High-Insulinogenic Nutrition—An Etiologic Factor for Obesity and the Metabolic Syndrome?

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This report postulates a critical role for the quantity and quality of dietary carbohydrate in the pathogenesis of obesity and the metabolic syndrome. Significant changes in human nutrition have occurred during the last 10,000 years, culminating in the current high-glycemic/high-insulinogenic nutrition. A high insulinogenic nutrition represents a chronic stimulus to the β cells that may induce an adaptive hypertrophy and a progressive dysregulation of the cells, resulting in postprandial hyperinsulinemia, especially in genetically predisposed subjects. Significant evidence suggests that postprandial hyperinsulinemia promotes weight gain and the development of insulin resistance/metabolic syndrome. The hypothesis is able to explain the current epidemic of obesity and the metabolic syndrome in most industrialised countries, as well as some of the genetics of obesity, including the extreme high incidence of obesity and the metabolic syndrome in certain ethnic groups.

AN ALARMING increasing prevalence of obesity and of the metabolic syndrome is noted in most industrialised countries. In the United States for example, the increase in obesity has reached epidemic proportions, and a 33% increase in diagnosed diabetes was reported from 1990 and 1998. This trend is likely to continue in the years ahead.[1]

The reasons for this continuing trend remain unclear. It is widely held that obesity is a disorder in which ingestion of energy in excess of that being used results in excessive expansion of the adipose tissue mass. But contrary to this common belief, there is no consistent evidence that the current epidemic is due to an increase in caloric intake. In fact, dietary studies conducted in many developed countries suggest that for adults, the average caloric intake, particularly in the form of fats, is lower than in previous decades.[2]

The current report will explore whether the main reason for the current epidemic of obesity and the metabolic syndrome could be the significant increase in high-glycemic-index nutrition, especially during the last decades. The postulate is that the quantity and quality of dietary carbohydrate play a critical role in the pathogenesis of obesity and the metabolic syndrome. This hypothesis is based on 4 lines of evidence (Fig 1): (1) during the last 1.5 million years of human evolution (prior to the introduction of agriculture), our ancestors were flesh-eating hunters, who subsisted on a low-carbohydrate, high-protein diet, a diet that required small amounts of insulin only. (2) The current high-glycemic-index nutrition constitutes an extreme challenge to pancreatic β cells. (3) In susceptible persons, high-glycemic-index nutrition may induce hypertrophy, dysregulation, and dysfunction of β cells, resulting in postprandial hyperinsulinemia. (4) Postprandial hyperinsulinemia represents the main etiologic factor for the development of obesity and insulin resistance/metabolic syndrome.

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HYPERINSULINEMIA OF OBESITY—PRIMARY DEFECT OR ADAPTATION TO INSULIN RESISTANCE?

The hyperinsulinemia of obesity has generally been regarded as a compensatory adaptation to the peripheral insulin resistance that is characteristic of the obese state.[3] More recent studies have shown that in the initial phase of obesity, hyperinsulinemia is not due to insulin resistance, but constitutes a primary metabolic alteration caused by β-cell dysfunction or dysregulation.[4,5] The first metabolic abnormality during the course of obesity is a postprandial hyperinsulinemia, resulting from a delayed and higher pulse of insulin after normocaloric mixed meals, while fasting insulin levels and insulin sensitivity are normal.[4,5] Rapid weight gain occurs during this phase.[5] Insulin resistance, with permanent hyperinsulinemia in the fed as well as the fasting state, develops only later during the course of chronic obesity.

HYPERINSULINEMIA AND WEIGHT GAIN

Several lines of evidence support a critical role for acute insulin secretion in mediating weight gain and the development of obesity. In humans, hyperinsulinemia is a potent predictor of weight gain and obesity, particularly among individuals who are sensitive to insulin.[4,6] In randomized clinical trials in humans, treatment with insulin or with an insulin secretagogue (a sulfonylurea) leads to weight gain[7,8] and increased fat deposition.[9]

Animals with experimental lesions of the ventromedial hypothalamus (VMH) develop hyperinsulinemia in response to oral glucose or meals. Soon thereafter, the rats begin to gain weight and become morbidly obese. They become insulin-resistant weeks after the development of obesity.[10] However, if the parasympathetic innervation of the pancreas is severed at the same time by vagotomy, hyperinsulinemia is prevented and weight gain does not occur.[11]

The mechanism whereby hyperinsulinemia precipitates weight gain is not clear. Most important seems the fact that insulin promotes fat storage and causes preferential oxidation of carbohydrate over fat in response to mixed meals.[12] It has also been suggested that hyperinsulinemia may cause obesity via inhibition of lipolysis,[13] reduced thermic effect,[14] or increased appetite.[15] Recurrent postprandial hyperinsulinemia would, therefore, promote continued fat accumulation, especially in the presence of high dietary fat intake.

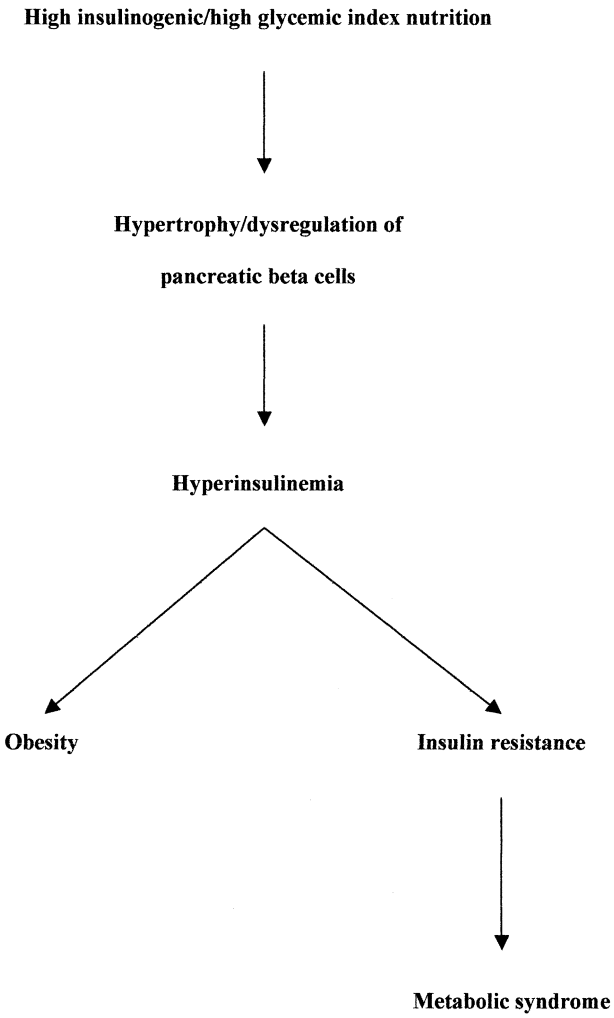

Fig 1. Graphic depiction of the developmental process proposed.

HYPERINSULINEMIA AND INSULIN RESISTANCE

There is significant evidence that hyperinsulinemia not only promotes the development of obesity, but also causes insulin resistance.

From both the human and animal studies it appears that the primary lesion leading to the insulin-resistant state is a long-term rise in plasma insulin levels.[16] For example, intravenous infusions of insulin into humans over a 40-hour interval produces insulin resistance.[17] Evidence also comes from a cross-sectional study of obese children.[5] Those with short-duration obesity (<4.5 years) had normal insulin sensitivity and insulin levels that were high postprandially but not in the fasting state. Insulin resistance developed only in longer duration obesity.

In VHM lesion rats,[10] or monkeys,[18] as well as gold-thiaglucose–treated rats,[18] insulin sensitivity decreases as a consequence of prolonged hyperinsulinemia.

Thus, studies in humans as well as in experimental animals indicate that insulin resistance represents a reaction/adaptation to hyperinsulinemia rather than a genetic defect. This view is supported by the finding that reducing the hyperinsulinemia through diet or destruction of the pancreatic β cells diminishes or even eliminates the insulin resistance.[19]

The development of insulin resistance seems to limit further weight gain.[20] A fast and early development of insulin resistance prior to significant weight gain would explain the existence of insulin resistance in up to 25% of the normal-weight population.[21]

HYPERINSULINEMIA, INSULIN RESISTANCE, AND THE METABOLIC SYNDROME

Insulin resistance and hyperinsulinemia are conditions well known to be associated with and predict the incidence of type 2 diabetes, hypertension, ischemic heart disease, and dyslipidemia. A cluster of these abnormalities is frequently observed in the same individual, ie, the metabolic syndrome.[21,22]

Hyperinsulinemia has been shown to be an independent predictor of morbidity and mortality for coronary heart disease[22] and hypertension.[23] Some studies report a significant correlation between the level of plasma insulin and blood pressure.[24]

Previous prospective studies have consistently demonstrated that insulin resistance[25] and hyperinsulinemia[26] are strong predictors of type 2 diabetes mellitus. Insulin resistance is now recognized as the earliest metabolic "defect" in the development of type 2 diabetes mellitus.[27]

HIGH-CARBOHYDRATE NUTRITION AS AN ETIOLOGIC FACTOR FOR THE DEVELOPMENT OF POSTPRANDIAL HYPERINSULINEMIA?

The evidence presented suggests that postprandial hyperinsulinemia represents a major pathogenic factor for the development of obesity and insulin resistance, and results from an overproduction of insulin, most probably due to an increase in β-cell mass and to β-cell dysfunction. Since the composition of the diet has an important influence on the postprandial insulin secretion, excessive chronic β-cell stimulation related to alimentation may be the main cause.

Two factors are responsible for the development of postprandial hyperinsulinemia: (1) chronic high-insulinogenic nutrition leads to hypertrophy, functional dysregulation, and overresponsiveness of the pancreatic β cells; (2) genetic predisposition results in a higher susceptibility of the β cells to carbohydrate nutrition.

This view corresponds well with the fact that significant changes in human nutrition have occurred during the last 10,000 years. Over the millennia, hominoids and hominids have subsisted on different diets, depending on climate, hunting proficiency, food processing technology, and available food.[28] The *Australopithecines*, early hominids who lived between 3 and 4 million years ago, as well as *Homo habilis*, who appeared about 2.5 million years ago, were scavengers. They supplemented a vegetarian diet with meat from carcasses that were left by true predators.[28,29] *Homo erectus*, who appeared about 1.5 million years ago was a hunter, who used stone tools and had the ability to make fires and presumably to cook or roast in the flames or coals.[28] About 500,000 years ago, *Homo erectus* was followed by *Homo sapiens*, hunter-gatherers who subsisted

on meat from small animals as well as large game, and on carbohydrate from roots, leafy vegetables, nuts, berries, and fruits. Especially during the Ice Ages (9 in total during the last 700,000 years), when large parts of the world had little vegetation, hunting of large game animals rather than gathering of carbohydrate food was their principal source of energy.[30] The *Neanderthals*, who lived about 50,000 years ago, were cold-climate hunters of large game and presumably subsisted primarily on game during the coldest periods. Similarly, early European *Homo sapiens* lived on an abundance of animal protein and only minimal amounts of carbohydrates about 30,000 years ago.[28]

That means that during a very long period of human evolution, our ancestors ate a diet high in protein and low in carbohydrate.[30,31] Most of the wild plants, such as leafy vegetables, herbs, roots, berries, and tubers, were fibrous. They contained some amounts of carbohydrate, mostly in the form of glucose and fructose, but probably not a great deal. Glucose is absorbed very slowly in the presence of large amounts of fiber, and fructose produces a small insulin response only.[32] Thus, in effect, any carbohydrate foods were low-glycemic-index foods, a diet that elicits a small insulin response. Since the effect of dietary protein on insulin secretion is small too (<30% of that resulting from glucose ingestion[33]), the challenge to the β cells was minimal during several million years of evolution.

Beginning about 10,000 years ago, agriculture began to develop. The Agricultural Revolution brought a sharp increase in the quantity and quality of the carbohydrates consumed. However, legumes and cereals which were coarsely ground or flaked are classed as low-glycemic-index foods.[34] Therefore, although the carbohydrate content of the diet had increased, the β cells were not unduly stressed.

The Industrial Revolution, and especially the development of high-speed steel roller mills in the 19th century, offered the possibility to grind cereals very fine. The starch was thus made much more digestible, thereby increasing the postprandial glycemic and insulin response, resulting in much higher stress to the β cells. At the same time, potatoes and refined sugar, a new high-glycemic-index food, were introduced into Western diets.

The current high-glycemic-index "Western" nutrition, with large amounts of sugar, refined cereals, potatoes, and "fluffy" white rice is therefore a new phenomenon, which stresses the β cells to a very high extent, much higher than previous high-carbohydrate diets, and represents a chronic challenge to the β cells. It is easy to imagine that this massive chronic stimulus may cause hypertrophy and dysfunction of the β cells, resulting in postprandial hyperinsulinemia, especially in genetically predisposed subjects

This idea is supported by several histological and experimental studies: hyperinsulinemia and insulin resistance develop when normal rats are fed diets high in sucrose,[35] fructose,[36] or starch.[37] Excessive glucose intake in the rat has been shown to stimulate β-cell function and increase β-cell mass.[35] In addition, rat puppies fed a high-carbohydrate milk formula during the early weeks of postnatal life developed hyperinsulinemia within 24 hours. Alterations in the secretory pathway of pancreatic islet cells and molecular changes induced increased expression of pro-insulin. At 2 months, the rats started gaining weight and eventually became obese. These metabolic alterations were even passed on to the next generation.[38] Furthermore, marked obesity in human is associated with hypertrophy of the islets of Langerhans.[39] Finally, in humans, high-glycemic-index food significantly increases the risk of obesity,[40] hypertension,[41] cardiovascular disease,[42] and non–insulin-dependent diabetes.[43]

Epidemiological studies offer more support. Marked hyperinsulinemia is a common characteristic of several ethnic groups with a high prevalence of diabetes, such as Native Americans,[25] Mexican Americans,[44] and Pacific Islanders.[45] The reason these populations develop postprandial hyperinsulinemia may be due to a limited genetic adaptation of their β cells to high-carbohydrate nutrition, resulting from a shorter period of exposure to carbohydrates of these groups in the past.

Agriculture began 10,000 years ago in the Middle East and spread throughout Europe long before it developed elsewhere. Many ethnic populations, for example, the Pima Indians, did not adopt agriculture until approximately 2,000 years ago.[46] Some populations, like the Eskimos and the Australian Aborigines, continued to maintain a hunter-gatherer lifestyle until recently.[47] The traditional carbohydrate foods of these and other ethnic populations have been shown to be low on the glycemic index, producing relatively small increases in plasma glucose and insulin.[48]

When these populations urbanize and are exposed to high-glycemic-index nutrition, they develop hyperinsulinemia and very high rates of type 2 diabetes mellitus, as in Aborigines[49] and Native Americans.[25] In Pima Indians, Nauruans, and Mexican Americans, type 2 diabetes mellitus and obesity have reached epidemic proportions.[44,50] Eskimos, once thought to be resistant, are now developing diabetes in increasing numbers.[47] Their β cells, not adapted to high-glycemic-index nutrition, are prone to hyperinsulinemia on the one hand; on the other hand, they are often not able to keep up the high insulin production necessary to overcome the increasing insulin resistance.

It should be noted that a reversion to the traditional low-carbohydrate nutrition improves or normalises the metabolic alterations.[51]

Europeans and their offspring may have a relatively low incidence of diabetes, compared with other populations, because they were among the first to adopt agriculture, and their diet has been high in carbohydrate for 10,000 years. Their β cells have been exposed to high-carbohydrate nutrition for longer than any other group, and thus they are better adapted to such a diet. However, the dramatic increase in consumption of high-glycemic-index food during the last decades, in part as a result of low-fat, high-carbohydrate diets, together with a progressive increase in sucrose consumption (up to 70 kg/150 lb per capita in most Western countries[52]) has stressed the β cells of even better adapted persons beyond limits. This would explain the current epidemic of obesity and of the metabolic syndrome in many Western societies.

Genetic factors of obesity can also be explained by this hypothesis. The fact that obesity runs in families[53] may simply be due to a genetically determined higher susceptibility of the β cells to insulinogenic stimuli, a trait that is passed on to the next generation.

CONCLUSION

Obesity is not simply a matter of too many calories, but of too many "wrong" calories in the form of high-insulinogenic carbohydrates. The hypothesis proposed is consistent with specific aspects of obesity and the metabolic syndrome. It can explain the relationship and common association between obesity, insulin resistance, hyperinsulinemia, and the metabolic syndrome. Obesity and the metabolic syndrome, accordingly, are "symptoms" of the same metabolic disorder: hyperinsulinemia/insulin resistance.

The hypothesis can further explain the current epidemic of obesity in many industrialized countries, and specific genetic factors like the high prevalence of obesity and diabetes in specific ethnic populations.

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