatty acid oxidation in human peripheral blood mononuclear cells and HepG2 cells. *Annals of nutrition & metabolism, 58 2*, 133-40 .

Rodahl, K., C. R. Shaw, and H. F. Drury (1954). Studies on the blood and blood pressure in the eskimo and the significance of ketosis under arctic conditions. *Norsk Polar Institute, Skrifter*, 102.

Schwab, T.M., Hendey, G.W., & Soliz, T. (1999). Screening for ketonemia in patients with diabetes. *Annals of emergency medicine, 34 3*, 342-6 .

Sinclair, H. M. (1953). The diet of canadian indians and eskimos. *Proceedings of the Nutrition Society*, 12(1):6982.

Stojanovic, V., & Ihle, S.L. (2011). Role of beta-hydroxybutyric acid in diabetic ketoacidosis: a review. *The Canadian veterinary journal = La revue veterinaire canadienne, 52 4*, 426-30 .

Tutwiler, G.F., & Dellevigne, P. (1979). Action of the oral hypoglycemic agent 2-tetradecylglycidic acid on hepatic fatty acid oxidation and gluconeogenesis. *The Journal of biological chemistry, 254 8*, 2935-41 .

van Schothorst, E.M., Flachs, P., Hal, N.L., Kuda, O., Bunschoten, A., Molthoff, J.W., Vink, C., Hooiveld, G.J., Kopecký, J., & Keijer, J. (2008). Induction of lipid oxidation by polyunsaturated fatty acids of marine origin in small intestine of mice fed a high-fat diet. *BMC Genomics, 10*, 110 - 110.

Volek, J. and S. Phinney (2012). “The art and science of low carbohydrate performance : a revolutionary program to extend your physical and mental performance envelope”. Beyond Obesity.

Zammit, V. A. (2011). “Comprehensive Physiology”, chapter in Regulation of Ketogenesis in Liver. John Wiley & Sons, Inc.