European Journal of Clinical Nutrition (2002) 56, 30–35
 0954–3007/02 $25.00
www.nature.com/ejcn

ORIGINAL COMMUNICATION

The 'carnivore connection' — evolutionary aspects of insulin resistance

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Insulin resistance is common and is determined by physiological (aging, physical fitness), pathological (obesity) and genetic factors. The metabolic compensatory response to insulin resistance is hyperinsulinaemia, the primary purpose of which is to maintain normal glucose tolerance. The 'carnivore connection' postulates a critical role for the quantity of dietary protein and carbohydrate and the change in the glycaemic index of dietary carbohydrate in the evolution of insulin resistance and hyperinsulinaemia. Insulin resistance offered survival and reproductive advantages during the Ice Ages which dominated human evolution, during which a high-protein low-carbohydrate diet was consumed. Following the end of the last Ice Age and the advent of agriculture, dietary carbohydrate increased. Although this resulted in a sharp increase in the quantity of carbohydrate consumed, these traditional carbohydrate foods had a low glycaemic index and produced only modest increases in plasma insulin. The industrial revolution changed the quality of dietary carbohydrate. The milling of cereals made starch more digestible and postprandial glycaemic and insulin responses increased 2 – 3 fold compared with coarsely ground flour or whole grains. This combination of insulin resistance and hyperinsulinaemia is a common feature of many modern day diseases. Over the last 50 y the explosion of convenience and takeaway 'fast foods' has exposed most populations to caloric intakes far in excess of daily energy requirements and the resulting obesity has been a major factor in increasing the prevalence of insulin resistance.
European Journal of Clinical Nutrition (2002) **56,** Suppl 1, S30 – S35. DOI: 10.1038/sj/ejcn/1601351

Keywords: diet; diabetes mellitus; carbohydrate; protein; evolution

Introduction

Insulin resistance is a common underlying abnormality in a number of chronic conditions which cluster together and have collectively been referred to as the 'metabolic syndrome' (Reaven, 1988). In this paper we develop the theme that insulin resistance is an evolutionary response to the carnivorous diet of our ancestors because it provided survival and reproductive advantages. With the high-protein low-carbohydrate diet which they consumed, insulin resistance would not have induced compensatory hyperinsulinaemia. However with the progressive replacement of protein with carbohydrate in human diets over the past 10 000 y, and more recently with the increase in the glycaemic index of many carbohydrate foods since the industrial revolution, insulin resistance is now accompanied by significant hyperinsulinaemia, a combination which is associated with conditions which increase the risk of premature coronary heart disease.

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Insulin resistance

Although insulin has a number of metabolic effects, insulin resistance is normally defined in terms of the blood glucose lowering effect of insulin. It is a state in which 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. The term is often used interchangeably with diminished insulin action or decreased insulin sensitivity.

Many methods have been used to assess insulin resistance. Some are dependent on endogenous insulin (intravenous glucose tolerance test, fasting insulin), while others assess response to exogenous insulin (euglycaemia clamp). There is reasonable agreement between the two most commonly used experimental methods — the euglycaemic hyperinsulinaemic clamp and the intravenous glucose tolerance test with minimal modelling (Saad *et al*, 1994). Neither of these two experimental methods is suitable for epidemiological studies and for this purpose fasting insulin, with or without modelling, is commonly used as a surrogate for insulin resistance.

There is no uniform quantitative definition of insulin resistance and therefore of what constitutes normality/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. However, an individual with normal glucose tolerance who is in the most insulin resistant quartile of the population is considered to be insulin resistant.

Some comparative data are available for Mexican Americans (Haffner *et al*, 1992) and Australian Aborigines (Proietto *et al*, 1992) consistent with the view that insulin resistance is more common in non-diabetic individuals of these populations. We have studied 100 Aboriginal people (mean age 34 y, mean body mass index (BMI) 27) with normal glucose tolerance and assessed insulin resistance by homeostasis model assessment (HOMA, Matthews *et al*, 1985). Fifty-nine percent had an insulin resistance value in the lowest quartile compared with 20% of normal-weight young non-Aboriginal people.

Within populations, insulin resistance has been shown to vary more than 4-fold in individuals with normal glucose tolerance and insulin resistance measures in approximately 25% of these individuals do not differ substantially from those of people with type 2 diabetes (Reaven *et al*, 1993). In a study of men with normal glucose tolerance we found 22% of young (mean age 23.6 y), normal-weight (mean BMI 22.9) men had values in the lowest quartile and this increased to 85% in older (mean age 53.6 y) overweight (mean BMI 29) men, an observation which is consistent with the increase in prevalence of the metabolic syndrome with age (DeFonzo & Ferrannini, 1991).

Determinants of insulin resistance

Physiological, pathological and genetic factors determine insulin resistance and are summarised in Figure 1. Insulin sensitivity is affected by age and may be determined by the intrauterine and early life environment. In adult life glucose tolerance decreases with increasing age predominantly due to decreasing tissue insulin sensitivity secondary to post-receptor event(s), possibly due to a decrease in glucose transporters (DeFronzo, 1981). Body weight is universally recognised to influence insulin resistance irrespective of glucose tolerance (Caro, 1991). Increasing weight by more than 35–40% above ideal body weight results in a decline in insulin sensitivity by 30–40% (DeFronzo & Ferrannini, 1991). The distribution of adipose tissue has a major influence with an accumulation of intra-abdominal or visceral fat having the strongest association with insulin resistance (Kissebah & Peiris, 1989). Increased physical fitness enhances insulin sensitivity and this effect can be demonstrated after 4–6 weeks of intensive physical training and is rapidly reversed by immobilisation (Koivisto *et al*, 1986). It is unlikely that these environmental factors act independently to determine insulin sensitivity. 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.

Environmental factors do not fully explain the observed variation in insulin sensitivity suggesting that genetic determinants influence insulin resistance. The gene or genes have not been identified but studies in non-diabetic Pima Indians demonstrate that insulin sensitivity has a familial aggregation and may be determined by a single gene with a codominant mode of inheritance (Bogardus *et al*, 1989) linked to chromosomal markers on 4q (Prochazka *et al*, 1993).

The metabolic syndrome

The metabolic compensatory consequence to insulin resistance is hyperinsulinaemia, the primary purpose of which is to maintain normal glucose tolerance. The combination of insulin resistance and hyperinsulinaemia is associated with a cluster of abnormalities which increase cardiovascular risk. This cluster is referred to as the metabolic syndrome, although the term insulin resistance syndrome may be more appropriate (Balkau & Charles, 1999). In non-diabetic individuals the syndrome is characterised by insulin resistance/fasting hyperinsulinaemia and two of the following: glucose intolerance (but not diabetes), hypertension, dyslipidaemia and central obesity (Balkau & Charles, 1999).

Glucose intolerance/type 2 diabetes

Type 2 diabetes is common and increasing in prevalence throughout the world. Although the most populated countries make the biggest contribution to the total number of people with diabetes, prevalence rates in Western countries are also increasing. A recent population-based survey of people aged 25 and older in Australia involving oral glucose tolerance testing has shown prevalence rates of diabetes of 7.5%, of whom only half were diagnosed, and another 16.6% had an abnormality of glucose tolerance. These results indicate that nearly 1 in 4 people in Australia aged 25 and over have abnormal glucose tolerance.

A major metabolic characteristic of type 2 diabetes is insulin resistance, which antedates the onset of the disease (Eriksson *et al*, 1989; Gulli *et al*, 1992; Warram *et al*, 1990).

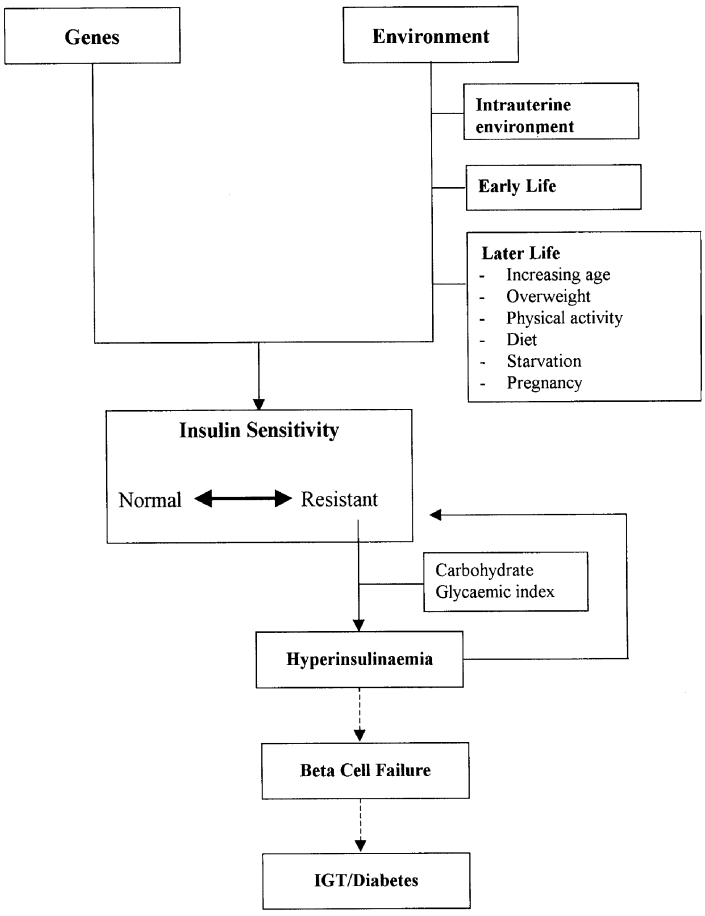

Figure 1 Determinants and consequence of insulin sensitivity.

Glucose tolerance in an insulin-resistant individual is determined by the degree to which insulin secretion can be increased in response to the severity of the insulin resistance. For a given level of insulin resistance, an appropriate increase in insulin secretion will maintain normal glucose tolerance, a lesser increase will result in impaired glucose tolerance and an even smaller increase results in type 2 diabetes (Lillioja *et al*, 1988).

Other features of the metabolic syndrome

Insulin resistance has been causally linked to other components of the metabolic syndrome. Insulin-mediated glucose uptake is reduced by 30–40% in people with essential hypertension (Ferrannini *et al*, 1987), an abnormality demonstrated in both non-obese and obese individuals with hypertension (Reaven, 1991) and in young normotensive subjects who are at increased risk of developing hypertension (Beatty *et al*, 1993). Furthermore, this abnormality continues to be present even after the hypertension has been treated effectively (Reaven, 1991).

Insulin resistance and/or hyperinsulinaemia leads to an increased secretion by the liver (Reaven & Chen, 1988) and a decreased clearance of VLDL triglycerides resulting from resistance to the action of insulin on lipoprotein lipase (DeFronzo & Ferrannini, 1991). These abnormalities result in high plasma triglyceride levels and various associated abnormalities of plasma lipoprotein metabolism, eg low HDL cholesterol concentrations and the presence of smaller and denser LDL particles.

The evolution of insulin resistance and hyperinsulinaemia

Debate continues about the relative contribution of genetic and environmental influences. Neel originally proposed the 'thrifty gene' hypothesis and postulated that cycles of food scarcity and abundance selected for individuals with mechanisms to increase the deposition of food energy as body fat during periods of plenty for subsequent use during periods of food scarcity. With the sustained availability of food this protective mechanism became deleterious leading

to an increase in type 2 diabetes (Neel, 1962,1992). Subsequently others have suggested that insulin resistance is the phenotypic expression of the thrifty gene (Wendorf & Goldfine, 1991; O'Dea, 1991). On the other hand, Hales and Barker have proposed the 'thrifty phenotype' hypothesis which invokes maternal and infant malnourishment to explain the increase in modern day diseases (Hales & Barker, 1992). This hypothesis is based on epidemiological data suggesting that low weight at birth and during the first year of life is associated with an increased risk of cardiovascular disease, diabetes and hypertension (Hales & Barker, 1992).

We have postulated a critical role for the quantity and quality of dietary carbohydrate in the pathogenesis of insulin resistance and hyperinsulinaemia (Brand Miller & Colagiuri, 1994). This 'carnivore connection' hypothesis proposes that insulin resistance offered survival and reproductive advantages during the Ice Ages which dominated the last 2 million years of human evolution. While carbohydrate was scarce, compensatory hyperinsulinaemia would not have been needed to maintain normal glucose tolerance. However, beginning about 10 000 years ago following the end of the last Ice Age and the development of agriculture, dietary carbohydrate increased. Traditional carbohydrate foods have a low glycaemic index and produce only modest post-prandial increases in plasma insulin. Yet the constant supply of highly refined high glycaemic index carbohydrate in modern diets results in significant postprandial hyperinsulinaemia, exposing the disadvantages of the insulin resistance genotype and predisposing to the metabolic syndrome.

Historical dietary changes and the development of insulin resistance

Carbohydrate was an important part of the diet of our prehuman ancestors (Gaulin & Konner, 1977) who lived in Africa 2–4 million years ago. About 2.5 million years ago, a severe Ice Age reduced global temperatures converting the moist African woodland into much drier open savanna (Fagan, 1992) and forest dwelling chimpanzees yielded to bipedal hominids who became increasingly carnivorous. *Homo habilis*, who lived 2 million years ago, was almost certainly a scavenger who supplemented a vegetarian diet with meat left over from predators' kills. *H. erectus*, who lived 1.5 million years ago, is known to have actively hunted (Garn & Leonard, 1989). Hunting is believed to have been the pressure that selected for the large brain of *H. sapiens* (ie man the hunter; Lee & DeVore, 1968).

During the nine Ice Ages over the last 700 000 years, hunting and fishing became a dominant way of life, not just in high latitudes but also in warmer environments. Ice Ages lock a large amount of water into ice caps, making the whole planet drier. Hence plant growth is mainly in the form of grasslands which only herbivores can utilise. About 50 000 years ago, 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 on which they subsisted during the coldest periods (Garn & Leonard, 1989). Similarly, Cro-Magnon man who replaced the Neanderthals from 35 000 years ago, lived through the coldest of the Ice Ages on a high-protein diet. Their diets contained virtually no carbohydrate except the minor amounts found in the liver or gut contents of animals and in seasonal roots and berries. Other items which were gathered included nuts and shellfish, but these contain little or no carbohydrate.

A low-carbohydrate, high-protein diet was therefore the nutritional 'backdrop' during important stages in human evolution. The actual amount of carbohydrate eaten has been estimated to range from as little as 10 g up to 125 g a day, which contrasts with the present day intake of 250–400 g (Gaulin & Konner, 1977). In addition the available carbohydrate foods were characterised by a low glycaemic index. 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 (Eaton & Konner, 1985).

Since our primate ancestors in Africa evolved on a high-carbohydrate diet, the brain and reproductive tissues evolved a specific requirement for glucose as a source of fuel (Sokoloff *et al*, 1977; Freinkel, 1980). With the advent of the Ice Ages and the change to a low-carbohydrate diet, metabolic adaptations were necessary to accommodate this low glucose intake and to meet the specific requirement for glucose of the brain, foetus and mammary gland. Chronic ingestion of a low-carbohydrate, high-protein diet results in increased hepatic glucose production and decreased peripheral glucose utilisation, ie insulin resistance (Phinney *et al*, 1983; Rossetti *et al*, 1989). Periodic starvation, which was also a feature of the existence of our ancestors, results in the same metabolic profile as that occurring with a low-carbohydrate, high-protein diet, ie increased gluconeogenesis and peripheral insulin resistance (DeFronzo *et al*, 1978; Newman & Brodows, 1983).

Thus, the phenotypic expression of the metabolic adaptation to a high-protein/low-carbohydrate diet with periodic starvation 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 for successful reproduction. During pregnancy the demand for glucose increases and to meet this increased demand humans become progressively resistant to the peripheral action of insulin (Ryan *et al*, 1985; Buchanan *et al*, 1990).

The evolution of dietary carbohydrate

The glucose and insulin responses to dietary digestible carbohydrate are influenced by the amount and type of carbohydrate. Digestible carbohydrate has been traditionally characterised chemically as complex or simple and it was believed that complex carbohydrate was slowly digested and

therefore had a modest effect in increasing blood glucose and insulin levels while simple carbohydrate was rapidly digested and resulted in a larger increase in blood glucose and insulin. However many studies have demonstrated that there are significant differences in blood glucose and insulin responses to different types of simple and complex carbohydrates which lead to the emergence of the concept of the glycaemic index (Jenkins *et al*, 1984).

During the evolution of insulin resistance, low amounts of dietary carbohydrate were consumed and what little carbohydrate was available had a low glycaemic index. The advent of the agricultural revolution increased the amount of digestible carbohydrate, but these carbohydrate foods would have had a uniformly low glycaemic index as has been shown for many of the traditional carbohydrate foods of the Pima Indians, Pacific Islanders and Australian Aborigines (Thorburn *et al*, 1987; Brand *et al*, 1990).

Although the agricultural revolution brought a sharp increase in the quantity of carbohydrate consumed, the industrial revolution which occurred in the nineteenth 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 very finely grind cereals removed almost all of the indigestible material and increased the yield and palatability. The starch was thus made much more digestible and the postprandial glycaemic and insulin responses were 2–3-fold higher compared to coarsely ground flour or whole grain (Brand *et al*, 1985; Heaton *et al*, 1988). At about the same time potatoes were introduced into Western diets and they too have been shown to produce high glycaemic and insulin responses (Jenkins *et al*, 1988). The modern high glycaemic index diet is therefore a relatively recent phenomenon.

These evolutionary changes in carbohydrate can be linked to the pathogenesis of type 2 diabetes. The insulin response to the ingestion of carbohydrate in an insulin-resistant individual will depend on the blood glucose response which in turn will be influenced by the amount and glycaemic index of the carbohydrate. Provided the individual's insulin response continues to be appropriate normal glucose tolerance will be maintained. At the end of the last Ice Age the population was insulin resistant. The introduction of increased quantities of low glycaemic index carbohydrate with the advent of agriculture elicited only a small postprandial glucose and insulin response (Jenkins *et al*, 1984; Heaton *et al*, 1988). Thus, although the carbohydrate content of the diet had increased as a result of agriculture, the insulin-producing pancreatic beta cells were not unduly stressed.

However with the introduction of high glycaemic index foods which characterise the carbohydrate staples of modern Western diets, significant quantities of insulin are required after a meal and the pancreatic beta cells must be capable of secreting large amounts of insulin for a lifetime and if unable to do so will progressively lead to glucose intolerance and type 2 diabetes. Furthermore, hyperinsulinaemia and high glycaemic index diets can worsen insulin resistance. Support for this scenario is provided by two large epidemiological studies in men and women which link glycaemic load and the development of type 2 diabetes (Salmeron *et al*, 1997a,b).

The situation has been further aggravated over the last 50 y by the explosion in the range of available convenience and takeaway 'fast foods'. This has resulted in the exposure of most populations to caloric intakes far in excess of daily energy requirements and has been responsible for the increased prevalence of obesity in Western and developing societies which has been an important factor in determining the prevalence of insulin resistance in any population.

Summary

Evolutionary changes in the quantity and quality of carbohydrate are a plausible explanation for the development of insulin resistance, hyperinsulinaemia and the metabolic syndrome. Aspects of our ancestors' diets protected against the metabolic abnormalities which are increasingly common in modern societies. Consequently the diets of our ancestors may provide some insight into future dietary recommendations in our attempts to curtail the increasing prevalence of the chronic diseases which are increasingly affecting both developed and developing populations.

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