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Evolutionary Aspects of Diet and Insulin Resistance

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Contents

75	Introduction
75	Insulin Resistance: Fundamentals and Epidemiology
77	Determinants of Insulin Resistance
78	Mechanism of Insulin Resistance
78	Consequences of Insulin Resistance and Hyperinsulinemia
79	Glucose Intolerance (IGT) and NIDDM
79	Coronary Heart Disease
79	Hypertension
80	Dyslipidemia
80	Other Abnormalities
80	Prevalence of the Components of the Metabolic Syndrome
80	Human Evolution and Insulin Resistance
83	Evidence for a 'Carnivore Connection' In Insulin Resistance
83	The Low Carbohydrate Existence
86	How Much Meat Did We Eat?
87	Metabolic and Biochemical Characteristics of Carnivores
89	Insulin Resistance: A Consequence of Low Carbohydrate Intake?
91	Consequences of a Low Carbohydrate Diet during Pregnancy
93	Metabolic Consequences of Dietary Changes since the Last Ice Age
97	Support for the 'Carnivore Connection' Hypothesis
99	Conclusion
99	The Future
100	References

Introduction

The terms ‘metabolic syndrome’ and syndrome X are used to describe a cluster of conditions that have insulin resistance as a common underlying abnormality [1]. The acute metabolic response to insulin resistance is hyperinsulinemia. The long-term result of insulin resistance and compensatory hyperinsulinemia is a variety of clinical and biochemical abnormalities which combine to significantly increase the risk of non-insulin-dependent diabetes mellitus (NIDDM) and coronary heart disease.

Insulin resistance is common in most populations and the diseases associated with it have reached epidemic proportions in groups such as the Australian Aborigines and Pima Indians. We propose that insulin resistance is common because it provided survival and reproductive advantages for our ancestors who ate a high meat ‘carnivorous’ diet. With a high-protein, low-carbohydrate diet, insulin resistance would *not* have induced compensatory hyperinsulinemia. However, with the progressive replacement of protein with carbohydrate in human diets over the past 10,000 years and more recently with the increase in the glycemic index of post-industrial diets, the underlying insulin resistance has resulted in deleterious hyperinsulinemia and the development of the metabolic syndrome.

This paper addresses the following issues: (1) basic considerations of insulin resistance and its epidemiology; (2) the consequences of insulin resistance and compensatory hyperinsulinemia; (3) various hypotheses which seek to explain the evolutionary changes resulting in the underlying insulin resistance, and (4) evidence in support of the ‘carnivore connection’ hypothesis.

Insulin Resistance: Fundamentals and Epidemiology

‘Insulin resistance’ is defined either as a state where greater than normal insulin levels are required to elicit a quantitatively normal (glucose) response in the whole body, a tissue or at the cellular level, or where physiological concentrations of insulin produce a less than normal biological response. The term is often used interchangeably with diminished insulin action or decreased insulin sensitivity. The importance of these subtle differences on conflicting research findings is not known. Furthermore a number of methodological difficulties have limited research endeavours.

Many methods have been used to assess insulin resistance. There is reasonable agreement between the two most commonly used methods – the euglycemic hyperinsulinemic clamp and the intravenous glucose tolerance test with minimal modelling [2]. It can be difficult to compare results of methodologies

which estimate insulin resistance in the basal state where the major determinant is insulin control of hepatic glucose output and in the insulin-stimulated state where the determinants include insulin-mediated glucose disposal, predominantly by muscle, and to a lesser extent insulin suppression of hepatic glucose output. A major limitation to population research remains the lack of a suitable method for assessing insulin resistance for epidemiological studies.

Unfortunately, there is no uniform quantitative definition of insulin resistance and therefore of what constitutes normality or abnormality. Quantitative comparisons of resistance to the action of insulin are difficult between populations and between individual subjects because of the need to standardise for age, gender, weight, physical fitness, glucose tolerance and blood pressure. A possible working definition of insulin resistance in an individual with normal glucose tolerance is a value in the range found in people with NIDDM.

The ability of insulin to stimulate cellular uptake of glucose varies considerably both within and between populations. However, the extent of this variation between populations has not been widely documented because of the general unsuitability for epidemiological studies of established methods of measuring insulin resistance. Insulin resistance is often inferred from elevated plasma insulin levels but these can be difficult to interpret because of the variables which influence insulin levels and also debate about what the assay is actually measuring.

Using the euglycemic hyperinsulinemic clamp method, in most populations, the mean M value (i.e. rate of glucose infusion during the clamp) for young normal weight subjects with normal glucose tolerance is of the order of 7–8 mg/kg body weight/min. This compares to values of 3–4 mg/kg/min in the extensively studied Pima Indians in whom insulin resistance is a common finding [3]. However, the direct comparison of these results is difficult because of the common occurrence of confounding variables such as obesity.

Some comparative data are available for Mexican Americans [40] and Australian Aborigines [5] consistent with the view that insulin resistance is more common in nondiabetic individuals of these populations. We have studied 100 aboriginal people (mean age 34 years, mean BMI 27) with normal glucose tolerance and assessed insulin resistance by homeostasis model assessment (HOMA) [6]. Nearly 60% had an insulin resistance index in the lower quartile compared with 20% of normal weight young nonaboriginal people.

Within populations, insulin resistance has been shown to vary more than fourfold in individuals with normal glucose tolerance. The defect in insulin action in approximately one quarter of these individuals does not differ substantially from that of patients with NIDDM [7]. In a study of men with normal glucose tolerance, we found 22% of young (mean age 24 years), normal weight (mean BMI 23) men had M values in the lowest quartile and this

Table 1. Physiological and pathological factors associated with muscle insulin resistance

Physiological factors	Pathological factors
Increasing age	Obesity, particularly visceral adiposity
Higher body fat	NIDDM
Sedentary lifestyle	Metabolic (insulin resistance) syndrome
Puberty	Coronary heart disease
Pregnancy	Low muscle mass (sarcopenia)
Lactation	Low physical fitness
High-fat diet (in animal models)	Trauma
High-protein diet	Sepsis
Low-carbohydrate diet	Starvation
Insulin-resistant genotype (ethnic differences)	

increased to 85% in older (mean age 54 years) overweight (mean BMI 29) men, an observation which is consistent with the increase in prevalence of the metabolic syndrome with age [8].

In summary, insulin resistance comparable with that seen in NIDDM is found in glucose tolerant individuals with varying frequency in all populations.

Determinants of Insulin Resistance

Both physiological and pathological factors are known to modulate insulin-mediated glucose disposal (table 1). Puberty, pregnancy, starvation, major trauma and sepsis are associated with insulin resistance. The benefits of insulin resistance under these conditions are various but would include redirecting blood glucose away from skeletal muscle and toward vital organs like the brain and placenta. Aging has a deleterious effect on glucose tolerance. For each decade of life fasting plasma glucose increases by 0.05 mmol/l and 1–2 h postprandial plasma glucose increases by 0.4–0.7 mmol/l. This deterioration is predominantly due to a decreased tissue sensitivity to insulin secondary to postreceptor event(s), possibly a decrease in glucose transporters [9, 10].

Obesity is universally recognized to increase insulin resistance irrespective of glucose tolerance but variability in the quantitation of the effect probably relates to the different measures used to assess obesity [11]. Increasing weight by more than 35–40% over ideal body weight results in a decline in tissue sensitivity to insulin by 30–40% [8]. In Caucasians there is an inverse linear relationship between body fat and insulin sensitivity [12] whereas in Pima Indians a similar relationship exists up to a 26% excess of body fat after which further increases in body fat result in equal resistance in all subjects [13]. The relationship is further complicated by the importance of the distribution of

adipose tissue with an accumulation of intra-abdominal or visceral fat having the strongest association with insulin resistance [14].

Increased physical fitness enhances insulin-mediated glucose disposal and hepatic insulin sensitivity. This effect can be demonstrated after 4–6 weeks of intensive physical training [15]. Greater physical exertion in our evolutionary past would have produced greater muscle mass, the major site of insulin-dependent glucose disposal. While several factors determine an individual's resistance to the effect of insulin, it is unlikely that these act independently although the relative contribution of each is unknown. For example, the decreased insulin sensitivity observed with increased age may be related to decreasing lean body weight and increasing body fat, and to decreasing levels of fitness and activity.

The factors known to modulate insulin sensitivity do not fully account for the variation observed in insulin-mediated glucose disposal. Studies in healthy mono- and dizygotic twins have shown that fasting insulin, glucose and body fat (central and total) are under genetic influence and suggest that some components of the metabolic syndrome are influenced by a common set of genes [16]. Studies in nondiabetic Pima Indians have demonstrated that in vivo insulin action shows familial aggregation which accounts for approximately 34% of the variance in this measure and is independent of age, sex, degree of obesity and $VO_{2\max}$ [17]. Since insulin action was measured after a prolonged stay in a metabolic ward on a standard diet it is unlikely to have been due to environmental differences. Furthermore, the distribution of insulin action in Pima Indians is consistent with the hypothesis that insulin resistance is determined by a single gene with a codominant mode of inheritance [18] and there are data linking this putative gene to chromosomal markers on 4q [19].

Mechanism of Insulin Resistance

The underlying mechanism(s) for resistance to the action of insulin is not known. Skeletal muscle is the principal site of insulin-mediated glucose disposal. Potential mechanisms for decreasing insulin action in disposing of glucose include diminished blood flow and transendothelial transport of glucose, altered phospholipid composition of muscle membrane [20], decreased receptor binding, a defect in the glucose transporter system, and abnormalities of intracellular nonoxidative and oxidative glucose metabolism [21].

Consequences of Insulin Resistance and Hyperinsulinemia

The metabolic compensatory consequence of insulin resistance is hyperinsulinemia, the primary purpose of which is to maintain normal glucose toler-

ance. However, this may lead to a cluster of other abnormalities, either directly or in genetically susceptible people.

Glucose Intolerance (IGT) and NIDDM

A major metabolic characteristic of NIDDM is insulin resistance which antedates the onset of the disease [22–24]. Glucose tolerance in an insulin-resistant individual is determined by the degree to which insulin secretion can be increased in response to the degree of insulin resistance. For a given level of insulin resistance, an appropriate increase in insulin secretion will maintain normal glucose tolerance, a lesser will result in IGT and an even lesser increase results in NIDDM. As fasting hyperglycemia increases there is a further decline in insulin secretion in people with NIDDM [3].

It remains to be established why beta cell function declines in the face of insulin resistance and prolonged hyperinsulinemia. Possibilities include an intrinsic genetic β -cell defect or damage from glucose toxicity, amylin deposition [25], environmental factors such as maternal/infant malnutrition [26], obesity or a combination of several factors.

Coronary Heart Disease

In recent years there have been many studies linking hyperinsulinemia with cardiovascular disease and atherosclerosis. High fasting insulin levels appear to be an independent predictor of ischemic heart disease in middle-aged [27] and elderly men [28] after adjustment for known risk factors such as systolic blood pressure and family history as well as plasma triglycerides, apolipoprotein B, LDL cholesterol and HDL cholesterol. Fasting insulin levels only 20% above normal increase the risk of disease by 60–100%. These results support the notion that hyperinsulinemia increases the risk of heart disease through alterations in metabolic processes other than the related dyslipidemia. Higher levels of plasminogen activator inhibitor-1 (PAI-1) are found in people who have had myocardial infarction and are postulated to inhibit fibrinolysis and increase the risk of total occlusion of coronary arteries already narrowed by atherosclerosis. A highly significant inverse relationship between PAI-1 and insulin-mediated glucose uptake has been demonstrated [29].

Hypertension

Insulin-mediated glucose uptake is reduced by 30–40% in people with essential hypertension [30] and is limited to nonoxidative pathways of glucose disposal (i.e. decreased glycogen synthesis). Insulin resistance correlates directly with the severity of the hypertension [8].

This defect in insulin action can be demonstrated in both nonobese and obese individuals with hypertension [31] and in young normotensive subjects

who are at increased risk of developing hypertension [32]. Furthermore, this abnormality continues to be present even after the hypertension has been treated effectively [33].

Potential mechanisms that produce the hypertension include sodium retention, overactivity of the sympathetic nervous system, disturbed membrane ion transport and proliferation of the vascular smooth muscle [8].

Comparison of normotensive, untreated hypertensive and treated hypertensive patients shows higher plasma glucose and insulin levels and insulin resistance in both hypertensive and normotensive groups [33] indicating blood pressure alone does not determine the abnormalities.

Dyslipidemia

Insulin resistance and/or hyperinsulinemia leads to increased secretion and decreased clearance of VLDL triglycerides by the liver [34] resulting from resistance to the action of insulin on lipoprotein lipase [8]. These abnormalities result in high plasma triglyceride levels and various associated abnormalities of plasma lipoprotein metabolism, e.g. low HDL cholesterol concentrations and the presence of smaller and denser LDL particles.

Other Abnormalities

Hyperuricemia is associated with coronary heart disease. In nondiabetic volunteers, a significant association has been found between serum uric acid, insulin resistance and the plasma insulin response to oral glucose [35].

Prevalence of the Components of the Metabolic Syndrome

The prevalence of the components of the syndrome varies among populations. The phenotypic expression of the underlying metabolic defects, namely insulin resistance and hyperinsulinemia will be determined by the overall prevalence of the genetic defect in the population and by the modulating factors such as age, weight and physical fitness of the individual. In a population with a presumed relatively low frequency of the insulin resistance genes, e.g. Europeans, the prevalence of the metabolic syndrome is relatively low in young individuals but is high among people over 65 [8]. In other populations, e.g. Nauruans, Pima Indians, Australian Aborigines, the prevalence is high even in young people and increases further with increasing age.

Human Evolution and Insulin Resistance

The body's complex regulatory mechanisms for carbohydrate homeostasis afford ample potential for genetic influence on the initiation and progression

Table 2. Hypotheses put forward to explain the current high prevalence of NIDDM

Hypothesis name	Authors and date
The thrifty genotype	Neel, 1962, 1992 [36, 37]
Modified thrifty genotype	O’Dea, 1991 [38]
Modified thrifty genotype	Wendorf and Goldfine, 1991 [39]
The thrifty phenotype	Hales and Barker, 1992 [26]
The carnivore connection	Brand Miller and Colagiuri, 1994 [49]
The non-thrifty genotype	Allen and Cheer, 1996 [40]
The surviving small baby genotype	McCance et al., 1994 [46]
The primary hypersecretion of insulin	DeFronzo, 1997 [47]

of insulin resistance. Many investigators believe that certain biochemical mechanisms which were advantageous during prior evolutionary experience may actually foster more pronounced insulin resistance and/or cause NIDDM under current conditions. Various hypotheses have been put forward to explain the high prevalence of NIDDM today (table 2). The well-known ‘thrifty genotype’ hypothesis, proposed by Neel [36, 37] in 1962, argues that cycles of feast and famine during human evolution selected for a genotype that promotes excessive weight gain during times of food abundance, thereby providing survival advantages during food scarcity. Neel proposed a central role for insulin in stimulating weight gain. Underpinning Neel’s theory is the premise that the high frequency of an undesirable inherited trait which results in obesity and NIDDM today, must have had survival advantages in the past.

O’Dea [38] and others [39] have proposed that insulin resistance is the phenotypic expression of the thrifty genotype. However, if long periods of starvation (enough to make normal fat stores insufficient) is the key to a high prevalence of the thrifty gene or insulin resistance gene, then every population in the world should be the same. It would be hard to find a population that has not at some point or other in the last few millennia experienced serious starvation and population crashes [40]. In particular, Europeans have suffered repeated famines in historical times [40] and, therefore, according to the Neel’s hypothesis, ought to have a high prevalence of the thrifty genotype. While they do indeed appear to be susceptible to overweight and obesity in the present environment, they are unique in having a low prevalence of NIDDM and underlying insulin resistance [41]. The challenge is to explain how Europeans came to have a low prevalence and low susceptibility to NIDDM.

Furthermore, as Swinburn [42] and Eckel [43] both point out, insulin resistance is a state which is more likely to promote weight maintenance than

weight gain, i.e. it would inhibit the transport of glucose into liver and fat cells and thereby inhibit the conversion of glucose to fat. In fact, among nondiabetic Pima Indians followed for several years, *the most insulin-sensitive* individuals had a higher risk of gaining excessive weight than the most insulin resistant [44]. Despite little evidence to substantiate Neel's hypothesis, it is still widely invoked to explain the high prevalence of obesity and NIDDM.

More direct mechanisms (i.e. other than the ability to draw on greater fat stores) to cope with food scarcity, particularly a scarcity of carbohydrate foods during pregnancy, were probably of more immediate survival advantage. These would include the ability to avoid severe ketosis (which results in mental retardation in the infant exposed in utero) and blunt the usual decline in plasma glucose which occurs with prolonged fasting or carbohydrate deprivation [45]. The capacity to spare muscle protein stores from degradation for gluconeogenic purposes (while still maintaining adequate glucose levels) would have been aided if glucose uptake by muscles was inhibited. Insulin resistance in the liver and muscles may have been the direct mechanism which achieved this.

On the other hand, Hales and Barker [26] have dismissed a genetic basis for the high prevalence of insulin resistance, obesity and NIDDM and invoke environmental causes instead. Their 'thrifty phenotype' hypothesis rests on maternal and infant malnourishment to explain the increase in these modern day diseases. Barker and colleagues have shown that low birth weight (<2,500 g) predicts the development of diabetes, high blood pressure and cardiovascular disease and subsequent NIDDM. McCance et al. [46] on the other hand, argue that there is a high mortality among low-birth-weight infants and the survivors tend to be more insulin resistant than those who perish (the 'surviving small baby genotype' hypothesis). This supports the contention that insulin resistance confers a selective advantage for survival under certain conditions. The fetus derives its fuel supply exclusively from the glucose that crosses the placenta from the mother. Thus, a more insulin-sensitive fetus may oxidise more glucose and convert less to fat than those with greater insulin resistance. The insulin-resistant infant will therefore be born with greater fat stores and perhaps greater ability to survive the neonatal period.

Recently, DeFronzo [47] has proposed that primary hypersecretion of insulin represents the basic genetic disturbance in NIDDM, and insulin resistance develops secondarily to down-regulation of the insulin receptor signal transduction system, glucose transport, glucose phosphorylation, or glycogen synthase. The observation that sustained physiological hyperinsulinemia of only 15–20 $\mu\text{U/ml}$ can induce severe insulin resistance supports this hypothesis [48]. However, hypersecretion of insulin is a phenomenon directly linked to the amount and type of carbohydrate in the diet.

We have postulated a critical role for the quantity and quality of the dietary carbohydrate in the etiology of insulin resistance and hyperinsulinemia [49]. Briefly, the hypothesis (the ‘carnivore connection’) proposes that the selective force for insulin resistance was the low-carbohydrate, high-meat diet that prevailed in many parts of the world during the Ice Ages that spanned the last two million years of human evolution. In this environment, we argue that insulin sensitivity would have been a liability, compromising survival and reproductive performance. While plant food (carbohydrate) was scarce, compensatory hyperinsulinemia would not have been needed to maintain normal glucose tolerance. But beginning about 10,000 years ago, following the end of the last Ice Age and the development of agriculture, the selection pressure for insulin resistance was relaxed in those groups consuming more carbohydrate. The prevalence of insulin resistance genes would have gradually declined in the European population and any other group exposed to high carbohydrate intake for long enough. Westernisation of previously ‘unexposed’ populations brings not only an increase in the quantity of carbohydrate, but also a change in the quality (to refined high glycemic index carbohydrate) that results in pronounced postprandial hyperinsulinemia and worsening insulin resistance. The insulin-resistant genotype is then disadvantageous and predisposes to the development of the metabolic syndrome. Our hypothesis is summarised in figure 1. In the following sections we describe in detail the arguments in favour of a ‘carnivore connection’ in the evolution of insulin resistance.

Evidence for a ‘Carnivore Connection’ in Insulin Resistance

The Low Carbohydrate Existence

Carbohydrate was an important part of the fruit-based diet of our prehuman ancestors [50] who lived in the warm, wet environment of Africa 3–4 million years ago. This changed, however, about 2.5 million years ago, when the first of a long series of glacials (Ice Ages) reduced global temperatures and converted the moist African woodland into drier open savanna [51]. Rainfall and vegetation were dramatically altered because large amounts of water were locked into the Earth’s ice caps, making the whole planet drier. Tundra and grasslands eventually covered much of Eurasia and herbivores and ungulates proliferated. In Africa, forest dwelling chimpanzees yielded to bipedal hominids who became increasingly carnivorous. *Homo habilis* began to manufacture stone tools 2 million years ago and the succeeding species *Homo erectus* actively hunted and consumed a much larger amount of meat about 1.6–1.8 million years ago [52].

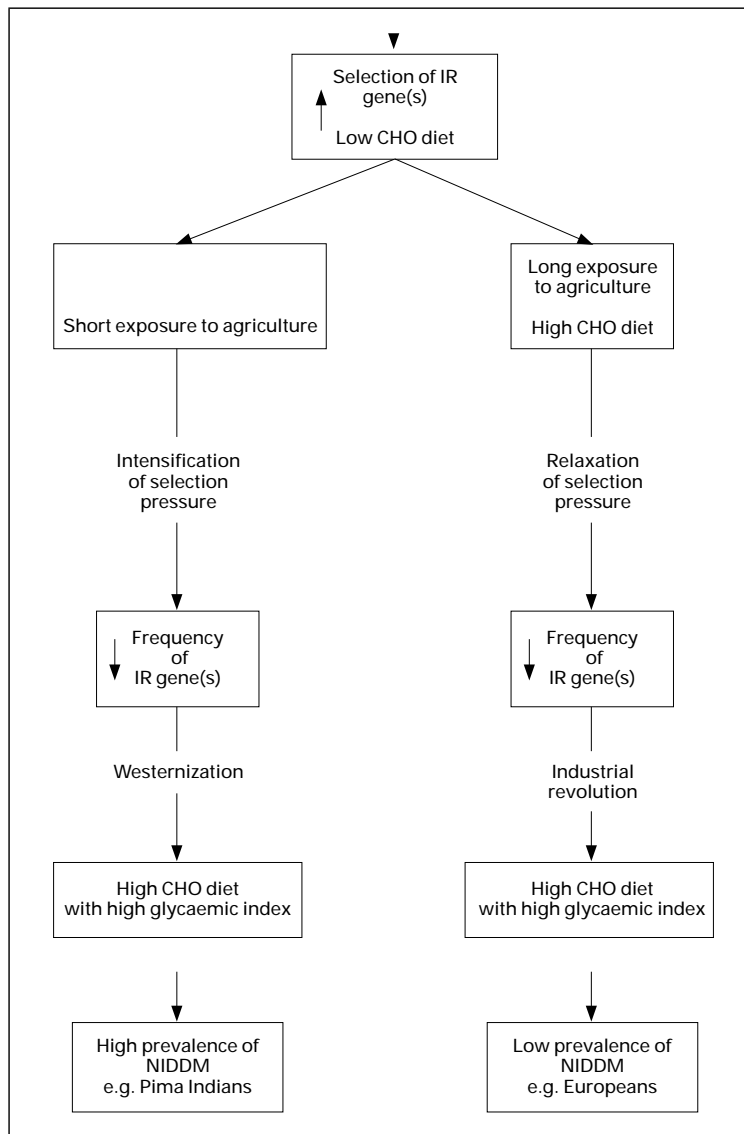


Fig. 1. The carnivore connection hypothesis argues that both the *quantity* and *quality* of carbohydrate in the diet during the last 2 million years of human evolution have played a role in selecting for and exposing the insulin resistant/NIDDM genotype.

Humans left Africa for more northerly latitudes by at least 1 million years ago and probably earlier [53]. We now have strong evidence that they lived in Spain (> 40 degrees N) by at least 750,000 years ago, in England (> 50 degrees N) by 500,000 years ago and in Germany (> 50 degrees N) by 400,000 years ago [54]. There is astonishing evidence that early man may have lived as far north as 60 degrees N by 260,000 years ago. The consumption of plant foods is severely restricted at higher latitudes even during warm interglacials (such as the present day) but especially during the long Ice Ages which characterized human evolution.

The archeological evidence that early human beings ate considerable quantities of meat lies in the large accumulations of animal remains that are found where they lived, the tools that they used (which were mainly geared toward processing game), plus the fact that their living sites were specifically located in areas where there were large herds of grazing animals [52]. Recently, the oldest complete set of hunting weapons to date was discovered at a 400,000-year-old site in Germany [55]. Found in association with stone tools and the butchered remains of 10 horses, the spears strongly suggest that systematic hunting involving foresight, planning and the use of appropriate technology was part of the behavioural repertoire of pre-modern humans [55]. Thieme [55] concludes that meat from hunting may have provided a larger dietary contribution than has previously been acknowledged.

The importance of vegetable foods is harder to assess, since plant remains are poorly preserved. Fossilized fruit pits and nuts are commonly found, but tools for processing plants foods are noticeably absent. *Homo erectus* and early *Homo sapiens* are thought to have obtained 50% of their energy from animal sources [56]. About 50,000 years ago during the last Ice Age, Neanderthal man was distributed from what is now Germany and France to parts of Russia, the Middle East and North Africa. They were cold-climate hunters of large game [52]. However, when the Cro-Magnons and other truly modern human beings (*Homo sapiens sapiens*) replaced Neanderthals, concentration on big-game hunting increased. Thus, Cro-Magnon man, our direct ancestor, would have lived through the coldest of the Ice Ages on a low carbohydrate diet.

The Mongoloid ancestors of both Pima Indians and Nauruans occupied the Siberian mammoth steppe during the final 20,000 years before the end of the last Ice Age [57]. Their diets were based solely on animals and animal products and contained virtually no carbohydrates except for the minor amounts found in the milk, the liver or gut contents of animals and in seasonal roots and berries. The ancestors of the Australian Aborigines who arrived in Australia 50,000 years ago led a hunting and shellfish-gathering existence [58]. Although seasonally and geographically variable, Australian Aboriginal diets

were characteristically dominated by animals with plant foods playing a supplemental role [59]. The Eskimos are the most recognized example of a group whose traditional diet was almost devoid of readily absorbable carbohydrate [60]. Many native American Indians of Northwest Canada have only recently incorporated any significant amount of carbohydrate in their diet [61].

Even at latitudes closer to the Equator, diets were often dominated by animal foods. Recent studies among the Aché who occupy the tropical forests of Paraguay (and who have had only recent contact with the outside world) show that animal foods represented 80% of the energy in the diet [62]. Honey, fruit and other plant foods would have supplied some carbohydrate, especially at these latitudes, but probably not a great deal. A high proportion of this carbohydrate was nonstarch polysaccharide [63] and fructose which elicits only a small insulin response [64]. Sugars and starches would have been absorbed very slowly in the presence of large amounts of fibre. Root vegetables are generally low in carbohydrate (< 7%) and those that grow in cool climates contain inulin (rather than starch) that is not digested and absorbed. Starchy tubers such as cassava, potatoes and yams took considerable effort to obtain. Starch intake was minimal because cereals did not feature in human diets in any significant way until after agriculture [56]. Thus, carbohydrate foods (when and where available) were characterized by a low glycemic index. Although carbohydrate intake would have increased during previous interglacials when temperatures were as warm as today, the present interglacial is unique because of the advent of agriculture and the intake of large amounts of starch for the first time in human existence [56]. A low-carbohydrate, high-protein diet was therefore the nutritional ‘backdrop’ during important stages in human evolution.

How Much Meat Did We Eat?

The ratio of plant to animal food in paleolithic diets is a subject of some contention and undoubtedly varied from place to place. Lee’s [65] analysis of world-wide hunter-gatherer subsistence ratios concluded that the average ratio of plant to animal food (on an energy basis) in recent hunter-gatherer diets was 65:35. Eaton and Konner [56] used this ratio in their analysis of the nutrient composition of paleolithic diets. However, these proportions are now considered to be incorrect because Lee failed to include shellfish and the fishing of large aquatic animals in his analysis. Recently, Cordain [66] re-analysed the plant:animal subsistence ratios data in the Ethnographic Atlas for all world-wide 181 hunter-gatherer populations which have been studied either historically or by contemporary anthropologists. The analysis shows that plant food represents 35% or less of the total foods utilized in the majority of cases, the average ratio being 35:65 (plant:animal), the opposite of Lee’s

conclusion. In Cordain's analysis, only 2% of hunter gatherers derived 66% or more of their total foods from plants. More importantly for our hypothesis, 1 in 5 hunter-gatherer societies subsisted on diets in which greater than 75% of the energy was derived from animal foods.

What then were the average contributions of protein, fat and carbohydrate to the energy content of a diet dominated by animal foods? There is no doubt that protein intake was probably twice as high as it is today. Eaton et al. [67] estimated that the average protein intake of paleolithic human beings was 37% of energy, even while assuming the majority of energy was derived from plant foods. Protein intake would be higher still in areas where animal foods predominated. Eskimos whose all-meat diet led to high protein intakes approached 45% of calories as protein. In her classic study of Australian Aborigines who temporarily reverted to a hunter-gatherer existence, O'Dea [68] showed that protein intake was 54% of the total energy. The maximal or absolute ceiling of dietary protein intake that is physiologically possible in humans is thought to be about 50% of energy intake or roughly 300–375 g [69]. The amount of carbohydrate in animal-dominated diets has been estimated to range from as little as 10 g up to 125 g or 1–17% of energy [50]. Recent analyses of Australian Aboriginal foods indicate that carbohydrate intake would have been around 100 g if one assumed that plant foods provided 20% of energy [70]. Thus, if protein provided half the dietary energy, this leaves us with a range of 33–54% energy as fat, most of it of animal origin (nuts and other tree seeds could also have been high sources of fat).

Metabolic and Biochemical Characteristics of Carnivores

Hominids have evolved important metabolic and biochemical adaptations which are indicative of an increasing physiological dependence upon animal-based foods. The plant-based diet of pongids requires a large and metabolically active gut to process the fibrous plant foods which compose over 90% of their dietary intake. In contrast, the human gut is much smaller and less metabolically active than the ape gut. This adaptation (reduction in gut size and metabolic activity) is presumed to have evolved in humans because the inclusion of nutrient-dense, animal-based foods by our early hominid ancestors allowed the selective pressure for a large metabolically active gut to be relaxed [71].

In comparing the metabolic and biochemical dietary adaptations of cats (obligate carnivores) and with those in humans (omnivores), it becomes apparent that evolution has shaped both feline and hominid metabolic machinery towards an animal-based diet. Obligate carnivores, such as cats, must obtain all of their nutrients from the flesh of other animals and have therefore evolved certain biochemical adaptations which are indicative of their total dietary

dependence upon animal-based foods. Most of these biochemical adaptations involve either the loss (or reduced activity) of certain enzymes required for the synthesis of essential nutrients. These adaptations generally occurred because the selection pressure (need) to maintain these metabolic pathways was relaxed as cats evolved from omnivorous animals to obligate carnivores. The examples below, while not directly relevant to insulin resistance, support our argument that high-meat, low-carbohydrate diets have shaped human metabolism in various ways.

Vitamin B₁₂ is an essential nutrient for both herbivorous and carnivorous mammals. Because B₁₂ is not found in higher plants, herbivorous mammals rely on the absorption of B₁₂ from bacteria which synthesize it in their gut [72]. Cats can neither synthesize B₁₂ nor absorb bacterially produced B₁₂ from their gut, and are consequently wholly dependent upon animal flesh as their source of this nutrient. Similarly, humans are unable to synthesize or absorb bacterially produced vitamin B₁₂ and are reliant upon animal sources [72]. The absence of this ability is indicative of the long evolutionary history of animal foods in our diet.

Taurine is an amino acid which is not found in any plant food [73] and which is an essential nutrient in all mammalian cells. Herbivores are able to synthesize taurine from precursor amino acids derived from plants, whereas cats have completely lost the ability [74]. Since all animal foods (except cow's milk) are rich sources of taurine [73], the selective pressure for taurine synthesis has been relaxed in cats. Humans, unlike cats, still maintain the ability to synthesize taurine in the liver, but this is limited and inefficient when compared to herbivores. Vegan vegetarians following diets devoid of animal products display exceptionally low levels of both plasma and urinary taurine [75]. Similar to cats, this inability to efficiently synthesize taurine has come about because the selective pressure to produce this amino acid has been gradually reduced with humankind's long reliance upon animal food.

Plant-based foods contain 18 carbon fatty acids of both the Ω -3 and Ω -6 families, but are virtually devoid of the 20 and 22 carbon fatty acids required for the functioning of all mammalian cells. Herbivores have evolved hepatic enzymes (desaturases and elongases) which allow these precursor plant-based 18 carbon fatty acids to be chain elongated and desaturated to their 20 and 22 carbon products. In contrast, cats have extremely low levels of these enzymes [76]. The selection pressure to synthesize these compounds has been almost entirely lifted because cats obtain ample quantities by eating animal tissues. Humans are similar to cats and have inefficient elongase and desaturase enzymes [76]. Again, this metabolic change has occurred largely because the need to desaturate and chain elongate 18 carbon plant fatty acids to their 20 and 22 carbon products has been reduced in humans by diets high in animal foods.

Vitamin A is not found pre-formed in any plant and herbivores must synthesize it in the liver from β -carotene. Cats have lost the ability to synthesize vitamin A from β -carotene [77], and obtain all of their requirement from the organs (liver, kidney) of their prey. Recently, it has been shown that humans also have limited capacity to synthesize vitamin A from β -carotene [78], presumably because humans consumed vitamin A-rich animal food sources during much of evolution. Vitamin A deficiency is common in many parts of the world today where plant foods are the main source of energy.

The most widespread nutrient deficiency in the western world is iron deficiency [79]. Human infants become iron depleted after 4–6 months of breast-feeding because human milk provides little and infant stores become low by this time. All the commercial infant weaning foods based on cereals need to be iron-fortified to cater for this need. In the past, a predominantly meat-based weaning diet would have relaxed the need for bigger iron stores or increased absorptive capacity. Iron deficiency in childhood is extremely serious, recent studies suggesting that it interferes with both physical and intellectual development [79]. This dependency on high iron intake provides further evidence that humans adapted over long periods of evolutionary time to a largely carnivorous diet.

These examples, as well as the anthropological evidence provided by contemporary studies of hunter-gatherer diets, provide strong evidence for the central role of meat and animal tissues in the human diet. Although it is true that human populations can survive under broad plant:animal subsistence ratios, the consensus evidence supports the notion that whenever it was ecologically possible, animal foods would have always represented the majority of the total daily energy intake.

Insulin Resistance: A Consequence of Low Carbohydrate Intake?

Since our primate ancestors in Africa evolved for over 60 million years on a high-carbohydrate diet, the brain, fetus and mammary gland evolved a specific dependence on glucose as a source of fuel [80, 81]. With the advent of the Ice Ages and the change to a low-carbohydrate diet in many parts of the world, metabolic adaptations were probably necessary to accommodate this low glucose intake. Early European explorers who lived with hunter-gatherer groups in temperate, arctic and subarctic climates describe a syndrome called 'rabbit starvation' which they suffered when forced to rely on diets that were composed entirely of lean game meat and/or marine animals [82]. Nausea, hunger, stomach discomfort, diarrhoea and even death were commonly described by the explorers [83].

Chronic ingestion of a low-carbohydrate, high-protein diet has also been shown to result in increased hepatic glucose production and decreased pe-

ripheral glucose utilisation, i.e. insulin resistance in both animals and man [84, 85]. These studies show that the average insulin-sensitive subject finds a low-carbohydrate, high-protein diet difficult to tolerate [86] whereas insulin-resistant subjects and genetically obese animals appear to tolerate them very well [68, 87–89].

Underlying insulin resistance in the muscles and liver would have been an advantage because it would redirect glucose away from the muscles and ensure that plasma glucose levels were stable despite the lack of dietary carbohydrate and the hyperinsulinemia generated by high-protein meals. The insulin response produced by protein feeding has been well described [90]. As the quantity of the protein increases, the insulin response increases in a dose-dependent manner. In healthy individuals, the effect of protein is relatively weak: 50 g protein has roughly a third of the potency of 50 g glucose to stimulate insulin [91]. In diabetic subjects, however, protein is almost as potent as glucose [90, 92]. Thus, relative to normal individuals, type 2 diabetic subjects showed nearly 4-fold higher insulin levels after protein ingestion [90]. The reason for these differences is unknown but Krezowski et al. [91] speculated that the protein-stimulatory mechanism is ‘more primitive’ and better maintained in the presence of β -cell dysfunction. Perhaps insulin’s original function had more to do with amino acid than glucose metabolism.

Consumption of protein also stimulates glucagon secretion [93, 94] which promotes glycogenolysis and gluconeogenesis and is thought to offset any insulin-induced decline in glucose levels. However, while some studies report stable or small declines in plasma glucose after protein ingestion [90, 91], others document a rise [87]. One of the sources of difference is the type of subject – in some studies they were Caucasian, while in others, they were subjects with a predisposition to insulin resistance such as Australian Aborigines. The latter show greater degrees of underlying insulin resistance, even when young and healthy.

We postulated therefore that glycemic and insulin responses after protein meals may therefore be related to the degree of insulin resistance. In a recent study [95], we determined the relationships between insulin sensitivity (assessed by euglycemic-hyperinsulinemic clamp) and the plasma glucose, insulin, C-peptide and glucagon responses to a 75-gram protein load (lean beef steak) in 16 lean, healthy Caucasian subjects (mean \pm SD age 25 ± 6 years, BMI 23 ± 2). M values were found to correlate inversely with the plasma glucose response to the protein meal ($r = -0.58$, $p = 0.03$; fig. 2), i.e. the most insulin-sensitive subjects showed the greatest declines in plasma glucose, while the more insulin-resistant individuals showed little change (fig. 3). In contrast, there was no correlation between the insulin or glucagon response after the protein load and the M value, nor between responses (glucose, insulin and

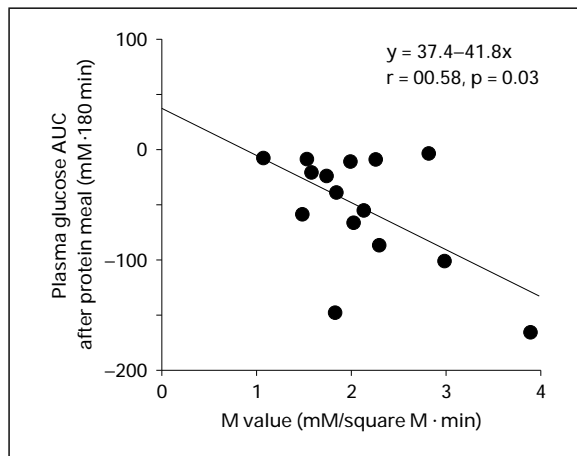


Fig. 2. Relationship between insulin sensitivity (M value) and the decremental area under glucose curve after the 75-gram protein meal (n = 16). From Gan et al. [95].

glucagon) after a similar glucose load and insulin sensitivity. These findings suggest that insulin-resistant individuals are better able to maintain gluconeogenesis after a protein meal compared with more sensitive subjects.

Prolonged fasting or days without food were undoubtedly features of the existence of our ancestors. Fasting results in the same metabolic profile as that occurring with a low-carbohydrate, high-protein diet, i.e. increased gluconeogenesis and peripheral insulin resistance [45, 85, 96]. Initially hepatic glycogen is mobilized but subsequently gluconeogenesis from precursors such as endogenous amino acids is increased. The oxidation of non-esterified fatty acids produced from lipolysis leads to suppression of glucose utilisation and oxidation via the glucose/fatty acid cycle [45, 97]. Thus, the phenotypic expression of the metabolic adaptation to a high protein/low carbohydrate diet and/or periodic fasting is insulin resistance, both in the liver and the peripheral tissues. In this dietary environment, insulin sensitivity would be a disadvantage not only for survival, but also, as described in the next section, for successful reproduction.

Consequences of a Low Carbohydrate Diet during Pregnancy

During pregnancy the demand for glucose increases markedly because the fetus relies on glucose crossing the placenta as its sole source of fuel. To meet this increased demand pregnant humans become progressively resistant to the peripheral action of insulin [98, 99]. Glucose is redirected away from muscles towards the placenta. Even on a high-protein diet, synthesis of glucose

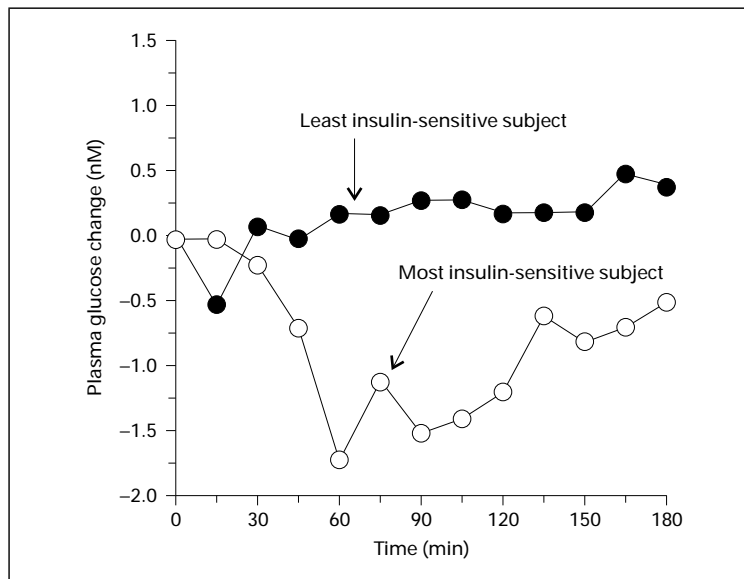


Fig. 3. Plasma glucose response after the 75-gram protein meal in the most insulin-sensitive and least insulin-sensitive subjects. From Gan et al. [95].

from gluconeogenic amino acids cannot meet the full demand [100]. Indeed, the upper ceiling on protein intake may be reduced during pregnancy [101]. Some ‘semi-carnivores’ such as dogs have difficulty reproducing on a low carbohydrate diet unless the protein intake is sufficiently high [102, 103]. Furthermore, in true carnivorous animals like the cat, gluconeogenesis from amino acids is more or less permanently ‘switched on’ [77] with maximal gluconeogenesis occurring in the absorptive phase immediately following a meal. The cat reproduces well on a low carbohydrate intake [102] and appears to have underlying insulin resistance [104].

Lactation makes further demands on carbohydrate requirements because glucose is the starting product for the synthesis of lactose in milk [105]. In lactating rats, insulin resistance develops in muscle while the mammary gland becomes extremely sensitive [106]. Whole body insulin sensitivity appears to be the same as the non-lactating animal yet glucose uptake by specific tissues is markedly different. The development of tissue-specific insulin resistance redirects glucose towards preferential utilisation by the mammary gland [105, 106].

We argue that human reproduction would be severely compromised in insulin-sensitive individuals because of an inability to adapt sufficiently to the

low dietary glucose supply and extra demands for glucose during reproduction. Low-carbohydrate diets during human evolution may well have selected for insulin-resistant females whose metabolism would conserve glucose necessary for foetal survival and milk production.

Metabolic Consequences of Dietary Changes since the Last Ice Age

Agriculture began in the near East and spread rapidly to Europe, resulting in a dramatic increase in the consumption of cultivated cereals and other plant foods [56]. Carbohydrate intake therefore increased several fold, to levels which had never been seen in the previous 1–2 million years (fig. 4) [107]. The spread of agriculture, however, was more gradual throughout Asia and the Americas. MesoAmericans did not adopt agriculture until approximately 5,000 years ago and Pima Indians only 2,000 years ago [51]. Indeed, many PaleoIndians continued to maintain an arctic-like hunter-gatherer lifestyle which featured a reliance on big game species as the major source of food [39]. The early settlers of Nauru and other Pacific atolls consumed a diet dominated by fish and coconuts, i.e. low in carbohydrate and high in protein [108]. Attempts to cultivate root crops on tropical islands were thwarted by drought, barren soils and natural phenomena such as hurricanes. Australian Aborigines never developed agriculture [58].

Agriculture markedly altered human nutritional patterns: within a few thousand years, the proportion of meat declined drastically while vegetable foods came to make up as much as 90% of energy [67]. This shift had major anthropometric consequences: early European *Homo sapiens sapiens*, who ate large amounts of animal protein 30,000 years ago, were on average 15 cm taller than their descendants who lived after the development of farming. The same pattern was repeated later in the New World.

Our hypothesis proposes that insulin resistance was the normal genotype for much of the world's population at the end of the last Ice Age. If such an individual consumes a diet high in carbohydrate, hyperinsulinemia is the metabolic adaptation required to maintain normal glucose tolerance [1]. The advent of agriculture would have increased plasma insulin responses to meals to overcome the insulin resistance. However, the *quality* of carbohydrate was different to that of today and the degree of hyperglycemia and hyperinsulinemia produced by meals was low compared with the typical response produced after oral ingestion of glucose. Early carbohydrate was in a form which was slowly digested and absorbed, eliciting small postprandial insulin responses [109, 110]. Legumes and cereals which are coarsely ground or flaked have a low glycemic index [111, 112]. Similarly, many of the traditional carbohydrate foods of the Pima Indians, Pacific Islanders and Australian Aborigines have been shown to be low glycemic index foods, producing relatively small increases

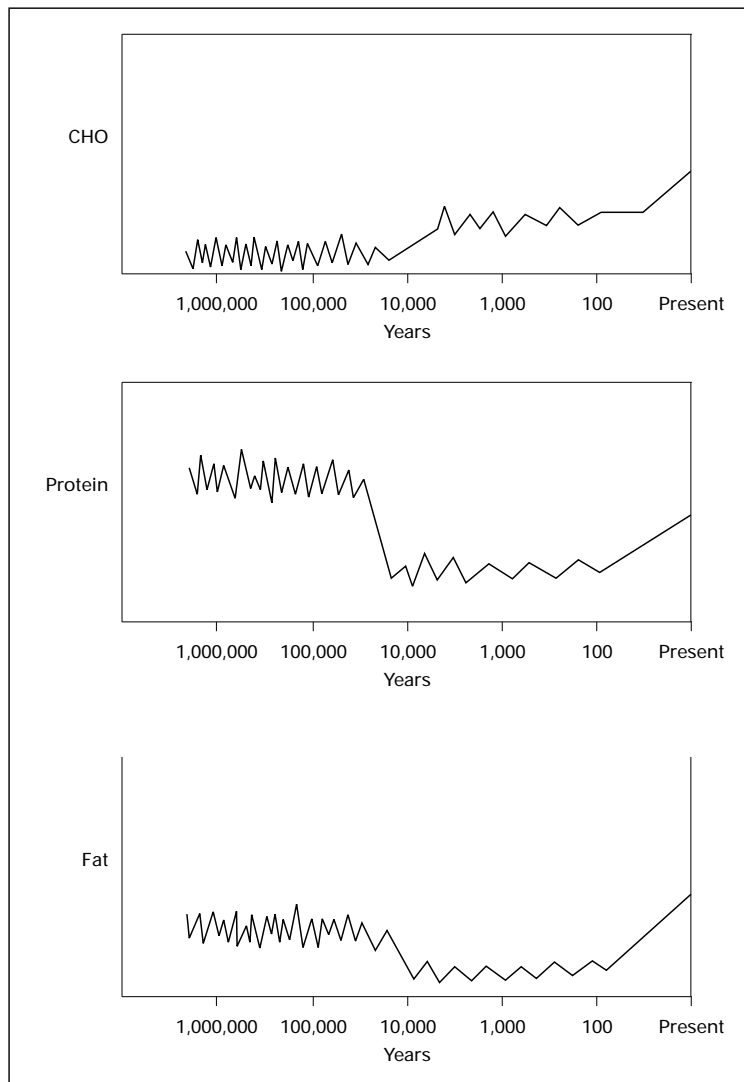


Fig. 4. Estimated changes in carbohydrate, protein and fat consumption in humans over time. From Hirsch [107].

in plasma glucose and insulin [113, 114]. Thus, although the carbohydrate content of the diet had increased as a result of agriculture, the β -cells were not unduly stressed. Some degree of hyperinsulinemia would have been detectable, but this was unlikely to have reached the levels seen today in insulin-resistant individuals with the metabolic syndrome.

The increase in dietary carbohydrate would have resulted in a relaxation of the selection pressure for insulin resistance. This would have progressed at different rates in different populations depending on their length of exposure to agriculture. Hence, we would expect the prevalence of genes producing insulin resistance to be lower in the European population and any other group exposed to agriculture for sufficiently long. While 1–2 million years was necessary for dietary forces to select positively for insulin resistance, relaxation of this selection process over a period as short as 10,000 years may bring about a reversion to a low incidence. We know that 10,000 years is long enough to alter the frequency of an allele because lactase persistence during adulthood became the norm in this population over the same period of time [115, 116]. In fact, Allen and Cheer [40] have proposed that the advent of dairying and the availability of lactose in milk led to the relaxation of the pressure for the ‘thrifty genotype’ in the European population (the ‘non-thrifty’ genotype hypothesis). In support, they point out the inverse relationship between lactase persistence and the incidence of NIDDM around the world.

Consequently, the frequency of alleles varies in different parts of the world and some of these have important health implications for modern man (e.g. lactase persistence, gluten-sensitive enteropathy, favism). *Basic* nutritional needs seem not to have varied significantly since paleolithic times because all humans require similar ranges of both macro- and micronutrients and all human groups have similar anatomical, physiological and endocrine function in regard to diet and nutrition. The reason for these similarities is because of our common evolutionary experience – we were all hunter-gatherers dependent upon wild animals and plants (albeit in different amounts) and these selective pressures shaped our present day nutritional requirements.

Changes in the Quality of the Carbohydrate. Although the agricultural revolution brought a sharp increase in the quantity of carbohydrate consumed, the industrial revolution which began in the 17th century was responsible for changing the *quality* of dietary carbohydrate. The milling of cereals significantly changed the rate of digestion and absorption of the carbohydrate. The use of high-speed roller mills to produce finely ground cereal flours, removed almost all of the indigestible material and increased the yield and palatability. The starch became more easily and quickly gelatinised and digested and the postprandial glycemic and insulin responses were 2- to 3-fold higher compared to the coarsely ground flour or whole grain (fig. 5) [110, 111, 117]. At about the same time, potatoes were introduced into western diets and they too have been shown to produce exceptionally high glycemic and insulin responses [109]. Diabetes rates rose sharply in Britain at this time, well before sugar consumption had begun to increase [118].

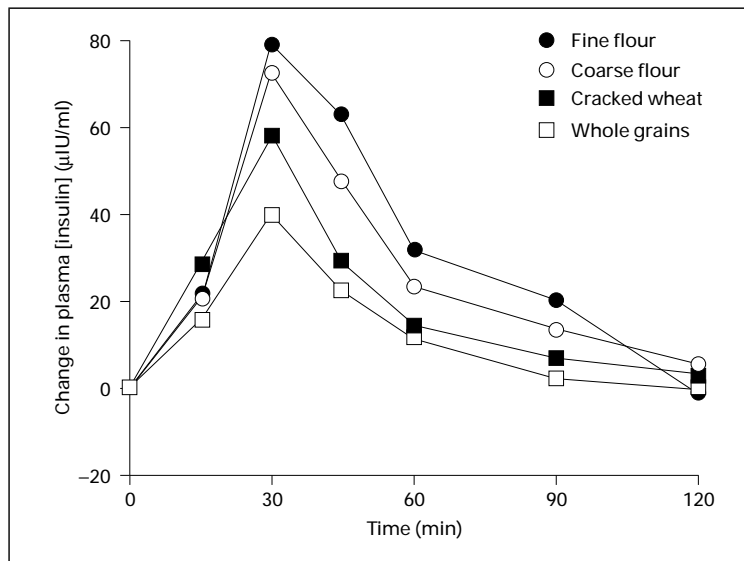


Fig. 5. Effect of milling of wheat on glucose and insulin responses. From Holt et al. [111].

The modern high glycemic index diet is therefore a relatively recent phenomenon which stimulates the β -cells to a much greater extent than previous diets based on meat and low glycemic index carbohydrate. Only the carbohydrate staples of modern western diets require β -cells capable of secreting large amounts of insulin for a lifetime. In addition, the metabolic consequences of modern carbohydrate diets are even more pronounced in insulin-resistant populations such as Australian Aborigines and Pima Indians [119, 120]. We showed that the insulin response to potatoes in lean young, healthy Aborigines was twice as large as that seen in Caucasians (fig. 6) [120].

Modern Lifestyles, Fast Foods. Insulin resistance has been further aggravated over the last 50 years by sedentary lifestyles (lower muscle mass, reduced fitness) and the availability of a cheap, very palatable and high-fat food supply. This has resulted in the exposure of most populations to energy intakes in excess of daily energy requirements and a high prevalence of obesity in western and developing societies. Obesity induced insulin resistance is then superimposed on underlying genetically-determined insulin resistance. Thus the degree of hyperinsulinemia experienced after a typical modern high glycemic index meal is far higher (perhaps of the order of 3–10 times) than humans ever experienced in our evolutionary hunter-gatherer lifestyle. Chronic but physiological levels of hyperinsulinemia (15–20 μ U/ml) have been shown to induce insulin resistance even in healthy young subjects with no family history of type 2 diabetes [48].

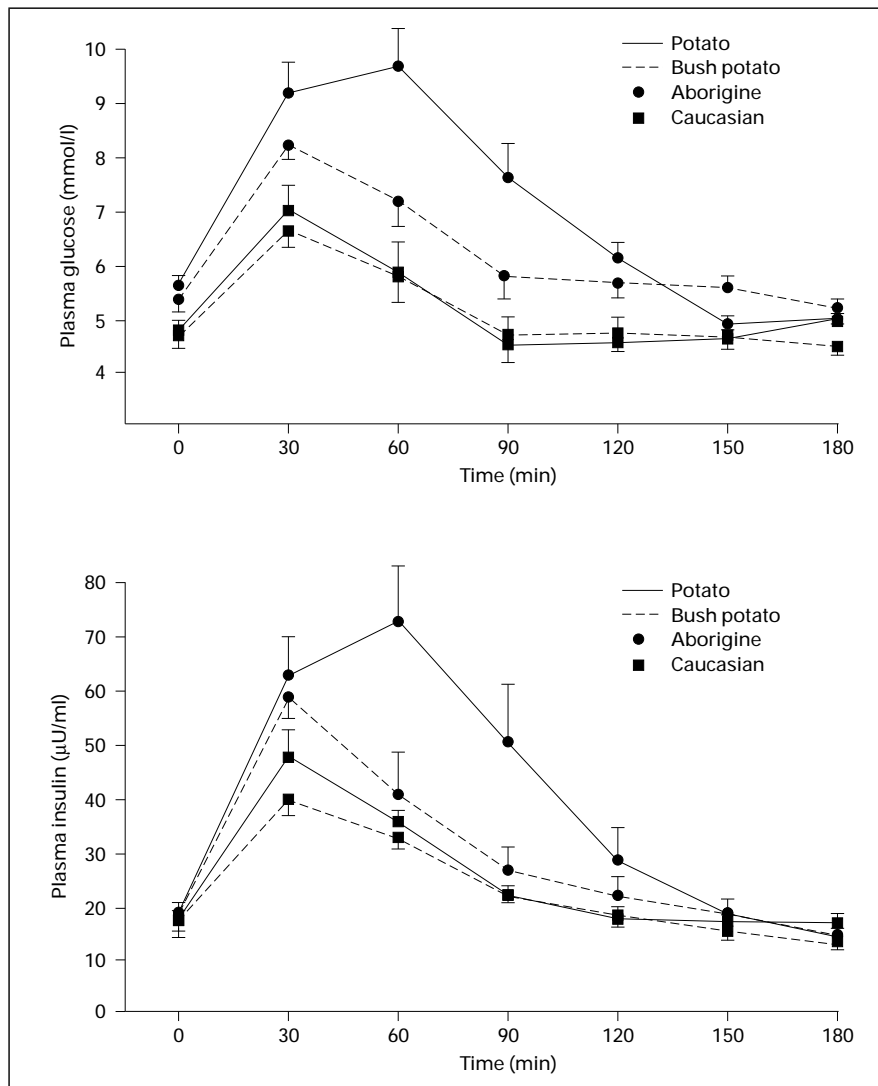


Fig. 6. Insulin response to a high glycemic index food (potatoes) in young, lean, healthy Australian Aboriginal subjects compared to that in Caucasians. From Thorburn et al. [120].

Support for the 'Carnivore Connection' Hypothesis

The carnivore connection hypothesis has two components – it argues that both the quantity and quality of carbohydrate are important in explaining the high prevalence of NIDDM today. Other than the arguments put forward above, there is currently no direct evidence to support a role for the *quantity*

of carbohydrate in the evolution of the insulin-resistant genotype. In contrast there is good evidence for the *quality* of carbohydrate in worsening insulin resistance and precipitating NIDDM. Long-term studies in rats show that high glycemic index starch, when compared with identical diets composed of low glycemic index starch, increase fasting insulin levels and promote insulin resistance [121, 122]. High glycemic index starches also promote faster weight gain, higher body fat levels, higher adipocyte volume and hypertriglyceridemia [123], all of which are components of the insulin-resistance syndrome.

In humans, recent epidemiological studies indicate that the glycemic index of the diet is probably the most significant dietary factor in precipitating NIDDM. Two large-scale prospective studies, one in nurses and one in male health professionals, show that diets with a high glycemic load (glycemic index \times carbohydrate content) increase the risk of developing NIDDM by 50% after controlling for known risk factors such as age and body mass index [124, 125]. Importantly, the amount and type of fat were *not* risk factors. The underlying mechanism was postulated to be the demand for insulin generated by high glycemic index foods. Similarly, a large-scale study from China also suggests that the *quality* of carbohydrate has important implications for the metabolic syndrome [126]. Population groups relying on wheat as the source of carbohydrate had higher levels of sex-hormone-binding globulin and other risk factors for insulin resistance than groups that had rice as the staple carbohydrate. Again, the authors speculated that the difference was due to the lower glycemic and insulin response to the rice diet compared with the wheat diet.

Recently an 'insulin index' of foods based on 1,000 kJ portions has been developed [127]. Bread and potato, confectionery and bakery products produced the highest insulin index scores. Protein foods and unrefined high-carbohydrate foods produced the lowest scores. Since hyperinsulinemia is linked with all the facets of the 'metabolic syndrome' (insulin resistance, hyperlipidemia, hypertension and visceral obesity), the glycemic and insulin index of foods are relevant to coronary heart disease. In healthy people as well as those with NIDDM, high-carbohydrate diets have been shown to worsen aspects of the blood lipid profile including the TG, vLDL, HDL and Lp(a) [128, 129]. Individuals with insulin resistance are more susceptible to these adverse effects, presumably because the hyperinsulinemia elicited by high glycemic index foods is more pronounced. However, this effect of high-carbohydrate diets is almost certainly linked to the glycemic index of the carbohydrate because high-soluble-fibre diets which slow down carbohydrate digestion do not produce adverse effects [130]. The concerns with typical high-carbohydrate diets have led several experts to recommend the replacement of animal fat in western diets *not* with carbohydrate but with monounsaturated and polyunsaturated oils [131].

One test of the carnivore connection hypothesis would be to determine the level of insulin resistance or prevalence of NIDDM in carnivorous animals fed a high-carbohydrate diet. This 'experiment' is actually taking place in the real world with the recent introduction of commercial dry foods for cats which contain large amounts of carbohydrate. It may be relevant therefore that NIDDM in cats is now much more common and associated with islet amyloidosis in much the same way as occurs in humans [132].

Conclusion

Evolutionary changes in the quantity and quality of carbohydrate are a plausible explanation for the development of insulin resistance, hyperinsulinemia and the metabolic syndrome. A high-protein, low-carbohydrate diet was the nutritional backdrop for the last two million years of human evolution for at least some if not most human groups. We postulate that an insulin-resistant genotype would have provided survival advantages on this type of diet. Others have also proposed that an insulin-resistant genotype would have offered a survival advantage to specific populations consuming a low-carbohydrate, high-protein diet [38, 39]. However, this has been proposed as a mechanism to cope with alternating periods of food excess and shortage as postulated by Neel [36, 37]. Our hypothesis differs in that it recognises that direct mechanisms were needed to cope with a shortage of carbohydrate coupled with a high-protein intake. Only our hypothesis encompasses an explanation for why Europeans are the exception in not having high rates of NIDDM. Quantitative and qualitative changes in carbohydrate and different lengths of exposure to these changes could explain the population differences in the prevalence of the various components of the metabolic syndrome.

The Future

What can we do now while we wait thousands of years for evolutionary forces to override unfavourable environmental influences? Targeted intervention is likely to produce the best results. Simpler methodologies are required to identify insulin-resistant people. In these individuals intervention should aim to modify factors such as diet, obesity and physical inactivity which can affect insulin resistance and hyperinsulinemia. Perhaps the situation has progressed too far in developed countries but opportunities exist in developing societies to embrace the beneficial aspects of modern living while at the same time avoiding its disadvantages. Traditional carbohydrate foods with a low

glycemic index need to be embraced and less emphasis placed on western starchy staples such as bread and flour products. Diets providing more than 30% of energy as protein may have beneficial effects on insulin sensitivity as well as plasma lipoproteins. Certainly, the quality and quantity of carbohydrate needs careful examination as a causative factor in the metabolic syndrome.

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