Hyperinsulinemic diseases of civilization: more than just Syndrome X[☆]

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Abstract

Compensatory hyperinsulinemia stemming from peripheral insulin resistance is a well-recognized metabolic disturbance that is at the root cause of diseases and maladies of Syndrome X (hypertension, type 2 diabetes, dyslipidemia, coronary artery disease, obesity, abnormal glucose tolerance). Abnormalities of fibrinolysis and hyperuricemia also appear to be members of the cluster of illnesses comprising Syndrome X. Insulin is a well-established growth-promoting hormone, and recent evidence indicates that hyperinsulinemia causes a shift in a number of endocrine pathways that may favor unregulated tissue growth leading to additional illnesses. Specifically, hyperinsulinemia elevates serum concentrations of free insulin-like growth factor-1 (IGF-1) and androgens, while simultaneously reducing insulin-like growth factor-binding protein 3 (IGFBP-3) and sex hormone-binding globulin (SHBG). Since IGFBP-3 is a ligand for the nuclear retinoid X receptor α, insulin-mediated reductions in IGFBP-3 may also influence transcription of anti-proliferative genes normally activated by the body's endogenous retinoids. These endocrine shifts alter cellular proliferation and growth in a variety of tissues, the clinical course of which may promote acne, early menarche, certain epithelial cell carcinomas, increased stature, myopia, cutaneous papillomas (skin tags), acanthosis nigricans, polycystic ovary syndrome (PCOS) and male vertex balding. Consequently, these illnesses and conditions may, in part, have hyperinsulinemia at their root cause and therefore should be classified among the diseases of Syndrome X.
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1. Introduction

Almost 60 years have passed since clinicians and researchers first suspected that tissue resistance to the actions of insulin may play a role in certain chronic disease states (Reaven, 1998). The recognition that insulin resistance and its metabolic sequel, compensatory hyperinsulinemia, represented a unifying link common to type 2 diabetes, coronary artery disease (CAD), hypertension, obesity and dyslipidemia (increased plasma triacylglycerols, decreased high density lipoproteins, and smaller, denser low-density lipoproteins) is a more recent phenomenon dating to the past decade or so (Reaven, 1988, 1994; DeFronzo and Ferrannini, 1991). This cluster of maladies is frequently referred to as the metabolic syndrome or Syndrome X (Reaven, 1994). In addition, abnormalities of fibrinolysis and hyperuricemia also appear to be

members of the collection of diseases comprising Syndrome X (Reaven, 1994).

A total of 63% of men and 55% of women over age 25 in the United States are either overweight or obese (Must et al., 1999) and the estimated number of deaths ascribable to obesity is 280 184 per year (Allison et al., 1999). More than 60 000 000 Americans have one or more types of cardiovascular disease, which represents the leading cause of mortality (40.6% of all deaths) in the US (American Heart Association, 2000). A total of 50 000 000 Americans are hypertensive, 10 000 000 have type 2 diabetes (American Heart Association, 2000), and 72 000 000 adults in the US maintain total cholesterol/high-density lipoprotein (HDL) cholesterol ratios of 4.5 or greater (Carroll et al., 1993). Accordingly, diseases of insulin resistance represent far and away the major health problem, not just in the US, but in virtually all of western civilization (Reaven, 1995; Seidell, 2000). Astonishingly, these maladies are either rare or virtually non-existent in hunter–gatherer and other, less westernized societies living and eating in their traditional manner (Schaeffer, 1971; Trowell, 1980; Eaton et al., 1988; Cordain et al., 2002). Hence, Syndrome X diseases have been dubbed, 'Diseases of Civilization' by numerous authors (Burkitt, 1973; Eaton et al., 1988; Reaven, 1995).

In the past 5 years, emerging evidence suggests that the web of diseases and abnormalities associated with hyperinsulinemia extend far beyond the common maladies (obesity, intra-abdominal obesity, type 2 diabetes, hypertension, dyslipidemia and CAD) that are frequently concurrently present in patients. Such diverse illnesses and conditions as acne, the secular trend for a reduced age of menarche, certain epithelial cell carcinomas (breast, colon and prostate), the secular trend for increased stature, myopia, cutaneous papillomas (skin tags), acanthosis nigricans, polycystic ovary syndrome (PCOS) and male vertex balding may all be linked to hyperinsulinemia by hormonal interaction.

2. Hyperinsulinemia, insulin resistance and compensatory hyperinsulinemia

2.1. Hyperinsulinemia

Upon digestion, dietary carbohydrates can be converted to glucose by enzymatic action in the gastrointestinal tract. In the first 2 h following carbohydrate consumption and digestion, glucose is rapidly absorbed and elevates plasma glucose concentrations. The subsequent hyperglycemia, along with increases in glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 secreted from the gut, stimulate pancreatic insulin secretion, causing an acute rise in plasma insulin concentrations. The degree of the acute hyperglycemic and hyperinsulinemic responses to dietary carbohydrate is primarily dependent upon the glycemic index (Foster-Powell and Miller, 1995) and the glycemic load [glycemic index×carbohydrate content per serving size] (Ludwig, 2002) of the carbohydrate ingested. Consumption of mixed meals containing protein and fat along with the carbohydrate may lower the total glycemic and insulinemic response (Wolever and Jenkins, 1986). However, in spite of this evidence, it is established that repeated consumption of high-glycemic-index mixed meals results in higher mean 24-h blood glucose and insulin concentrations when contrasted to low-glycemic-index mixed meals of identical caloric content (Jenkins et al., 1987; Miller, 1994).

2.2. Insulin resistance

When skeletal muscle resists insulin-mediated uptake of glucose, clinically defined insulin resistance occurs. Although skeletal muscle is the principal site of insulin-stimulated glucose uptake in peripheral tissues, adipose tissue, liver and endothelial cells also develop insulin resistance (Beck-Nielsen, 2002). While the molecular basis for peripheral insulin resistance is complex and incompletely understood (Najjar, 2001), the proximate causes are known and result from an interplay of four dietary related elements: (1) chronic and substantial elevations of blood glucose (Rossetti et al., 1990; McClain, 2002); (2) insulin (Del Prato et al., 1994; Thomson et al., 1997); (3) very low-density lipoproteins (VLDL) (Zammit et al., 2001); and (4) free fatty acids (Boden and Shulman, 2002) in conjunction with susceptibility genes (Busch and Hegele, 2001).

2.3. Compensatory hyperinsulinemia

When peripheral tissues become resistant to the plasma glucose-lowering effects of insulin, long-term glucose concentrations do not necessarily rise in a pathological fashion initially because the

Table 1
Glycemic load (glycemic index × carbohydrate content in 100-g portions)

Western refined foods			Unrefined traditional foods		
Food	Glycemic index	Glycemic load	Food	Glycemic index	Glycemic load
Glucose	97	96.8	Parsnips	97	19.5
Rice Krispie cereal	88	77.3	Baked potato	85	18.4
Cornflakes	84	72.7	Boiled millet	71	16.8
Lifesavers	70	67.9	Boiled broad beans	79	15.5
Rice cakes	82	66.9	Boiled couscous	65	15.1
Table sugar (sucrose)	65	64.9	Boiled sweet potato	54	13.1
Shredded wheat cereal	69	57.0	Boiled brown rice	55	12.6
Graham crackers	74	56.8	Banana	53	12.1
Grapenuts cereal	67	54.3	Boiled yam	51	11.5
Cheerio cereal	74	54.2	Boiled garbanzo beans	33	9.0
Rye crispbread	65	53.4	Pineapple	66	8.2
Vanilla wafers	77	49.7	Grapes	43	7.7
Corn chips	73	46.3	Kiwi fruit	52	7.4
Mars bar	68	42.2	Carrots	71	7.2
Stone wheat thins	67	41.9	Boiled peas	48	6.8
Shortbread cookies	64	41.9	Boiled beets	64	6.3
Granola bar	61	39.3	Boiled kidney beans	27	6.2
Angel food cake	67	38.7	Apple	39	6.0
Bagel	72	38.4	Boiled lentils	29	5.8
Doughnuts	76	37.8	Pear	36	5.4
White bread	70	34.7	Watermelon	72	5.2
Waffles	76	34.2	Orange	43	5.1
All bran cereal	42	32.5	Cherries	22	3.7
Whole wheat bread	69	31.8	Peach	28	3.1
Fructose	23	22.9	Peanuts	14	2.6

The glycemic reference is glucose with a glycemic index of 100 (Foster-Powell and Miller, 1995).

pancreas secretes additional insulin. The maintenance of normal blood glucose via elevated plasma concentrations of insulin is referred to as compensatory hyperinsulinemia—the fundamental metabolic disturbance underlying Syndrome X diseases (Reaven, 1988, 1994; DeFronzo and Ferrannini, 1991). The onset of impaired glucose tolerance or type 2 diabetes marks a failure of the pancreas to maintain this state of compensatory hyperinsulinemia.

3. High dietary glycemic loads and insulin resistance

Of the four major proximate dietary causes of peripheral insulin resistance (chronic and substantial elevations in plasma glucose, insulin, VLDL and free fatty acid concentrations), consumption of high-glycemic-load carbohydrates has the potential to promote all four. In the early (1–2 h) postprandial periods, blood glucose levels are significantly higher following consumption of high-glycemic-index meals (Ludwig, 2002). Plasma insulin concentrations are also higher in the early (1–2 h) postprandial period following consumption of high-glycemic-index carbohydrates (Holt et al., 1997; Ludwig, 2002). Compared to low-glycemic-load meals, consumption of high-glycemic-load meals acutely elevates plasma non-esterified free fatty acid (FFA) concentrations in the late (4–6 h) postprandial period via enhanced lipolysis of adipocyte triacylglycerol (Ludwig, 2002). High-glycemic-load meals cause increased hepatic secretion of VLDL particles during the fasting and post-absorptive state (Mittendorfer and Sidossis, 2001). Furthermore, insulin becomes stimulatory for VLDL secretion in the postprandial state when the interprandial period is short and plasma insulin levels cannot fall to basal levels (Zammit et al., 2001). Taken together, the endocrine and homeostatic changes elicited by habitual consumption of high-glycemic-load carbohydrates over a 24-h period, particularly under hypercaloric conditions, promote the development of insulin resistance and compensatory hyperinsulinemia (Ludwig, 2002).
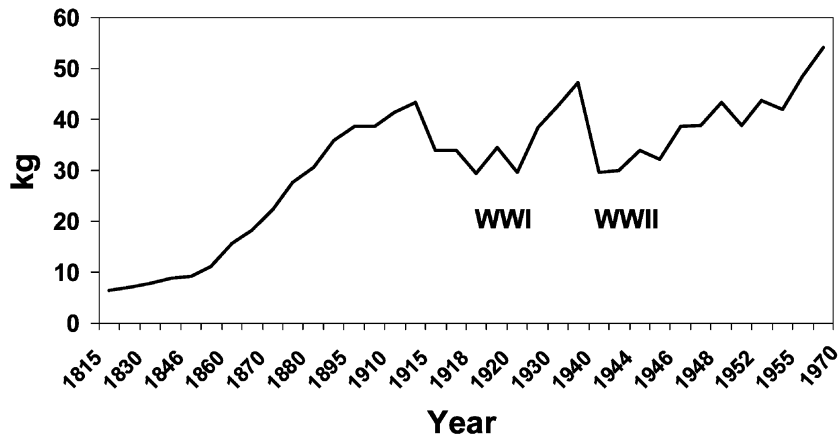
Fig. 1. Per capita consumption of sucrose in England from 1815 to 1970. Adapted from Cleave (1974).

3.1. Fructose

Although dietary fructose (Table 1) maintains a low glycemic index and load, paradoxically it is routinely used to induce insulin resistance in rats (Zavaroni et al., 1980; Hwang et al., 1987; Thorburn et al., 1989) and hamsters (Kasim-Karakas et al., 1996; Taghibiglou et al., 2000) at high (35–65% energy) dietary concentrations. Furthermore, high fructose feeding (usual diet +1000 kcal extra fructose per day) in healthy normal humans also causes an impairment in insulin sensitivity (Beck-Nielsen et al., 1980). Diets containing lower concentrations (20% energy) of fructose worsened insulin sensitivity in hyperinsulinemic men (Reiser et al., 1989a), and more recently it has been demonstrated that fructose infusions in healthy normal men and women induce both hepatic and extrahepatic insulin resistance (Dirlewanger et al., 2000).

Although pure (100%) crystalline fructose elicits a minimal insulin response following oral consumption, it is strikingly insulinotropic when blood glucose levels are even moderately elevated (Dunnigan and Ford, 1975; Reiser et al., 1987). The primary sources of fructose in the US diet are high-fructose corn syrup (HFCS) 42 and HFCS 55 (Park and Yetley, 1993) which are liquid mixtures of fructose and glucose (42% fructose/53% glucose and 55% fructose/42% glucose, respectively) (Hanover and White, 1993). Hence, the consumption of fructose in its most common manufactured form (HFCS 42 and HFCS 55) will elicit both high glycemic and insulinotropic responses similar to honey (42% fructose, 34%

glucose) (Foster-Powell and Miller, 1995) because of the concurrent presence of glucose and fructose.

Analogous to high-glycemic-load carbohydrates, fructose has also been shown to elevate serum triacylglycerol and VLDL concentrations, particularly when fructose diets were compared to fructose-free diets under rigorous control of food intake by providing subjects with all food (Hallfrisch et al., 1983; Reiser et al., 1989b). A recent study showed that even at concentrations that could be achieved in a normal diet (17% energy), fructose elevated serum triacylglycerol concentrations in healthy subjects (Bantle et al., 2000). Dietary fructose may also contribute to hepatic and peripheral insulin resistance via its unique ability among all sugars to cause a shift in balance from oxidation to esterification of serum non-esterified free fatty acids (Mayes, 1993).

4. Secular increases in high-glycemic-load carbohydrate, sucrose and fructose consumption

4.1. Secular changes in sucrose consumption

Although refined sugars and cereals are common elements of the modern urban diet, these high-glycemic-load carbohydrates were eaten sparingly or not at all by the average citizen in 17th and 18th century Europe and only started to become available to the masses in high quantities after the industrial revolution (Teuteberg, 1986). Fig. 1 shows that the per capita consumption of sucrose in England increased steadily from 6.8 kg in 1815 to 54.5 kg in 1970. Similar trends in sucrose consumption have occurred in the US and most

Table 2
Per capita consumption of sweeteners in the United States from 1970 to 2000

Sweetener	Consumption (kg/year)						
	1970	1975	1980	1985	1990	1995	2000
Refined sucrose	46.2	40.5	37.9	28.4	29.2	29.3	29.8
HFCS 42	0.2	2.2	6.1	7.0	9.2	10.4	11.2
HFCS 55	0	0	2.5	13.5	13.3	15.7	17.7
Glucose	6.3	8.2	7.1	7.3	8.0	9.2	8.2
Dextrose	2.1	2.0	1.6	1.6	1.7	1.8	1.5
Edible syrups	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Honey	0.5	0.5	0.4	0.4	0.4	0.4	0.5
Unbound, refined fructose	0.3	1.1	4.1	10.5	11.3	13.2	14.7
Total fructose	23.4	21.4	23.1	24.7	25.9	27.9	29.6
Unbound, refined glucose	8.6	11.5	13.1	18.4	20.3	23.3	23.3
Total glucose	31.7	31.8	32.1	32.6	34.9	38.0	38.2
Total sugar	55.5	53.5	55.8	58.4	62.0	67.1	69.1

Adapted from United States Department of Agriculture (2002).

European countries during the same time interval (Ziegler, 1967). Upon digestion, sucrose is hydrolyzed in the gut to its two equal molecular moieties of glucose and fructose. Consequently, the secular trend for increased sucrose consumption from the early 19th century until the mid-1970s metabolically resulted in an extraordinary increase in both fructose and glucose ingestion.

4.2. Secular changes in fructose and glucose consumption

In 1960, sucrose was the dominant sweetener in the US diet, accounting for approximately 90% of all sugars in the food supply (Park and Yetley, 1993). The balance of dietary sugars was comprised of corn sweeteners containing only glucose. With the advent of chromatographic fructose enrichment technology in the late 1970s, it became economically feasible to manufacture high-fructose corn syrup in mass quantity (Hanover and White, 1993). Table 2 demonstrates the rapid and striking increases in HFCS 42 and HFCS 55 that have occurred in the US food supply since their widespread introduction in the 1970s. As a direct consequence, the total amount of unbound fructose as a monosaccharide has increased by an astounding 4800% in the past 30 years, from 0.3 kg in 1970 to 14.7 kg in 2000. The total amount of dietary fructose (unbound fructose + fructose from the hydrolysis of sucrose in the gut) has increased by 26%, from 23.4 kg in 1970 to 29.5 kg in 2000, and total dietary sugar intake has increased from 55.5 kg in 1970 to 69.1 kg in 2000 (Table 2).

Fig. 2 shows that the per capita sugar consumption in the US increased by 64% from 1909 to
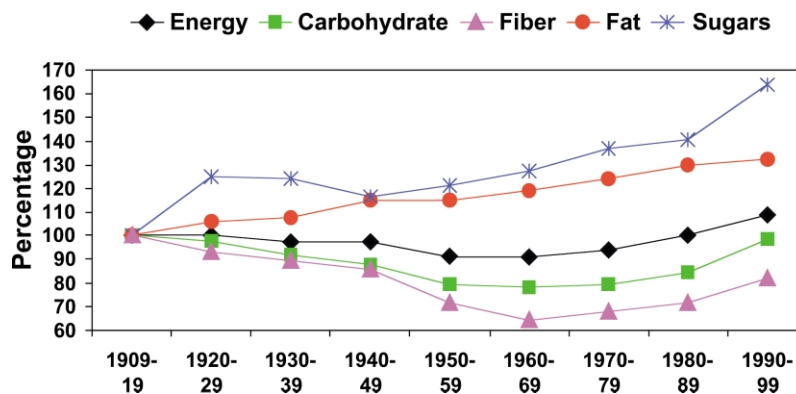

Fig. 2. Trends in per capita consumption of food energy and selected nutrients in the United States as a percentage of 1909–1919 values. Data adapted from Gerrior and Bente (2002).
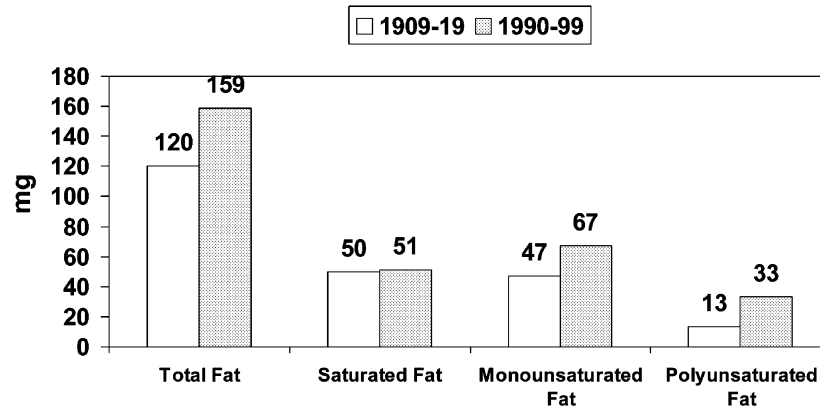
Fig. 3. Changes in daily per capita consumption of dietary fat from 1909–1919 to 1990–1999. Adapted from Gerrior and Bente (2002).

1999, while fiber intake declined by 17.9% during this same period. Total carbohydrate remained fairly constant from 1909–1989 until 1990–1999 when it rose ~10%. However, as the fiber data suggest, there have been important qualitative changes in carbohydrate consumption, in addition to increased dietary sugar, that have occurred in the past 200 years. High-glycemic-load refined cereal products now comprise 85.3% of all the grain products consumed in the US (United States Department of Agriculture, 1997), and in 1999 grain products comprised 23.7% of total per capita energy (United States Department of Agriculture, 1997). Accordingly, high-glycemic-load grain products supply 20% of the energy in the typical US diet. Only with the introduction of steel roller mills in the late 19th century (~1880) did fiber-depleted wheat flour of low extraction (≤70%) become widely available (Cleave, 1974). Consequently, there has been a secular increase in refined grain products that has paralleled the trend demonstrated for refined sugars.

In the typical US diet, high-glycemic-load sugars (HFCS 42, HFCS 55, sucrose, glucose, honey, syrups) now supply 16.1% of total energy (United States Department of Agriculture, 1997) and high-glycemic-load refined cereal grains supply 20% of energy. Hence, at least 36% of the total energy in the typical US diet is supplied by foods that are known to promote the four proximate causes of insulin resistance (chronic and substantial elevations in plasma glucose, insulin, VLDL and free fatty acid concentrations). Although high-glycemic-load sugars and grains now represent a dominant element of the modern urban diet, these foods were rarely or never consumed as recently as 200 years ago.

5. Dietary fat and insulin resistance

Fig. 2 demonstrates that per capita dietary fat increased by 32% from 1909–1919 to 1990–1999, while total energy increased by 9%. Fig. 3 shows that the daily per capita increase in fat occurred primarily from increased consumption of monounsaturated and polyunsaturated fats, while saturated fat consumption remained nearly constant over the past 90 years. Hence, the increased consumption of dietary fat parallels that of dietary sugars; however, fat alone and under isocaloric conditions, unlike refined sugars, does not cause insulin resistance in humans (Borkman et al., 1991; Swinburn, 1993). A recent human experiment using a hyperinsulinemic euglycemic clamp revealed that a range of isocaloric diets containing up to 83% fat did not directly cause insulin resistance, and the 83% fat diet actually improved certain aspects of glucose homeostasis (Bisschop et al., 2001). Only under hypercaloric situations, when increased dietary fat leads to obesity, does insulin resistance result (Swinburn, 1993).

Table 3 shows that high-glycemic-index foods are often high-fat foods as well. High-glycemic-load carbohydrates frequently initiate a cycle of insulin-induced hypoglycemia followed by hyperphagia, in which high-glycemic-index carbohydrates are preferentially consumed (Ludwig, 2002). Hence, the energy-dense fat component of the high-glycemic-index foods listed in Table 3 is frequently consumed simultaneously with the high-

Table 3
Composition of foods with both a high fat content and a high–medium glycemic index

Food (100 g)	Energy (kcal)	Fat (% energy)	Carbohydrate (% energy)	Glycemic index
Vanilla wafers	483	42	53	77
Doughnut	421	49	47	76
Corn chips	539	56	42	72
Mars bar	480	45	52	68
Croissants	406	47	45	67
Wheat thin crackers	483	39	54	67
Shortbread cookies	482	45	54	64
Ice cream (10% fat)	201	49	47	61
Cheese pizza	238	36	48	60

Adapted from Foster-Powell and Miller (1995).

glycemic elements (refined sugars, refined cereals) that promote insulin resistance.

6. Hyperinsulinemia and insulin-like growth factor (IGF) and IGF-binding proteins

The metabolic ramifications of chronic hyperinsulinemia are complex and diverse. It has been shown that the compensatory hyperinsulinemia that characterizes adolescent obesity chronically suppresses hepatic synthesis of insulin-like growth factor-binding protein-1 (IGFBP-1) which in turn serves to increase free insulin-like growth factor-1 (IGF-1), the biologically active part of circulating IGF-1 (Nam et al., 1997; Attia et al., 1998). The increase in circulating levels of insulin and IGFBP-1 vary inversely throughout the day, and the suppression of IGFBP-1 by insulin (Brismar et al., 1994) and hence elevation of free IGF-1, may be maximal when insulin levels exceed 70–90 pmol/l (Holly, 1991). In addition, growth hormone (GH) levels fall via negative feedback of free IGF-1 on GH secretion, resulting in reductions in IGFBP-3 (Attia et al., 1998). These experiments show that both acute (Attia et al., 1998) and chronic (Nam et al., 1997; Attia et al., 1998) elevations of insulin result in increased circulating levels of free IGF-1 and reductions in IGFBP-3. Free IGF-1 is a potent mitogen for virtually all of the body's tissues (Ferry et al., 1999).

The reductions in IGFBP-3 stimulated by elevated serum insulin levels (Nam et al., 1997; Attia et al., 1998) or by acute ingestion of high-glycemic carbohydrates (Liu, 2000) may also contribute to unregulated cell proliferation. IGFBP-3 has been shown to act as a growth inhibitory factor in murine knockout cells lacking the IGF receptor

(Valentinis et al., 1995). Accordingly, in this capacity IGFBP-3 is inhibitory to growth by preventing IGF-1 binding to its receptor. Because consumption of refined sugars and starches promotes both acute and chronic hyperinsulinemia, these common foods in the western diet have the potential to elevate free IGF-1 and lower IGFBP-3 concentrations in serum, and thereby stimulate growth in a wide variety of tissues throughout the body.

7. Hyperinsulinemia, IGFBP-3 and retinoid receptors

Insulin-mediated reductions in IGFBP-3 may further promote unregulated tissue growth by its influence upon the nuclear retinoid signaling pathway. Retinoids are natural and synthetic analogues of vitamin A that inhibit cell proliferation and promote apoptosis (Evans and Kaye, 1999). The body's natural retinoids (*trans*- and 9-*cis*-retinoic acid) act by binding two families of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXR). Retinoid receptors, in turn, activate gene transcription by binding as RAR/RXR heterodimers or RXR/RXR homodimers to retinoic acid response elements located in the promoter regions of target genes, the function of which is to limit growth in many cell types (Yang et al., 2001).

IGFBP-3 is a ligand for the RXR alpha nuclear receptor and enhances RXR/RXR homodimer-mediated signaling (Liu et al., 2000). Studies in knockout rodents show that the RXR alpha gene is required for actions of the two endogenous retinoic acid ligands, *trans*- and 9-*cis*-retinoic acid, (Chiba et al., 1997; Wendling et al., 1999), and
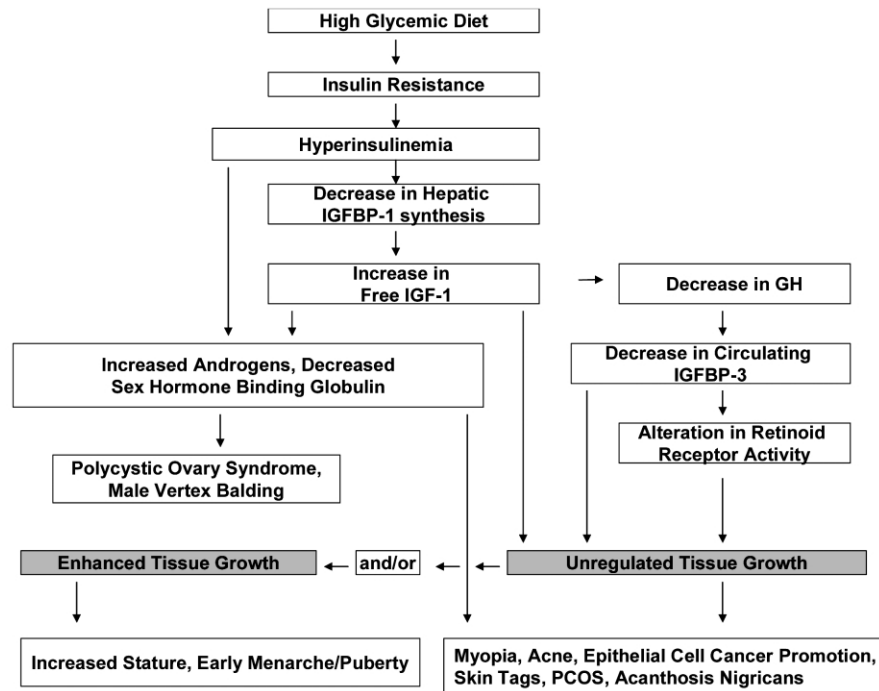
Fig. 4. Schematic representation of hormonal events induced by insulin resistance leading to conditions of enhanced and unregulated tissue growth and other abnormalities.

both RXR alpha agonists and IGFBP-3 are growth inhibitory in many cell lines (Grimberg and Cohen, 2000). In addition, RXR alpha is the major RXR receptor in epithelial tissue (Thacher et al., 2000). Consequently, low plasma levels of IGFBP-3 induced by hyperinsulinemia may reduce the effectiveness of the body's natural retinoids to activate genes that would normally limit epithelial cell proliferation in a variety of tissues.

8. Hyperinsulinemia, IGF-1 and sex steroids

Hyperinsulinemia may also influence the development of abnormalities involving unregulated tissue growth and/or other conditions via its well-established androgenic effects. Both insulin and IGF-1 stimulate the synthesis of androgens in ovarian (Barbieri et al., 1988; Cara, 1994) and testicular (De Mellow et al., 1987; Bebakar et al., 1990) tissues. Furthermore, insulin and IGF-1 inhibit the hepatic synthesis of sex hormone-binding globulin (SHBG) (Singh et al., 1990; Crave et al., 1995), thereby increasing the bio-availability of circulating androgens to tissues. Observational studies support the clinical data and demonstrate inverse relationships between serum

SHBG and insulin (Pugeat et al., 1991) and IGF-1 (Erfurth et al., 1996; Pfeilschifter et al., 1996; Vermeulen et al., 1996). Consequently, high-glycemic-load carbohydrates that encourage hyperinsulinemia may concurrently elevate serum androgen concentrations. Chronically elevated testosterone, as well as estradiol, may also partially contribute to peripheral insulin resistance (Livingstone and Collison, 2002). Moreover, elevations in androgen concentrations are not without physiologic consequence and directly influence the development and progression of PCOS (Falsetti and Eleftheriou, 1996), acne (Thiboutot, 1997), male vertex balding (Randall et al., 2000) and epithelial cell cancers (Secreto and Zumoff, 1994; Gupta et al., 2002).

9. Hyperinsulinemia: more than Syndrome X diseases

Fig. 4 schematically demonstrates how diet-induced hyperinsulinemia may in part promote such diverse abnormalities as PCOS, acne, myopia, skin tags, acanthosis nigricans, certain epithelial cell cancers (breast, prostate and colon) and the secular trends for a reduced age of menarche and

increased stature. Although these conditions and illnesses may appear to be seemingly unrelated, nearly all are characterized by enhanced or unregulated tissue growth that may be operative in part through insulin-induced elevations in free IGF-1 and reductions in IGFBP-3 concentrations. In addition, in many cases insulin-induced hyperandrogenesis may play a contributory or central role in disease promotion.

9.1. Early menarche and increased stature

Free IGF-1 is a potent mitogen for virtually all of the body's tissues (Ferry et al., 1999), as well as a stimulant for increased growth velocity during puberty (Juul et al., 1995). Numerous studies have confirmed that low levels of IGF-1 are associated with reduced stature (Blum et al., 1993; Lindgren et al., 1996) and, conversely, high levels are known to result in increased stature (Gourmelen et al., 1984; Binoux and Gourmelen, 1987; Blum et al., 1993). Human recombinant IGF-1 therapy has also been shown to improve linear growth (Camacho-Hubner et al., 1999). Furthermore, hyperinsulinemic subjects with elevated levels of free IGF-1 are more sexually mature than subjects with superior insulin sensitivity (Travers et al., 1998; Wong et al., 1999), and recombinant IGF-1 therapy accelerates the tempo of puberty in a primate model (Wilson, 1998). Wong et al. (1999) have provided metabolic evidence showing that African American girls were more advanced in their pubertal development and taller than a comparable group of white girls. Furthermore, circulating levels of IGFBP-1 were lower, and circulating insulin and free IGF-I were higher, suggesting that the metabolic cascade (insulin resistance → hyperinsulinemia → decrease in hepatic IGFBP-1 production → increase in circulating free IGF-1 → accelerated growth) was responsible for these effects. Collectively, this evidence supports the view that increased levels of IGF-1 act systemically to cause increased stature and an earlier age of menarche.

In industrialized countries, there has been a steady and progressive secular increase in stature and reduction in pubertal age in the 200–250 years since the advent of the industrial revolution (Tanner, 1973; Malina, 1990). The standard explanation for this trend has been that improvements in nutrition, particularly increases in protein and fat from animal sources, and in hygiene operate to increase stature (Roche, 1979). Generally, most prospective cohorts have been unable to confirm these predictions and have demonstrated either weak or no relationships between dietary fat and protein and age at menarche (Meyer et al., 1990; Maclure et al., 1991; Petridou et al., 1996). In contrast, increasing stature and obesity have frequently been shown to correlate positively with an early age of menarche (St George et al., 1994; Petridou et al., 1996; Koprowski et al., 1999; Wattigney et al., 1999).

Ziegler (1967, 1969) has demonstrated that the secular increase in stature correlates highly with the secular increase in sucrose consumption in England, Japan, the Netherlands, Sweden, Norway, Denmark, the United States and New Zealand. In support of Ziegler's hypothesis, data from Schaeffer (1970) on recently acculturated Eskimos shows that stature increased (4.6 cm in men and 2.9 cm in women) and age of puberty decreased (−2.0 years) simultaneously during a 30-year period (1938–1968) when a several-fold increase in the consumption of sucrose and refined carbohydrates occurred. Moreover, animal protein intake declined by 60% as stature was increasing. In a study examining the relationship of dietary fiber to age of menarche in girls from 46 countries, a high positive correlation ($r = 0.84$) was demonstrated (Hughes and Jones, 1985). More recently, a prospective cohort ($n = 637$) established that higher dietary fiber intakes were associated with a later age of menarche (Koo et al., 2002). Because dietary fiber is inversely related to the glycemic index (Foster-Powell and Miller, 1995), this relationship supports the hypothesis that increasing consumption of high-glycemic-load refined sugars and starches, which are nearly devoid of fiber, may accelerate pubertal development. Furthermore, multiple studies have demonstrated that hyperinsulinemia and insulin resistance occurs in females with premature menarche when compared to females with normal menarche (Loffer, 1975; Ibanez et al., 1998).

Taken together, these studies indicate that consumption of high-glycemic-load carbohydrates, with their unique ability among macronutrients to promote insulin resistance, correlate well in time and space with the secular trends for increased stature and decreased menarcheal age.

9.2. Breast, prostate and colon cancers

Although the etiology of cancer almost certainly involves multiple environmental elements interact-

ing with genetic susceptibility, there is an emerging body of evidence indicating that elevated plasma IGF-1 and reduced IGFBP-3 represents a substantial risk factor for certain epithelial cell cancers (breast, colon and prostate) (Giovannucci, 1999, 2001). IGF-1 may be an important factor in carcinogenesis because of its direct mitogenic effect on neoplastic cells or as an anti-apoptotic agent (Giovannucci, 1999, 2001). In addition, IGFBP-3 has been shown to cause apoptosis directly in prostate cancer cells, breast cancer cells and other cell types (Gill et al., 1997; Rajah et al., 1997). Hence, low serum concentrations of IGFBP-3 induced by high-glycemic-load carbohydrates (Liu, 2000) may impede programmed cell death in cancerous cells. Low serum concentrations of IGFBP-3 may not only directly influence oncogenesis by impairing apoptosis, but may also operate indirectly by influencing retinoid receptor activity. Prostate and breast cancer cell growth has been shown to be inhibited by retinoids (Roman et al., 1992; Pili et al., 2001). Hence, the hyperinsulinemia-induced reductions in IGFBP-3, both by itself and/or via its influence upon nuclear retinoid receptor activity, may augment the stimulatory effects of IGF-1, and thereby further facilitate unregulated tissue growth.

Increased stature (Hunter and Willett, 1993), early age of menarche (Stoll, 1998) and insulin resistance (Bruning et al., 1992) are all well-established risk factors for breast cancer. In addition, increased adult stature has long been recognized as an independent risk factor for many cancers (Albanes et al., 1988). Hence, diet-induced insulin resistance elicited by habitual consumption of high-glycemic-load foods and subsequent elevation of IGF-1, reduction in IGFBP-3 and alteration in retinoid receptor activity may represent the common hormonal pathway responsible for the association among these variables.

In support of the notion that high-glycemic-load carbohydrates may represent the environmental liaison common to increased stature, early menarche and certain epithelial cell cancers are studies examining the role of refined sugar and starch intakes and cancer incidence. The data on international per capita sugar intakes suggest a consistent positive correlation with breast cancer mortality rates (Burley, 1998). For colon cancer, Bostick et al. (1994) reported that high sucrose intakes were associated with a greater risk in 12 of 14 epidemiological studies. Two recent case–

control studies have demonstrated positive associations with dietary glycemic load and colorectal (Franceschi et al., 2001) and breast cancer (Augustin et al., 2001).

Men with fast-growing benign prostatic hyperplasia (BPH) have been shown to be taller and more obese, and to maintain a greater incidence of symptoms of the metabolic syndrome compared to men with slow-growing BNP (Hammarsten and Hogstedt, 1999, 2001). Numerous epidemiologic studies as reviewed by Giovannucci (2001) have confirmed that symptoms of insulin resistance (glucose intolerance, type 2 diabetes, dyslipidemia, increased body mass index) are more prevalent in colon cancer patients.

Taken together, these studies support the concept that diet-induced insulin resistance elicited by habitual consumption of high-glycemic-load carbohydrates may in part underlie the development and progression of breast, colon and prostate cancer.

9.3. Juvenile-onset myopia

Myopia or near-sightedness develops when the axial length of the vitreal chamber is excessive relative to the refractive power of the cornea and lens, thereby resulting in an image that is focused in front of the retina. The excessive near work of reading has most frequently been cited as the single environmental factor responsible for the development of juvenile onset myopia (Mutti et al., 1996). During childhood growth and development, the near work of reading reduces the activity of non-foveal retinal neurons and causes a blurred retinal image (form deprivation) (Meyer et al., 1999). Because of the unique physical characteristics of the printed page (a narrow range of luminance, achromaticity and high spatial frequency of text), the near work of reading represents a more potent inducer of form deprivation than other forms of near work (Chew and Balakrishnan, 1992). The blurred image is sensed by the retina, which in turn signals the scleral tissue to grow and lengthen in an attempt to correct the length of the eyeball to the image. The chemical messenger linking the retinal image clarity to appropriate growth rates in scleral tissue has recently been shown to be retinoic acid, synthesized by both the retina and choroid (Bitzer et al., 2000; Mertz and Wallman, 2000). Reduced retinal and choroidal synthesis of retinoic acid increases scleral growth,

whereas increased synthesis of retinoic acid slows growth. Consequently, excessive near work induces myopia because form deprivation causes the retina to produce too little retinoic acid. Because compensatory hyperinsulinemia may adversely influence retinoid receptor activity via reductions in plasma IGFBP-3, then the retinoid acid signal may be impaired, thereby augmenting the increase in scleral tissue growth initially caused by form deprivation. In support of the concept that diet-induced hyperinsulinemia may contribute to the etiology of myopia are data showing that low incidences of myopia occur in literate populations with limited access to high-glycemic-load carbohydrates, whereas higher incidences of myopia may be present in illiterate populations consuming typical western diets (Cordain et al., 2002a).

A number of human studies have shown that myopes have more dental caries than non-myopes (Goldstein et al. 1971; Hirsch and Levin, 1973), and that the degree of myopia may be related to the caries incidence (Hirsch and Levin, 1973). More recently, it has been shown that progressive myopes have a higher incidence of dental caries than stable myopes (Edwards and Chan, 1995). The mechanistic nature of this relationship has remained obscure. However, with the realization that high-glycemic-load carbohydrates, such as sucrose and refined cereal products made with sucrose, may induce hyperinsulinemia, and that hyperinsulinemia increases free IGF-1, lowers IGFBP-3 and influences retinoid receptor activity, the causal mechanism likely involves sucrose's well-known cariogenic effect and its hyperinsulinemic effect. High-sucrose, low-protein diets in both rabbits (Gardiner and MacDonald, 1957) and rats (Bardiger and Stock, 1972) have been shown to lower the amount of hypermetropia (i.e. produce refractive changes in a myopic direction) that was not reversible upon a sucrose-free diet (Bardiger and Stock, 1972).

As was the situation with cancer patients, myopes are both taller and have an earlier age of menarche when compared to non-myopes (Teikari, 1987; Teasdale and Goldschmidt, 1988; Cordain et al., 2002a), and diets that are known to improve insulin sensitivity have been shown to slow the progression of myopia (Gardiner, 1958; Cordain et al., 2002a). These experiments are suggestive that high-glycemic-load carbohydrate diets may induce permanent changes in the development and progression of refractive errors, particularly during periods of growth.

9.4. Acne

The pathophysiology of acne vulgaris results from the interplay of three factors: (1) hyperkeratinization and obstruction of sebaceous follicles, resulting from abnormal desquamation of follicular epithelium; (2) androgen-stimulated increase in sebum production; and (3) proliferation of *Propionibacterium acnes*, which generates inflammation (Thiboutot, 1996).

In support of the notion that insulin-triggered elevations in free IGF-1 may promote acne via hyperkeratinization are data showing that IGF-1 is required for keratinocyte proliferation in humans (Rudman et al., 1997), and that in transgenic mice over-expression of IGF-1 results in hyperkeratosis and epidermal hyperplasia (Bol et al. 1997). Furthermore, women with post-adolescent acne maintain elevated serum concentrations of IGF-1 (Aizawa and Niimura, 1995) and are mildly insulin-resistant (Aizawa and Niimura, 1996).

The reductions in IGFBP-3 stimulated by elevated serum insulin levels (Nam et al., 1997; Attia et al., 1998) or by acute ingestion of high-glycemic carbohydrates (Liu, 2000) may also contribute to unregulated cell proliferation in the follicle. Hyperinsulinemia causes overexpression of the epidermal growth factor receptor (EGF-R) by elevating plasma non-esterified fatty acids (Vacaresse et al., 1999), and also induces production of transforming growth factor-beta (TGF-beta1) (Schleicher and Weigert, 2000). Increased concentrations of EGF and TGF-beta1 depress localized keratinocyte synthesis of IGFBP-3, and thereby increase the availability of free IGF-1 to its keratinocyte receptors (Edmondson et al., 1999) which in turn promotes keratinocyte proliferation. In addition, low plasma levels of IGFBP-3 induced by hyperinsulinemia may reduce the effectiveness of the body's natural retinoids to activate genes that would normally limit follicular cell proliferation. Consequently, hyperkeratinization of sebaceous follicles may result synergistically from both elevations in free IGF-1 and reductions in IGFBP-3.

Elevated sebum production, essential to the development of acne (Thiboutot, 1997), is stimulated by androgens (Eichenfield and Leyden, 1991; Thiboutot, 1997). Both insulin and IGF-1 stimulate the synthesis of androgens in ovarian (Barbieri et

al., 1988; Cara, 1994; Nestler, 1997) and testicular (De Mellow et al., 1987; Bebakar et al., 1990) tissues. Furthermore, insulin and IGF-1 inhibit the hepatic synthesis of SHBG (Singh et al., 1990; Crave et al., 1995), thereby increasing the bio-availability of circulating androgens to tissues. Direct injections of recombinant IGF-1 in humans elicit both androgenesis and acne (Klinger et al., 1998). Higher serum androgen (Thiboutot et al., 1999), insulin (Aizawa and Niimura, 1995) and IGF-1 (Aizawa and Niimura, 1996) concentrations are associated with the presence of acne in women. These data are suggestive that the endocrine cascade induced by hyperinsulinemia enhances sebum synthesis and the development of acne.

Women with persistent adult acne are at increased risk for breast cancer (Moseson et al., 1993). Hence, diet-induced insulin resistance and its subsequent elevation of free IGF-1 serum concentrations, reduction in serum IGFBP-3 concentrations and potential to impair retinoid receptor activity may represent the common hormonal pathway responsible for the association between acne and breast cancer.

9.5. Polycystic ovary syndrome (PCOS)

Acne is a characteristic feature in PCOS patients, who are also frequently hyperinsulinemic, insulin-resistant and hyperandrogenic (Falsetti and Eleftheriou, 1996). These patients typically maintain elevated serum concentrations of androgens, IGF-1 and lower concentrations of SHBG (Falsetti and Eleftheriou, 1996; Nestler, 1997; Thierry van Dessel et al., 1999). Androgen levels can be lowered and disease symptoms alleviated by improving insulin sensitivity through weight loss (Pasquali et al., 1997) or by the use of pharmaceuticals such as metformin (Ehrmann, 1999) which improve insulin metabolism and ameliorate acne symptoms (Kolodziejczyk et al., 2000). Numerous studies (Cohen and Cohen, 1959; Bettley, 1961; Singh et al., 1961) have reported that tolbutamide, a sulfonylurea drug that improves beta cell function and lowers fasting insulin levels, leading to improved insulin sensitivity, is also therapeutically effective in treating acne.

Dietary interventions utilizing low-glycemic-load carbohydrates may be useful in the treatment of PCOS and acne because they improve insulin sensitivity (Frost et al., 1998). Recently, a large intervention study has demonstrated that diets rich in low-glycemic foods reduced serum testosterone and fasting glucose, while improving insulin metabolism and increasing SHBG (Berrino et al., 2001). These endocrine changes are consistent with those known to be therapeutic for both PCOS and acne patients, as well as for patients with other diseases of insulin resistance.

9.6. Cutaneous papillomas (skin tags)

Cutaneous papillomas (skin tags) are hyperproliferative skin lesions of idiopathic origin that typically develop on the neck, axilla and groin regions. They are a frequent finding in obese subjects (Levine, 1996; Garcia-Hidalgo et al., 1999) and are a cutaneous marker for type 2 diabetes (Kahana et al., 1987; Thappa, 1995; Hollister and Brodell, 2000) and insulin resistance (Mathur and Bhargava, 1997; Crook, 2000). Recently, cutaneous papillomas have been demonstrated to occur simultaneously with the dyslipidemic profile that characterizes insulin resistance (Crook, 2000).

As with acne, the etiology of skin tags may result from increased concentrations of IGF-1 and IGFBP-3 acting directly upon cutaneous epithelial cells, or perhaps from localized interaction of these hormones with EGF. In vivo studies examining skin tags have demonstrated an overexpression of the EGF-R in these tissues (Nanney et al., 1992). Because hyperinsulinemia chronically elevates non-esterified free fatty acids (Boden and Shulman, 2002) which in turn causes overexpression of EGF-R (Vacaresse et al., 1999), it is likely that induction of cutaneous papillomas results in part from elevated intracellular concentrations of EGF. Because hyperinsulinemia increases production of both EGF and TGF-beta1 (Schleicher and Weigert, 2000), a synergistic mitogenic effect likely occurs via interaction with free IGF-1 and IGFBP-3. Increased concentrations of EGF and TGF-beta1 depress localized keratinocyte synthesis of IGFBP-3, and thereby increase the availability of free IGF-1 to its keratinocyte receptors (Edmondson et al., 1999). Therefore, high-glycemic-load carbohydrates may in part underlie the development of cutaneous papillomas via elevations of serum concentrations of non-esterified free fatty acids and IGF-1, and from reductions in IGFBP-3 that may also negatively influence the endogenous retinoid receptor pathway.

9.7. Acanthosis nigricans

Acanthosis nigricans is a skin disorder that occurs most frequently as a result of hyperinsulinemia associated with obesity and more rarely as a paraneoplastic syndrome or as a trait of several genetic disorders (Torley and Munro, 2002). Acanthosis nigricans is characterized by hyperpigmentation and velvet hyperkeratosis that traditionally affect the neck and axilla, the groin and the knuckles. Histologically, the number of spinous cells in the epidermis is increased, which causes epithelial hyperplasia (Kerem et al., 2001). Acanthosis nigricans frequently occurs in PCOS patients (Flier et al., 1985) and has been found to afflict 7.1% of a randomized population of schoolchildren, with much higher incidences in children with darker complexions (Stuart et al., 1989). Oral metformin therapy markedly improves the lesions of acanthosis nigricans (Hermanns-Le et al., 2002).

It has been postulated that the underlying mechanism of acanthosis nigricans in obesity stems from excessive circulating concentrations of insulin binding to IGF-1 receptors (IGF-R) on keratinocytes and dermal fibroblasts (Cruz and Hud, 1992; Torley and Munro, 2002). Since free IGF-1 has a higher binding affinity to IGF-R than insulin, the mitogenic effect of hyperinsulinemia upon keratinocytes and dermal fibroblasts likely involves not only insulin, but also free IGF-1 and IGFBP-3 in a manner similar to acne and dermal papillomas. In addition, elevated serum concentration of non-esterified free fatty acids induced by hyperinsulemia (Boden and Shulman, 2002) up-regulates EGF-R (Vacaresse et al., 1999). Accordingly, increased intracellular concentrations of EGF also likely promote the development of acanthosis nigricans associated with hyperinsulinemic obesity.

9.8. Male vertex balding

With virtually all diseases of insulin resistance, there are both environmental and genetic factors that act concomitantly to elicit the phenotypic expression of the disease or condition. Male balding clearly has a genetic component (Birch and Messenger, 2001). However, it is well established that male pattern balding also is an androgen-dependent trait that occurs from elevated androgenesis after puberty (Randall et al., 2000). Consequently, any environmental factor or factors that would elevate serum androgen levels would promote increased balding, particularly in genetically susceptible individuals.

High-glycemic-load carbohydrates, by inducing hyperinsulinemia, along with a concomitant elevation of serum androgens and reduction in SHBG (Fig. 4) represent a likely environmental agent that may in part underlie the promotion of male vertex balding. In support of this endocrine cascade are studies showing that men with higher serum levels of testosterone and IGF-1, and lower circulating concentrations of IGFBP-3 were more likely to have vertex balding (Signorello et al., 1999; Platz et al., 2000). However, it is not known at present if elevations in IGF-1 and reductions in IGFBP-3 are directly involved in the origin of male vertex balding, or if they are simply markers for elevations in circulating androgens that are known to promote baldness (Randall et al., 2000). Nevertheless, the male vertex balding pattern is strongly associated with other Syndrome X diseases, such as CAD and hypertension (Lesko et al., 1993; Lotufo et al., 2000).

10. Summary

High-glycemic-load carbohydrates now comprise 36% or more of the daily energy in the typical US diet. Prior to the industrial revolution, refined sugars and cereal grains were rarely consumed by the average citizen. Accordingly, there has been a steady and continuous secular increase in the glycemic load of the typical western diet over the past 200–250 years. High-glycemic-load diets, coupled with susceptibility genes, initiate a hormonal cascade (Fig. 4) that facilitates unregulated or enhanced growth in many tissues throughout the body, particularly in tissues with rapid turnover rates, such as epithelial cells. This hormonal cascade ultimately results in a variety of ubiquitous diseases and maladies of western civilization. Dietary interventions utilizing low-glycemic-load carbohydrates may be useful in treating all diseases of insulin resistance via their therapeutic effects upon endocrine and cytokine function.

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