Review Article

The Carnivore Connection Hypothesis: Revisited

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The "Carnivore Connection" hypothesizes that, during human evolution, a scarcity of dietary carbohydrate in diets with low plant : animal subsistence ratios led to insulin resistance providing a survival and reproductive advantage with selection of genes for insulin resistance. The selection pressure was relaxed at the beginning of the Agricultural Revolution when large quantities of cereals first entered human diets. The "Carnivore Connection" explains the high prevalence of intrinsic insulin resistance and type 2 diabetes in populations that transition rapidly from traditional diets with a low-glycemic load, to high-carbohydrate, high-glycemic index diets that characterize modern diets. Selection pressure has been relaxed longest in European populations, explaining a lower prevalence of insulin resistance and type 2 diabetes, despite recent exposure to famine and food scarcity. Increasing obesity and habitual consumption of high-glycemic-load diets worsens insulin resistance and increases the risk of type 2 diabetes in all populations.

1. Introduction

Nearly two decades ago, Brand-Miller and Colagiuri published the Carnivore Connection hypothesis [1], proposing that dietary carbohydrate, both quantity and quality, played a critical role in the natural history of type 2 diabetes. We proposed that low glucose intake associated with a low-carbohydrate, high-protein carnivorous diet during the Ice Ages which dominated the last two million years of human evolution led to insulin resistance becoming a survival and reproductive advantage. When food energy was abundant, but dietary carbohydrate scarce, those with greater inherent insulin resistance were able to redirect glucose from maternal use to fetal metabolism, increasing birth weight and survival of offspring. In certain groups of people, other factors such as geographic isolation or starvation may have contributed further to positive selection for insulin resistance genes.

We also hypothesized that the selective pressure for insulin resistance was relaxed with the advent of agriculture and increased amounts of carbohydrate in the diet. Domestication of cereals first began around 12,000 years ago in

the Middle East and spread throughout Europe before it was developed elsewhere. Populations that have only recently adopted agriculture are therefore likely to have a higher prevalence of genes for insulin resistance compared with those exposed for longer timeframes. In susceptible populations, life style changes, including higher carbohydrate intake, weight gain, and sedentary habits, worsen insulin resistance and expose the genetic predisposition to type 2 diabetes. Westernization is associated with a high-carbohydrate, high-glycemic index (GI) diet, which produces sustained postprandial hyperinsulinemia, high insulin secretory capacity, and potentially β-cell dysfunction. The highest prevalence of type 2 diabetes is seen in recent hunter-gatherer populations who have rapidly westernized, including Pima Indians, Nauruans, and Australian Aboriginals [2–4].

Europeans and their descendants appear to be the only group with a relatively low predisposition to type 2 diabetes, even in the midst of the current epidemic of obesity [5].

Since the publication of the original hypothesis in 1994, there have been notable changes in the prevalence of type 2 diabetes and new findings relating to glucose metabolism
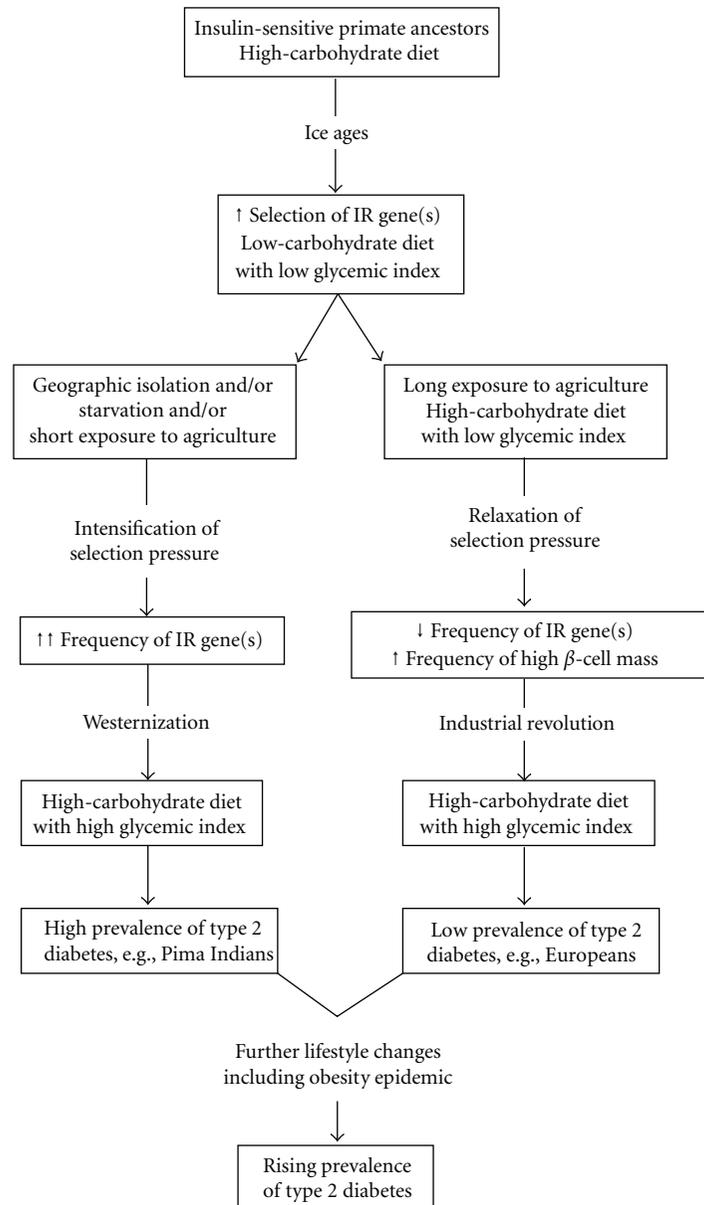
FIGURE 1: The Carnivore Connection hypothesis [1] and association with recent increased prevalence of insulin resistance (IR) and type 2 diabetes in susceptible (e.g., Pima Indian) and nonsusceptible (e.g., European) populations.

in pregnancy and in response to different types of diet. The aim of this paper is to update the hypothesis and examine recent evidence. The revised Carnivore Connection hypothesis is shown in Figure 1 and hinges on five (four old and one new) lines of evidence.

(1) During the last two million years of evolution, humans were increasingly carnivorous, that is, consumed a low-carbohydrate, high-protein diet.

(2) A low-carbohydrate, high-protein diet requires profound insulin resistance to maintain glucose homeostasis, particularly during reproduction.

(3) Genetic differences in insulin resistance and predisposition to type 2 diabetes can be explained by differences in exposure to carbohydrate during the past 12,000 years.

(4) Changes in the quality of carbohydrate can explain the higher prevalence of type 2 diabetes in susceptible populations.

(5) Habitual consumption of a high-glycemic-load diet worsens insulin resistance and contributes to the obesity and type 2 diabetes in all populations.

2. The Low-Carbohydrate Existence

Over 2.5 million years ago, our prehuman ancestors in Africa lived in a warm, moist environment in which carbohydrate derived from fruit and berries was an important source of energy [6]. However, with the beginning of the Pleistocene 2.5 million years ago, came at least 11 distinct glaciations, the last of which ended ~12,000 years ago, with the start of the Holocene. With the first severe Ice Age, global temperatures fell dramatically and resulted in moist African forest becoming dry, open woodland and savannah [7]. Hominids that were unable to utilize grasslands became increasingly carnivorous. The first stone tools in the fossil record coincide with the existence of *Homo habilis* 2 million years ago, suggesting that they may have supplemented a vegetarian diet with scavenged or hunted meat [8]. *H. erectus* who lived 1.5 million years ago is known to have actively hunted and was the first species to systematically make tools and use fire [8]. In Africa and Eurasia, hunted animals displaced gathered plant foods as the principal source of food, leading to a diet low in carbohydrate and high in protein for most of the year. Increased meat intake from wild terrestrial and marine animals would have also provided greater amounts of omega-3 fatty acids such as docosahexaenoic acid essential for brain development, facilitating the larger brain size of *H. sapiens* [9, 10].

Hunting and fishing continued to dominate the way of life through subsequent Ice Ages in a variety of geographical environments. Even during the warmer interglacials, parts of the world remained cold and humans maintained a hunting/fishing existence, for example, the historical Eskimo diet of arctic Canada, Alaska, Greenland, and Russia that was almost devoid of readily absorbable carbohydrate [11]. Where ecologically possible, hunter gatherer populations consumed high amounts of animal food [12]. Wild plant foods such as berries and root vegetables would have supplied some carbohydrate especially at lower latitudes and during interglacials. However, much of the carbohydrate was unavailable [13] and elicited a low glycemic response in part due to a large amount of fiber. The amount of carbohydrate may have ranged from as little as 10 g up to 125 g a day, much lower than the typical 250 to 400 g per day consumed in modern diets [6]. The diets of contemporary hunter-gatherers probably contained around 20–35% energy from protein and 20–40% of energy from carbohydrate [12]. Reconstruction of paleolithic diets in East Africa incorporating different foraging strategies generates similar values: 25–30% energy from protein and 40% energy from carbohydrate [14].

The advent of agriculture 12,000 years ago led to increased cereal consumption and high intakes of available starch for the first time in human evolution [15]. Agriculture began in the Middle East, and, after spreading rapidly to Europe, it extended gradually throughout Asia and the Americas. However, some groups such as the Meso-Americans and Pima Indians adopted agriculture only recently, that is, within the last 5,000 years, while Australian Aboriginal people never developed agriculture [16]. The early settlers of the Nauru and other Pacific atolls consumed a diet high in fish and coconuts supplemented at various times by root crops [17].

3. Metabolic Consequences of a Low-Carbohydrate, High-Protein Diet

Certain metabolic adaptations were necessary to accommodate low carbohydrate intake because the brain and reproductive tissues had evolved a specific requirement for glucose as a source of fuel [18, 19]. The phenotypic expression of this adaptation is insulin resistance in the liver and peripheral tissues. Long-term consumption of a low-carbohydrate, high-protein diet increases insulin resistance [20], with a rise in hepatic glucose production (mediated through an increased carbon flux through the gluconeogenic pathway) and a decrease in peripheral glucose utilization resulting from hypoinsulinemia [21]. In acute experiments using euglycemic hyperinsulinemic clamps, amino acids stimulate postprandial insulin and glucagon secretion without a commensurate change in plasma glucose [22]. In isoenergetic diets, insulin sensitivity as assessed by clamp was 33% lower after 6 wk of a high-protein diet than after 6 wk of a high-carbohydrate diet [23]. High-protein intake was associated with a tendency to increased protein expression in adipose tissue of the translation initiation factor serine-kinase-6-1, which is known to mediate amino-acid-induced insulin resistance.

In a low-carbohydrate environment, mild insulin resistance may have increased survival, but reproduction probably required greater degrees of intrinsic insulin resistance. Glucose is the main fuel for fetal growth [24–26], and low glucose availability would compromise fetal survival. Even though increased gluconeogenesis is one of the first adaptations to pregnancy, maternal glucose levels decline in early pregnancy [27, 28]. Greater insulin resistance in the maternal tissues would increase the likelihood of higher maternal glucose concentration. In healthy pregnant women, fetal growth is directly correlated with maternal glucose concentration [29], and larger infants (with greater likelihood of survival) are born to women with higher glucose concentrations [28]. Insulin-sensitive animals may not be able to meet the increased demand for preformed glucose during pregnancy. Obtaining adequate glucose for fetal growth from gluconeogenesis can be difficult, especially in younger women [27], but may be possible if dietary protein is sufficiently high [25, 26]. Offspring survival could also be affected due to the increased demand for glucose during lactation. In rats, utilization of glucose and other lipogenic precursors by the mammary gland is facilitated by muscular insulin resistance [30, 31].

Hence, a reproductive and survival advantage appears to exist in individuals with a greater degree of insulin resistance on a low-carbohydrate diet. This inherited insulin resistance may involve different genes/enzymes than dietary-induced insulin resistance. Insulin-sensitive subjects seem to find a low-carbohydrate, high-protein diet difficult to tolerate, with side effects such as nausea and headache [32, 33]. On the other hand, insulin resistant subjects [34, 35] and genetically obese animals [36] appear to tolerate a high-protein diet very

well. Studies have shown high-protein diets produce the most desirable metabolic profile in individuals with type 2 diabetes [37–39].

4. Differences in Predisposition to Type 2 Diabetes

Insulin resistance can lead to β-cell decompensation and eventually type 2 diabetes [40]. We propose that the selection pressure for insulin resistance was relaxed first in Europeans when dietary carbohydrate increased 12,000 years ago with the advent of agriculture [15]. In accordance with this long-term exposure, Europeans have experienced a lower prevalence of diabetes, even when overweight and obese (see Section 6), compared to other population groups. High carbohydrate intake over the past millennia may have also increased positive selection for genes associated with higher β-cell mass. In Swedish and Finnish populations, variants in 11 genes (*TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1,* and *HHEX*) are significantly associated with the risk of type 2 diabetes independently of clinical risk factors [41]. Variants in 8 of these genes were associated with impaired β-cell function. Populations that adopted agriculture more recently such as the Pima Indians are likely to have a higher prevalence of genes transcribing insulin resistance or impaired β-cell function than those exposed for thousands of years.

The Carnivore Connection hypothesis has been tested recently in sample populations from the Asian steppes [42]. Ten candidate genes for insulin resistance, anthropometry, and physiological measures, including HOMA insulin resistance, were compared in traditional herders (pastoralists = high-protein diet) and farmers (agriculturalists = high-carbohydrate diet). While none of the genes tested showed causal mutations with higher frequency in herders, tests of neutrality showed some genes (SLC30A8, LEPR, and KCNQ1) could have been involved in past adaptations to diet. Consistent with the Carnivore Connection hypothesis, the prevalence of insulin resistance was significantly greater in herders compared to farmers, despite no major differences in current diet.

Environmental pressures such as geographic isolation and/or starvation may have led to further increases in the prevalence of insulin resistance gene(s) in certain population groups. Geographic isolation has led to genetic bottlenecks and reduced genetic diversity in the Nauruans and Pima Indians [43]. Both populations have also been exposed to food shortages and starvation in the recent past. As occurs with low carbohydrate intake, starvation results in the need for increased gluconeogenesis and peripheral insulin resistance [44]. This may have selected for those with a profound degree of insulin resistance which was inherited by future offspring. Women with polycystic ovarian syndrome are known to be exceptionally insulin resistant and may represent a group that was highly fertile in a low-carbohydrate environment [45].

Insulin resistance has previously been proposed to be the mechanism for coping with variable food intake during evolution [46, 47]. Neel's thrifty gene hypothesis postulates that cycles of feast and famine selected for a "quick insulin trigger" (postprandial hyperinsulinemia) as a mechanism to increase fat stores during food abundance and available during food scarcity [48]. An alternative hypothesis by Reaven [49] suggests that muscle insulin resistance was the key to survival during food scarcity because it conserved glucose by minimizing gluconeogenesis and preserving lean body mass.

Both these hypotheses are based on the assumption that there were challenging periods of food scarcity prior to the advent of agriculture. However, this is not supported by the scientific literature [50]. While hunter gatherers would have been exposed to seasonal and geographical changes in food supply, severe food shortages or starvation were rare and more likely to occur *after* the transition to agriculture (preindustrialization). Specific mechanisms for coping with low carbohydrate intake, rather than total dietary energy, probably afforded the greatest reproductive and survival advantages.

Genome-wide scans and other research have been directed towards discovering the gene(s) associated with insulin resistance and type 2 diabetes. However, the complexity of human metabolism means that there are likely to be multiple gene systems involved, including those that influence insulin sensitivity and others that influence β-cell function [51]. PC-1 (plasma cell membrane glycoprotein-1), which interferes with insulin receptor tyrosine kinase activity, thereby inhibiting subsequent cellular signalling [52], has been associated with insulin resistance [53]. Reduced expression of the "susceptibility" gene CAPN10 (calpain-10) has been linked to decreased glucose uptake in skeletal muscle [54]. Recently, the ACAD10 (acyl coenzyme A dehydrogenase 10) gene has been associated with fatty-acid-induced insulin resistance [55] as it may catalyze mitochondrial fatty-acid oxidation [56].

5. The Quality of the Carbohydrate

Dietary carbohydrate quality changed markedly with the industrial revolution in the 17th century. Prior to this, cereals were typically eaten whole or coarsely ground or flaked, with large particles of intact fiber and starchy endosperm that was less easily gelatinized during cooking. As a result, cereal carbohydrates were slowly digested and absorbed, eliciting small postprandial glucose and insulin responses [57, 58]. Irrespective of GI, the high intake of insoluble cereal fiber likely reduced the burden on the β-cell by enhancing insulin sensitivity, perhaps via acceleration of GIP (glucose-dependent insulinotropic polypeptide) [59, 60]. Thus, the β-cells probably coped well on the postagriculture high-carbohydrate low-GI diet. Most traditional hunter-gatherer carbohydrate foods have been shown to be low in GI [61, 62]. While traditional hunter-gather diets did not provide cereal fiber, they would have contained soluble and insoluble fiber derived from fruits and vegetables [63], which acts to slow glucose absorption and enhance glycemic control [64].

The industrial revolution marked the era of the high-GI, high-glycemic load diet. New high-speed steel roller mills allowed cereal grains to be more finely ground and the fiber

separated and removed. The degree of gelatinization during cooking increased and thus the rate of carbohydrate digestion and absorption, producing greater postprandial increases in glycemia and insulinemia [58, 65]. High-GI varieties of potatoes were introduced to western diets at this time, contributing to a higher dietary glycemic load [66]. The modern high-carbohydrate, high-GI diet therefore elicits more insulin secretion, that is, a higher insulin demand. Oxidative stress within the β-cell could therefore contribute to increased apoptosis and gradual reduction in β-cell mass [67]. Eventually, in susceptible individuals with higher degrees of insulin resistance and reduced β-cell mass, impaired glucose tolerance and type 2 diabetes develop [40, 68]. Those with inborn, inherent insulin resistance face the greatest challenges when exposed to Westernization [69, 70].

Hales and Barker [71] suggest that β-cell dysfunction manifests in individuals exposed *in utero* and in early life to suboptimal nutrition. But both high- and low-birth-weight infants are predisposed to greater insulin resistance at birth [72]. High-carbohydrate-weaning diets are associated with greater insulin resistance and risk of type 2 diabetes in animal models. In gestational diabetes, exposure *in utero* to hyperglycemia stimulates fetal insulin secretion and fetal growth, resulting in high birth weight and increased appetite [73]. The U-shaped association between birth weight and risk of type 2 diabetes has been documented in the Pima Indians [74].

Consequently, both the quantity and quality of the carbohydrate in modern diets are relevant to the prevention of type 2 diabetes. Alternate dietary strategies that limit postprandial hyperglycemia, including high-protein diets, Mediterranean-style diets, and low-glycemic load diets, are associated with greater weight loss [75] and metabolic advantages in overweight individuals [76]. In meta-analyses, low-GI diets have improved diabetes control [77]. In large scale observational studies, low-GI and low-glycemic-load diets have been associated with reduced risk of developing type 2 diabetes [68, 78]. Low-GI diets may assist weight control by improving satiety and increasing the utilization of stored fuels [79]. In both animals [80, 81] and humans [82–84], low-GI diets have improved weight management.

6. The Obesity Epidemic and Recent Dietary Changes

In recent decades, overweight and obesity have risen to epidemic proportions in both developed and developing countries [85]. Rapid increases in body weight among children and younger age groups indicate that environment and lifestyle, not just genetic predisposition, play critical roles in the etiology of chronic disease [86]. Declining physical activity and energy expenditure worsen insulin resistance and the likelihood of incremental weight gain [87]. While the causes of the obesity epidemic are complex and multifactorial, worldwide dietary trends over the last three decades, including lower protein intake as a proportion of energy, higher consumption of refined cereals, and the substitution of carbohydrate for saturated fat, have led to substantial increases in average dietary glycemic load [88].

In a predominantly overweight and sedentary population, refined carbohydrates may cause greater metabolic damage than saturated fat [89].

While weight gain will occur whenever energy intake surpasses energy expenditure, diet composition has important influences on appetite, hunger/satiety, and therefore weight control. The Protein Leverage hypothesis [90] proposes that animals will overeat carbohydrate and fat in an effort to achieve a specific protein target. Overconsumption of energy on low-protein diets has been reported for insects, fish, birds, rodents, nonhuman primates, and humans, providing another example of metabolic pathways conserved by evolution. In large, well-designed randomized controlled trials, higher-protein diets have been associated with greater weight loss [91] and prevention of weight regain [92].

Diet composition also influences fuel partitioning, that is, the use of fatty acids versus glucose as the substrate for energy production [93]. Diets that increase postprandial hyperglycemia and hyperinsulinemia have been shown to promote carbohydrate oxidation at the expense of fat oxidation, an effect that may be conducive to increased adiposity [94, 95]. Low-GI diets may therefore enhance weight control by several mechanisms, including higher-satiety, higher-insulin sensitivity, and lower postprandial hyperinsulinemia. This hypothesis is supported by intervention studies showing that *ad libitum* consumption of low-GI foods promotes greater weight loss and prevention of weight regain than macronutrient matched diets based on high GI foods [92, 96, 97]. Long-term studies in animal models also show that high GI starch diets promote weight gain, visceral adiposity, and higher levels of lipogenic enzymes compared with isoenergetic, macronutrient-controlled low-GI starch diets [96, 97]. Finally, in healthy pregnant women, a high-GI diet is associated with higher birth weight and infant ponderal index than a nutrient-balanced low-GI diet [98]. In this way, epigenetic changes brought about by differences in diet composition during pregnancy could promote acceleration of obesity from one generation to the next [99].

Individuals that are capable of high postload insulin secretion may be the group most likely to accumulate fat on a high-glycemic-load diet and find weight loss difficult [100]. Thus, although Europeans may be less genetically susceptible to type 2 diabetes than other populations, the increasing prevalence of insulin resistance associated with obesity increases the likelihood of β-cell dysfunction and type 2 diabetes [101]. Any healthy diet that reduces postprandial glycemia and insulinemia, including high-protein, lower-carbohydrate diets, Mediterranean-style diets, and low-glycemic-load diets, may be preferable to the conventional high-carbohydrate, low-fat diet [75]. In a large European study, a modest increase in protein intake and a modest reduction in GI was associated with maintenance of weight loss and greater participant satisfaction [92].

A summary of the relationship between these lifestyle factors is shown in Figure 2.

7. Future Frontiers

Future research on fuel metabolism during pregnancy, gestational diabetes, and polycystic ovarian syndrome will
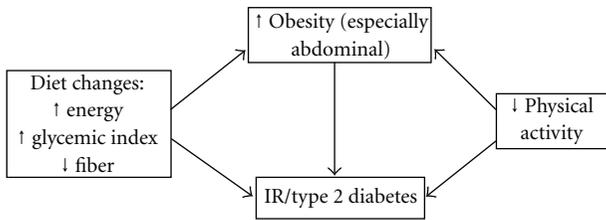
FIGURE 2: Interaction between modern lifestyle factors such as obesity, physical activity, and changing dietary intake (including energy density, glycemic index, and fiber) and the prevalence of insulin resistance (IR) and type 2 diabetes.

hopefully shed light on the origins of intrinsic insulin resistance in humans. The new field of metabolomics in which multiple plasma metabolites can be monitored in the postprandial state offers exciting opportunities. Anthropological studies in traditional hunter gatherers versus farmers and further animal studies, particularly in the pregnant state in carnivorous versus omnivorous mammals, will also provide data in support (or not) of the Carnivore Connection.

8. Conclusion

The Carnivore Connection argues that a scarcity of carbohydrate, rather than food energy, over the course of human evolution is intimately linked to the population risk of type 2 diabetes. We hypothesize that low glucose intake associated with a low-carbohydrate, high-protein diet during the Ice Ages led to positive selection of intrinsic insulin resistance as a survival and reproductive advantage. Alternate hypotheses, such as the thrifty genotype hypothesis, postulate that total dietary energy selected for insulin resistance, but there is currently no evidence that regular periods of food scarcity occurred prior to the advent of agriculture. Only the Carnivore Connection hypothesis explains the relatively low susceptibility to type 2 diabetes in Europeans versus other population groups. Consistent with the hypothesis, a recent trial found the prevalence of insulin resistance significantly greater in pastoralists compared to agriculturalists on the Asian steppes. Further research is required to determine whether genes associated with insulin resistance and β-cell function vary between recent hunter gatherers and longstanding farming populations. In the interim, protein intake and carbohydrate quality and quantity are relevant to the prevention and management of obesity and type 2 diabetes.

References

[1] J. C. Brand-Miller and S. Colagiuri, "The carnivore connection: dietary carbohydrate in the evolution of NIDDM," *Diabetologia*, vol. 37, no. 12, pp. 1280–1286, 1994.

[2] L. O. Schulz, P. H. Bennett, E. Ravussin et al., "Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S," *Diabetes Care*, vol. 29, no. 8, pp. 1866–1871, 2006.

[3] P. Zimmet, H. King, R. Taylor et al., "The high prevalence of diabetes mellitus, impaired glucose tolerance and diabetic retinopathy in nauru—the 1982 survey," *Diabetes Research*, vol. 1, no. 1, pp. 13–18, 1984.

[4] ABS, "Diabetes in Australia: a snapshot, 2004–6," in *Australian Bureau of Statistics*, Canberra, Australia, 2006.

[5] G. Dowse and P. Zimmet, "The thrifty genotype in noninsulin dependent diabetes," *British Medical Journal*, vol. 306, no. 6877, pp. 532–533, 1993.

[6] S. J. C. Gaulin and M. Konner, "On the natural diet of primates, including humans," in *Nutrition and the Brain*, R. J. Wurtman and J. J. Wurtman, Eds., pp. 1–86, Raven Press, New York, NY, USA, 1977.

[7] R. Bobe, A. K. Behrensmeyer, and R. E. Chapman, "Faunal change, environmental variability and late Pliocene hominin evolution," *Journal of Human Evolution*, vol. 42, no. 4, pp. 475–497, 2002.

[8] R. Lewin, *Human Evolution: An Illustrated Introduction*, Blackwell Publishing, Oxford, UK, 2005.

[9] L. C. Aiello and P. Wheeler, "The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution," *Current Anthropology*, vol. 36, pp. 199–221, 1995.

[10] L. Cordain, B. A. Watkins, and N. J. Mann, "Fatty acid composition and energy density of foods available to African hominids: evolutionary implications for human brain development," *World Review of Nutrition and Dietetics*, vol. 90, pp. 144–161, 2001.

[11] G. V. Mann, E. M. Scott, L. M. Hursch et al., "The health and nutritional status of Alaskan Eskimos: a survey of the Interdepartmental Committee on Nutrition for National Defence, 1958," *The American Journal of Clinical Nutrition*, vol. 11, pp. 31–39, 1962.

[12] L. Cordain, J. C. Brand-Miller, S. B. Eaton, N. Mann, S. H. A. Holt, and J. D. Speth, "Plant-animal subsistence ratios and macronutrient energy estimations in worldwide huntergatherer diets," *The American Journal of Clinical Nutrition*, vol. 71, no. 3, pp. 682–692, 2000.

[13] M. Kliks, "Paleodietetics: a review of the role of dietary fiber in preagricultural human diets," in *Topics in Dietary Fiber Research*, G. A. Spiller and R. F. Amen, Eds., pp. 181–202, Plenum Press, New York, NY, USA, 1978.

[14] R. S. Kuipers, M. F. Luxwolda, D. A. Dijck-Brouwer et al., "Estimated macronutrient and fatty acid intakes from an East African Paleolithic diet," *British Journal of Nutrition*, vol. 104, no. 11, pp. 1666–1687, 2010.

[15] S. B. Eaton and M. Konner, "Paleolithic nutrition: a consideration of its nature and current implications," *The New England Journal of Medicine*, vol. 312, no. 5, pp. 283–289, 1985.

[16] J. Flood, *Archaeology of the Dreamtime*, Angus and Robertson, Sydney, Australia, 1992.

[17] I. A. Prior, F. Davidson, C. E. Salmond, and Z. Czochanska, "Cholesterol, coconuts, and diet on Polynesian atolls: a natural experiment: the Pukapuka and Tokelau Island studies,"

The American Journal of Clinical Nutrition, vol. 34, no. 8, pp. 1552–1561, 1981.

[18] N. Freinkel, "Of pregnancy and progeny," *Diabetes*, vol. 29, no. 12, pp. 1023–1035, 1980.

[19] L. Sokoloff, G. G. Fitzgerald, and E. E. Kaufman, "Cerebral nutrition and energy metabolism," in *Nutrition and the Brain*, R. J. Wurtman and J. J. Wurtman, Eds., pp. 87–139, Raven Press, New York, NY, USA, 1977.

[20] T. Linn, B. Santosa, D. Grönemeyer et al., "Effect of long-term dietary protein intake on glucose metabolism in humans," *Diabetologia*, vol. 43, no. 10, pp. 1257–1265, 2000.

[21] L. Rossetti, D. L. Rothman, R. A. DeFronzo, and G. I. Shulman, "Effect of dietary protein on *in vivo* insulin action and liver glycogen repletion," *American Journal of Physiology*, vol. 257, no. 2, pp. E212–E219, 1989.

[22] P. Rossetti, F. Porcellati, N. B. Ricci et al., "Effect of oral amino acids on counterregulatory responses and cognitive function during insulin-induced hypoglycemia in nondiabetic and type 1 diabetic people," *Diabetes*, vol. 57, no. 7, pp. 1905–1917, 2008.

[23] M. O. Weickert, M. Roden, F. Isken et al., "Effects of supplemented isoenergetic diets differing in cereal fiber and protein content on insulin sensitivity in overweight humans," *The American Journal of Clinical Nutrition*, vol. 94, no. 2, pp. 459–471, 2011.

[24] D. R. Rosmos, H. J. Palmer, K. L. Muiruri, and M. R. Bensink, "The effect of dietary protein on *in vivo* insulin action and liver glycogen repletion," *American Journal of Physiology*, vol. 257, no. 2, pp. E212–E219, 1981.

[25] E. Kienzle, H. Meyer, and H. Lohrie, "Influence of carbohydrate-free rations with various protein/energy relationships on fetal development, viability of newborn puppies and milk consumption," *Advances in Animal Physiology and Animal Nutrition*, vol. 16, pp. 78–99, 1985.

[26] S. E. Blaza, D. Booles, and I. H. Burger, "Is carbohydrate essential for pregnancy and lactation in dogs?" in *Nutrition of the Dog and Cat*, I. H. Berger and J. P. W. Rivers, Eds., pp. 229–243, Cambridge University Press, Cambridge, UK, 1989.

[27] M. M. Thame, H. M. Fletcher, T. M. Baker, and F. Jahoor, "Comparing the glucose kinetics of adolescent girls and adult women during pregnancy," *The American Journal of Clinical Nutrition*, vol. 91, no. 3, pp. 604–609, 2010.

[28] N. F. Butte, "Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus," *The American Journal of Clinical Nutrition*, vol. 71, no. 5, pp. 1256S–1261S, 2000.

[29] B. E. Metzger, L. P. Lowe, A. R. Dyer et al., "Hyperglycemia and adverse pregnancy outcomes," *The New England Journal of Medicine*, vol. 358, no. 19, pp. 1991–2002, 2008.

[30] R. G. Vernon, "Endocrine control of metabolic adaptation during lactation," *Proceedings of the Nutrition Society*, vol. 48, no. 1, pp. 23–32, 1989.

[31] A. F. Burnol, M. Loizeau, and J. Girard, "Insulin receptor activity and insulin sensitivity in mammary gland of lactating rats," *American Journal of Physiology*, vol. 259, no. 6, pp. E828–E834, 1990.

[32] T. C. Crowe, "Safety of low-carbohydrate diets," *Obesity Reviews*, vol. 6, no. 3, pp. 235–245, 2005.

[33] P. A. Astrup, D. T. Meinert Larsen, and A. Harper, "Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss?" *The Lancet*, vol. 364, no. 9437, pp. 897–899, 2004.

[34] K. O'Dea, "Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle," *Diabetes*, vol. 33, no. 6, pp. 596–603, 1984.

[35] K. O'Dea and R. M. Spargo, "Metabolic adaptation to a low carbohydrate-high protein ("traditional") diet in Australian aborigines," *Diabetologia*, vol. 23, no. 6, pp. 494–498, 1982.

[36] J. Peret, A. C. Bach, B. Delhomme, B. Bois-Joyeux, M. Chanez, and H. Schirardin, "Metabolic effects of high-protein diets in Zucker rats," *Metabolism*, vol. 33, no. 3, pp. 200–207, 1984.

[37] B. Parker, M. Noakes, N. Luscombe, and P. Clifton, "Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes," *Diabetes Care*, vol. 25, no. 3, pp. 425–430, 2002.

[38] F. F. Samaha, N. Iqbal, P. Seshadri et al., "A low-carbohydrate as compared with a low-fat diet in severe obesity," *The New England Journal of Medicine*, vol. 348, no. 21, pp. 2074–2081, 2003.

[39] K. O'Dea, K. Traianedes, P. Ireland et al., "The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes," *Journal of the American Dietetic Association*, vol. 89, no. 8, pp. 1076–1086, 1989.

[40] R. Taylor, "Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause," *Diabetologia*, vol. 51, no. 10, pp. 1781–1789, 2008.

[41] V. Lyssenko, A. Jonsson, P. Almgren et al., "Clinical risk factors, DNA variants, and the development of type 2 diabetes," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2220–2232, 2008.

[42] L. Segurel, "Lifestyle and genetic diversity in human populations of Central Asia," in *Muséum National d'Histoire Naturelle*, Paris, France, 2010.

[43] S. Serjeantson and P. Zimmet, "Diabetes in the Pacific: evidence of a major gene," in *Diabetes Mellitus: Recent Knowledge on Aetiology, Complications and Treatment*, S. Baba, M. K. Gould, and P. Zimmet, Eds., pp. 23–30, Academic Press, Sydney, Australia, 1982.

[44] W. P. Newman and R. G. Brodows, "Insulin action during acute starvation: evidence for selective insulin resistance in normal man," *Metabolism*, vol. 32, no. 6, pp. 590–596, 1983.

[45] S. Corbett, A. McMichael, and A. Prentice, "Fertile on a famished road," Unpublished, 2011.

[46] K. O'Dea, "Westernisation, insulin resistance and diabetes in Australian Aborigines," *Medical Journal of Australia*, vol. 155, no. 4, pp. 258–264, 1991.

[47] M. Wendorf and I. D. Goldfine, "Archaeology of NIDDM: excavation of the "thrifty" genotype," *Diabetes*, vol. 40, no. 2, pp. 161–165, 1991.

[48] J. V. NEEL, "Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"?" *The American Journal of Human Genetics*, vol. 14, pp. 353–362, 1962.

[49] G. M. Reaven, "Hypothesis: muscle insulin resistance is the ("not-so") thrifty genotype," *Diabetologia*, vol. 41, no. 4, pp. 482–484, 1998.

[50] L. Cordain, J. Miller, and N. Mann, "Scant evidence of periodic starvation among hunter-gatherers," *Diabetologia*, vol. 42, no. 3, pp. 383–384, 1999.

[51] P. Z. Zimmet, "The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography," *Diabetes Care*, vol. 18, no. 7, pp. 1050–1064, 1995.

[52] B. A. Maddux and I. D. Goldfine, "Membrane glycoprotein PC-1 inhibition of insulin receptor function occurs via direct

interaction with the receptor α-subunit," *Diabetes*, vol. 49, no. 1, pp. 13–19, 2000.

[53] I. D. Goldfine, B. A. Maddux, J. F. Youngren et al., "The role of membrane glycoprotein plasma cell antigen 1/ectonucleotide pyrophosphatase phosphodiesterase 1 in the pathogenesis of insulin resistance and related abnormalities," *Endocrine Reviews*, vol. 29, no. 1, pp. 62–75, 2008.

[54] A. E. Brown, S. J. Yeaman, and M. Walker, "Targeted suppression of calpain-10 expression impairs insulin-stimulated glucose uptake in cultured primary human skeletal muscle cells," *Molecular Genetics and Metabolism*, vol. 91, no. 4, pp. 318–324, 2007.

[55] L. Bian, R. L. Hanson, Y. L. Muller et al., "Variants in ACAD10 are associated with type 2 diabetes, insulin resistance and lipid oxidation in Pima Indians," *Diabetologia*, vol. 53, no. 7, pp. 1349–1353, 2010.

[56] G. I. Shulman, "Cellular mechanisms of insulin resistance," *Journal of Clinical Investigation*, vol. 106, no. 2, pp. 171–176, 2000.

[57] D. J. A. Jenkins, T. M. S. Wolever, A. L. Jenkins, R. G. Josse, and G. S. Wong, "The glycaemic response to carbohydrate foods," *The Lancet*, vol. 2, no. 8399, pp. 388–391, 1984.

[58] K. W. Heaton, S. N. Marcus, P. M. Emmett, and C. H. Bolton, "Particle size of wheat, maize, and oat test meals: effects on plasma glucose and insulin responses and on the rate of starch digestion *in vitro*," *The American Journal of Clinical Nutrition*, vol. 47, no. 4, pp. 675–682, 1988.

[59] M. O. Weickert, M. Möhlig, C. Schöfl et al., "Cereal fiber improves whole-body insulin sensitivity in overweight and obese women," *Diabetes Care*, vol. 29, no. 4, pp. 775–780, 2006.

[60] M. O. Weickert, M. Mohlig, C. Koebnick et al., "Impact of cereal fibre on glucose-regulating factors," *Diabetologia*, vol. 48, no. 11, pp. 2343–2353, 2005.

[61] A. W. Thorburn, J. C. Brand, and A. S. Truswell, "Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor againt diabetes?" *The American Journal of Clinical Nutrition*, vol. 45, no. 1, pp. 98–106, 1987.

[62] J. C. Brand, B. J. Snow, G. P. Nabhan, and A. S. Truswell, "Plasma glucose and insulin responses to traditional Pima Indian meals," *The American Journal of Clinical Nutrition*, vol. 51, no. 3, pp. 416–420, 1990.

[63] M. Konner and S. B. Eaton, "Paleolithic nutrition: twenty-five years later," *Nutrition in Clinical Practice*, vol. 25, no. 6, pp. 594–602, 2010.

[64] P. Würsch and F. X. Pi-Sunyer, "The role of viscous soluble fiber in the metabolic control of diabetes: a review with special emphasis on cereals rich in β-glucan," *Diabetes Care*, vol. 20, no. 11, pp. 1774–1780, 1997.

[65] J. C. Brand, P. L. Nicholson, A. W. Thorburn, and A. S. Truswell, "Food processing and the glycemic index," *The American Journal of Clinical Nutrition*, vol. 42, no. 6, pp. 1192–1196, 1985.

[66] G. Fernandes, A. Velangi, and T. M. S. Wolever, "Glycemic index of potatoes commonly consumed in North America," *Journal of the American Dietetic Association*, vol. 105, no. 4, pp. 557–562, 2005.

[67] D. S. Ludwig, "The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease," *Journal of the American Medical Association*, vol. 287, no. 18, pp. 2414–2423, 2002.

[68] A. W. Barclay, P. Petocz, J. McMillan-Price et al., "Glycemic index, glycemic load, and chronic disease risk—a metaanalysis of observational studies," *The American Journal of Clinical Nutrition*, vol. 87, no. 3, pp. 627–637, 2008.

[69] S. Lillioja, B. L. Nyomba, M. F. Saad et al., "Exaggerated early insulin release and insulin resistance in a diabetes-prone population: a metabolic comparison of Pima Indians and caucasians," *Journal of Clinical Endocrinology and Metabolism*, vol. 73, no. 4, pp. 866–876, 1991.

[70] A. W. Thorburn, J. C. Brand, K. O'Dea, R. M. Spargo, and A. S. Truswell, "Plasma glucose and insulin responses to starchy foods in Australian Aborigines: a population now at high risk of diabetes," *The American Journal of Clinical Nutrition*, vol. 46, no. 2, pp. 282–285, 1987.

[71] C. N. Hales and D. J. P. Barker, "Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis," *Diabetologia*, vol. 35, no. 7, pp. 595–601, 1992.

[72] P. H. Whincup, S. J. Kaye, C. G. Owen et al., "Birth weight and risk of type 2 diabetes a systematic review," *Journal of the American Medical Association*, vol. 300, no. 24, pp. 2886–2897, 2008.

[73] M. R. G. Carrapato, "The offspring of gestational diabetes," *Journal of Perinatal Medicine*, vol. 31, no. 1, pp. 5–11, 2003.

[74] D. R. McCance, D. J. Pettitt, R. L. Hanson, L. T. H. Jacobsson, W. C. Knowler, and P. H. Bennett, "Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype?" *British Medical Journal*, vol. 308, no. 6934, pp. 942–945, 1994.

[75] A. E. Buyken, P. Mitchell, A. Ceriello, and J. C. Brand-Miller, "Optimal dietary approaches for prevention of type 2 diabetes: a life-course perspective," *Diabetologia*, vol. 53, no. 3, pp. 406–418, 2010.

[76] N. F. Sheard, N. G. Clark, J. C. Brand-Miller et al., "Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association," *Diabetes Care*, vol. 27, no. 9, pp. 2266–2271, 2004.

[77] J. C. Brand-Miller, S. Hayne, P. Petocz, and S. Colagiuri, "Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials," *Diabetes Care*, vol. 26, no. 8, pp. 2261–2267, 2003.

[78] I. Sluijs, Y. T. van der Schouw, D. L. van der A et al., "Carbohydrate quantity and quality and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study," *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 905–911, 2010.

[79] D. S. Ludwig, "Dietary glycemic index and the regulation of body weight," *Lipids*, vol. 38, no. 2, pp. 117–121, 2003.

[80] D. B. Pawlak, J. A. Kushner, and D. S. Ludwig, "Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals," *The Lancet*, vol. 364, no. 9436, pp. 778–785, 2004.

[81] F. Isken, S. Klaus, K. J. Petzke, C. Loddenkemper, A. F.H. Pfeiffer, and M. O. Weickert, "Impairment of fat oxidation under high- verus. low-glycemic index diet occurs before the development of an obese phenotype," *American Journal of Physiology*, vol. 298, no. 2, pp. E287–E295, 2010.

[82] T. M. Larsen, S. M. Dalskov, M. van Baak et al., "Diets with high or low protein content and glycemic index for weight-loss maintenance," *The New England Journal of Medicine*, vol. 363, no. 22, pp. 2102–2113, 2010.

[83] J. McMillan-Price, P. Petocz, F. Atkinson et al., "Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young

adults: a randomized controlled trial," *Archives of Internal Medicine*, vol. 166, no. 14, pp. 1466–1475, 2006.

[84] C. B. Ebbeling, M. M. Leidig, K. B. Sinclair, J. P. Hangen, and D. S. Ludwig, "A reduced-glycemic load diet in the treatment of adolescent obesity," *Archives of Pediatrics and Adolescent Medicine*, vol. 157, no. 8, pp. 773–779, 2003.

[85] WHO, "Obesity: preventing and managing the global epidemic," in *World Health Organization—Technical Report Series*, vol. 894, World Health Organization, Geneva, Switzerland, 2000.

[86] J. C. K. Wells, "The evolution of human fatness and susceptibility to obesity: an ethological approach," *Biological Reviews of the Cambridge Philosophical Society*, vol. 81, no. 2, pp. 183–205, 2006.

[87] US Department of Health and Human Services, "Physical activity and health: a report of the surgeon general," in *Atlanta*, 1996.

[88] WHO/FAO, "Diet, nutrition and the prevention of chronic diseases," in *World Health Organization*, Geneva, Switzerland, 2003.

[89] F. B. Hu, "Are refined carbohydrates worse than saturated fat?" *The American Journal of Clinical Nutrition*, vol. 91, no. 6, pp. 1541–1542, 2010.

[90] S. J. Simpson and D. Raubenheimer, "Obesity: the protein leverage hypothesis," *Obesity Reviews*, vol. 6, no. 2, pp. 133–142, 2005.

[91] T. L. Halton and F. B. Hu, "The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review," *Journal of the American College of Nutrition*, vol. 23, no. 5, pp. 373–385, 2004.

[92] T. M. Larsen, S. M. Dalskov, M. van Baak et al., "Diets with high or low protein content and glycemic index for weight-loss maintenance," *The New England Journal of Medicine*, vol. 363, no. 22, pp. 2102–2113, 2010.

[93] J. C. Brand-Miller, S. H. A. Holt, D. B. Pawlak, and J. McMillan, "Glycemic index and obesity," *The American Journal of Clinical Nutrition*, vol. 76, no. 1, pp. 281S–285S, 2002.

[94] E. Stevenson, C. Williams, and M. Nute, "The influence of the glycaemic index of breakfast and lunch on substrate utilisation during the postprandial periods and subsequent exercise," *British Journal of Nutrition*, vol. 93, no. 6, pp. 885–893, 2005.

[95] E. J. Stevenson, C. Williams, L. E. Mash, B. Phillips, and M. L. Nute, "Influence of high-carbohydrate mixed meals with different glycemic indexes on substrate utilization during subsequent exercise in women," *The American Journal of Clinical Nutrition*, vol. 84, no. 2, pp. 354–360, 2006.

[96] D. B. Pawlak, J. A. Kushner, and D. S. Ludwig, "Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals," *The Lancet*, vol. 364, no. 9436, pp. 778–785, 2004.

[97] D. B. Pawlak, J. M. Bryson, G. S. Denyer, and J. C. Brand-Miller, "High glycemic index starch promotes hypersecretion of insulin and higher body fat in rats without affecting insulin sensitivity," *Journal of Nutrition*, vol. 131, no. 1, pp. 99–104, 2001.

[98] R. G. Moses, M. Luebcke, W. S. Davis et al., "Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes," *The American Journal of Clinical Nutrition*, vol. 84, no. 4, pp. 807–812, 2006.

[99] K. M. Godfrey, A. Sheppard, P. D. Gluckman et al., "Epigenetic gene promoter methylation at birth is associated with child's Äôs later adiposity," *Diabetes*, vol. 60, no. 5, pp. 1528–1534, 2011.

[100] C. B. Ebbeling, M. M. Leidig, H. A. Feldman, M. M. Lovesky, and D. S. Ludwig, "Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial," *Journal of the American Medical Association*, vol. 297, no. 19, pp. 2092–2102, 2007.

[101] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030," *Diabetes Care*, vol. 27, no. 5, pp. 1047–1053, 2004.