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Two alternate hypotheses regarding the ketogenic diet are contrasted by the supposition of the first that ketosis is a stressor, mimicking starvation, whilst the second hypothesis posits that ketosis is natural and safe, attenuating evolutionary mismatch of the modern, post-agricultural diet. In support of the first hypothesis are findings that the levels of corticosteroid and thyroid hormones differ between subjects on ketogenic diets and those on high carbohydrate diets such that the measurements in ketogenic diets, if found under high carbohydrate conditions, could indicate illness or stress. However, ketogenic diets and high carbohydrate diets use distinct metabolic pathways in different proportions. It would be astonishing if all biomarker reference ranges were identical in both contexts, since they reflect metabolic processes. Moreover, the literature does not consistently interpret these hormonal markers as detrimental. In some cases, such interpretation would be contradictory. In fact, the same experimental results can be used to support the alternative hypothesis without introducing contradictions. As such, the second hypothesis has more explanatory power.

In a recent paper by Ebbeling et al. (2012) and the press release accompanying it (Boston Children's Hospital (2012)) three dietary interventions, low fat, very-low carbohydrate (VLC), and low glycemic index, were compared for their effects on measures of metabolic syndrome. The VLC diet performed significantly better, but was not recommended and was in fact cautioned against. The rationale for this choice was based on another measurement, urinary cortisol, which was mildly elevated in the VLC dieters, and which is associated with risk of cardiovascular disease. The concern is that while the VLC diet may improve some markers of metabolism, it may simultaneously increase risk for heart disease. As expressed in the press release, "The very low-carbohydrate diet produced the greatest improvements in metabolism, but with an important caveat: This diet increased participants' cortisol levels, which can lead to insulin resistance and cardiovascular disease." In other words, the mixed results are interpreted as a short-term improvement in symptoms at the expense of an ongoing underlying stressor, reflected only by the cortisol, that will eventually take a toll on health, ironically in the form of insulin resistance.

However, there is an alternative interpretation. In a study by Stimson et al. (2007) cited as confirmation of the effect, a small rise in cortisol in VLC dieters was shown to be a direct result of the reversal of cortisol dysregulation characteristic of metabolic syndrome. The reason is that in metabolic syndrome, cortisol levels are often moderately reduced due to impaired ability to compensate for increased clearance and reduced regeneration (Purnell et al. (2004), Purnell et al. (2009), Holt et al. (2007)). The VLC diet rescues this reduction. Therefore, the moderate increase in cortisol in the very low

carbohydrate arm of the study need not be viewed as a paradoxical marker of insulin resistance warranting caution. To the contrary, the lower cortisol levels found in the higher carbohydrate arms could be viewed as demonstrating inferior resolution of metabolic syndrome. This interpretation would be consistent with the other findings.

There is precedent for interpreting an increase in cortisol in response to dietary intervention as beneficial, but for other reasons. In the study of longevity, where the hard end-points of lifespan can definitively recommend one intervention over another, it is widely acknowledged that in animals with increased lifespan due to dietary restriction, cortisol levels are moderately increased relative to controls. In this context, the finding is interpreted as stemming from known anti-inflammatory and anti-carcinogenic actions of cortisol (Fontana and Klein (2007), Morgan et al. (2007), Klebanov (2007)). From the perspective of the hypothesis that ketosis is natural and safe, the relative lowering of cortisol in modern, post-agricultural diets could be viewed as a sign of disruption in processes that evolved to keep inflammation in check.

A second example of a metabolic marker that is known to differ significantly between high and low carbohydrate diets is the thyroid hormone triiodothyronine (T3). There are several situations not corresponding to hypothyroid disease in which T3 can appear to be low from a high carbohydrate lens, but is appropriate in context. A VLC diet is among those, and its function appears to be to preserve muscle mass (Kaptein et al. (1985), Yang and van Itallie (1984)). As with the case in enhanced cortisol levels, lower T3 is also a finding in longevity, not only in animal interventions where it is again, supposed to play a mechanistic role (Fontana et al. (2006)), but also in long lived humans (Baranowska et al. (2007), Rozing et al. (2010)). The relatively high levels of T3 seen as a result of high carbohydrate diets are therefore predictive of shorter lifespan from a purely statistical standpoint.

The comparison between ketogenic diets and starvation can make sense only from a worldview in which high carbohydrate diets are the default. Humans are naturally in ketosis without caloric deficit or inadequate protein levels so long as carbohydrates are restricted. This ability appears to be unique to our species, and is likely intimately related to our large brains, as it tracks developmentally with brain growth (Persson and J. (1966), Kraus et al. (1974), Bougneres et al. (1986)). This unique ketogenic facility in the fed state strongly suggests a selective advantage to ketosis that co-opted the previous function of starvation fuel. For this advantage to have been selected and developed to this degree, it must have been in frequent operation. That is, the low carbohydrate condition must have been prevalent.

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There are known common effects of ketogenic diets and caloric restriction, such as in metabolic efficiency as evidenced by increases in the NAD+:NADH ratio (Maalouf et al. (2007)), increases in mitochondrial biogenesis (Bough et al. (2006)), and decreases in radical oxygen species (Maalouf et al. (2007), Bough and Rho (2007)), and in such as effects on brain derived neurotrophic factor (Marosi et al. (2016)), nuclear factor kappa beta and the inhibition of histone deacetylases (Maalouf (2009)). Nonetheless, it should not be surprising if some effects of caloric restriction do not transfer to calorie and protein sufficient ketogenic diets, simply because satiety is signaled biochemically, and this signal would be chronically attenuated in caloric restriction, but not in an ad libitum ketogenic diet, by definition.

An example may come from the "disposable soma" theory of aging, which accounts for the observation that some animals shut down reproductive function and live longer in response to caloric restriction, with the explanation that prolonged lack of satiety signals an inopportune reproductive environment, and those species that responded to these signals by postponing reproduction until the environment improved were naturally selected (Kirkwood and Shanley (2005), Shanley and Kirkwood (2006), Hart and Turturro (1998), Turturro and Hart (1992)). However, in the protein and calorie sufficient ketogenic condition, there is no evidence of compromised reproductive ability or appearance of the "female athlete triad", a syndrome of chronic caloric restriction that presents as amenorrhea and osteoporosis. To the contrary, recent studies report that bone density is not adversely affected by a VLC diet (Bertoli et al. (2014), Brinkworth et al. (2016)), and there is preliminary evidence that infertility associated with polycystic ovarian syndrome may be improved by a VLC diet (McGrice and Porter (2017)). Relatedly, while children on ketogenic diets for the treatment of epilepsy do experience reduced growth when protein and calories are restricted, they do not when protein and calories are adequate (Nation et al. (2014)). It may be suggested that since infants and children have an evolved ability to remain in ketosis while fully fed and growing, that reproduction also regularly occurred under the same nutritional pressures.

In light of these observations, rather than viewing ketosis as mimicking starvation, and therefore conferring stress on humans in ketosis long-term, chronic ketosis may be considered a natural state. This perspective would resolve some apparent contradictions and concerns found in studies of very low carbohydrate dieters, and would explain our unique ketogenic readiness as a species.

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