# Western Diet, Insulin/IGF-I Signaling Pathway and Metabolic Syndrome

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The metabolic syndrome is a cluster of overlapping conditions resulting in an increased incidence of type 2 diabetes, cardiovascular disease, and cancer. In the last few decades, prevalence of the metabolic syndrome in the Western world has reached epidemic proportions and this is likely due to alterations in diet and the environment as well as decreased physical activity. The Western diet and lifestyle (Westernization) plays an important etiological role in the pathogenesis of the metabolic syndrome by exerting negative effects on activity of the insulin–insulin-like growth factor-I (insulin–IGF-I) system. Interventions that normalize/reduce activity of the insulin–IGF-I system may play a key role in the prevention and treatment of the metabolic syndrome. For successful prevention, limitation, and treatment of the metabolic syndrome, the focus should be primarily on changing our diets and lifestyle in accordance with our genetic make-up, formed in adaptation to Paleolithic diets and lifestyles during a period of several million years of human evolution.

Keywords: hyperinsulinemia ; IGF-I ; insulin resistance ; IGFBP-1 ; Metabolic Syndrome ; Westernization ; Overnutrition ; Paleoithic diet ; Mediterrerranean diet ; Prevention

## 1. The Insulin–IGF-I System

The insulin–IGF system is formed by insulin, two insulin-like growth factors (IGF-I and IGF-II), and six cell-membrane signal-transducing receptors (insulin receptor-A (IR-A), insulin receptor-B (IR-B), insulin-like growth factor-I receptor (IGF-IR) and their respective hybrids): the IRs and IGF-IR can be found at the cell surface as homodimers composed of two identical alpha/beta monomers, or as heterodimers composed of two different receptor monomers (aka hybrids) [1][2][3]. The system further contains the IGF-II scavenger transmembrane protein previously known as insulin-like growth factor “receptor”-II “(IGF2R), and six IGF-binding proteins (IGFBP-1-6), several IGFBP-related proteins and IGFBP proteases, which serve to tightly regulate IGF-I and IGF-II levels/bioavailability in circulation and at the cell surface [1][2][3][4][5][6]. Insulin and IGF-I show high structural similarities.

It has been postulated that IGF-I emerged at a very early stage in vertebrate evolution from an ancestral insulin-like gene [7]. This ancestral insulin-like gene was duplicated to form insulin and IGF-I in early (agnathan) vertebrates. Further gene duplications resulted in distinct IGF-I and IGF-II genes, which were first found during evolution in gnathosomes (jawed vertebrates) [8]. In vertebrates, insulin-like peptides predominantly functioned as growth factors promoting tissue growth and development. However, in vertebrates, this growth-promoting function has been subsumed by IGF-I and IGF-II, while insulin has acquired this new function and is primarily involved in metabolism. It has further been demonstrated that, in vertebrates, nutritional status is the key regulator of the activities of insulin and IGFs [9]. Consequently, insulin and IGFs regulate metabolism, growth and development in vertebrates in response to nutritional availability.

## 2. Insulin Resistance, Hyperinsulinemia and the Metabolic Syndrome

Insulin resistance and hyperinsulinemia appear to be central in the development of the metabolic syndrome [10][11].Insulin resistance and hyperinsulinemiaappear to be central in the development of the metabolic syndrome [10][12]. In the view of Reaven (see above) and in most traditional literature, obesity is considered the main cause of insulin resistance, and insulin resistance is the abnormality leading to hyperinsulinemia. In this model, hyperinsulinemia is a compensatory response to insulin resistance. However, an increasing number of (prospective) human studies suggests an alternative scenario: in this scenario, chronic hypersecretion of insulin is the primary abnormality leading to hyperinsulinemia and precedes, initiates, and causes insulin resistance. In this new scenario, hyperinsulinemia is the first event triggering insulin resistance, obesity, the metabolic syndrome, and type 2 diabetes [13][14][15][16][17][18][19][20][21][22][23]. In addition, in subjects with normal plasma glucose concentrations, it has been found that hyperinsulinemia per se induced insulin resistance by

insulin-induced downregulation of insulin receptor signaling [24][25]. This further supports the idea that hyperinsulinemia may be a primary driver of insulin resistance [25][26].

In a well-characterized cohort of apparently healthy adults, elevated fasting insulin at baseline was found to be an independent determinant over a 5-year period for the future development of the metabolic syndrome [27]. In addition, prospective evidence shows that—independently of obesity and body weight—hyperinsulinemia is related to the development of dyslipidemia and hypertension, suggesting that hyperinsulinemia precedes these disorders in the etiologic pathway [28][29][30]. Thus, hyperinsulinemia may indeed be an early and central feature of the cardiovascular risk of subjects with the metabolic syndrome [27]. Further support of a pathogenic role of hyperinsulinemia in the development of the metabolic syndrome was demonstrated in an animal model by Jeanrenaud et al. They showed that short-term hyperinsulinemia is a pathological driving force, which produces incipient obesity by overstimulating white adipose tissue and liver metabolic activity while concomitantly producing incipient muscle insulin resistance [31].

Barbara Corkey has proposed a model in which excessive beta-cell insulin secretory responses, possibly induced by consumption of the “modern” Western diet and over-nutrition, superimposed on a susceptible genetic background and metabolic programming, may be a major cause of hyperinsulinemia, insulin resistance, obesity, and type 2 diabetes [26]. As Corkey pointed out, many aspects of the Western diet may potentially promote hyperinsulinemia: excess nutrient ingestion, artificial sweeteners, mono-oleoylglycerol, the macronutrient ratio in the food, the characteristics of the carbohydrates, proteins and fat of the food, and insufficient dietary fiber intake [32]. In the model of Barbara Corkey, hyperinsulinemia is the dominant driver of insulin resistance. In addition, in her model, insulin resistance is an adaptive response protecting muscles from chronic hyperinsulinemia-mediated nutrient excess and intracellular hyperglycemia.

Emerging evidence suggests that not only pancreatic insulin secretion, but also lower hepatic insulin clearance, may contribute to hyperinsulinemia (=increased peripheral insulin levels). Bergman has suggested the following course of events in the development of type 2 diabetes: low(ered) hepatic insulin clearance causes peripheral hyperinsulinemia, which in turn exacerbates insulin resistance [33]. Consequently, insulin resistance will stress pancreatic beta-cells, and this may finally result in their ultimate failure and onset of frank type 2 diabetes. In addition, development of insulin resistance in muscles and fat cells is caused by of an overexposure of the (post-hepatic) peripheral tissues to endogenous insulin [33]. As a direct consequence of the peripheral hyperinsulinemia, peripheral insulin resistance develops to dampen hyperinsulinemia-mediated stimulating effects in muscles and fat cells [33].

## 3. Effects of Hyperinsulinemia on the Balance of the Insulin–GH–IGF-I Axis

In healthy individuals, the insulin–GH–IGF-I axis is in balance: insulin and GH stimulate hepatic IGF-I production, whereas IGF-I secreted by the liver feeds back to suppress both insulin and GH [34][35]. The typical modern Western diet can disturb this balance. Due to its continuous food intake, energy surplus, high content of sugars, corn-derived fructose syrup, saturated fats and proteins, the modern Western diet may induce hyperinsulinemia, which in turn increases IGF-I secretion [35]. Increased IGF-I subsequently induces suppression of GH secretion to lower levels than normal [36][37]. Only a few days of overeating may markedly suppress GH secretion before any measurable weight gain, and it has been suggested that, in these circumstances, the accompanying hyperinsulinemia is a likely mediator of this rapid reduction in GH secretion. Consequently, a shift of the insulin : GH ratio towards insulin (and IGF-I) and away from GH will occur. The higher insulin : GH ratio lowers energy expenditure and induces fat accumulation, thereby promoting energy storage and lipid synthesis and hindering lipid breakdown. This will promote obesity because of higher fat accumulation and lower energy expenditure.

## 4. Low(er) Activity of Insulin/IGF-I Signaling Pathway Protects against Type 2 Diabetes and Cancer

Laron syndrome is a disorder characterized by a lack of IGF-I production in response to GH [38]. It is caused by inherited GH receptor mutations and Individuals with the classic Laron syndrome present with short stature, obesity, low blood sugar, and congenital IGF-I deficiency (with low serum IGF-I) with decreased insulin/IGF-I signaling activity despite elevated basal serum GH [38]. Guevera-Aguire et al. found in individuals with Laron syndrome, in contrast to their healthy relatives with normal insulin/IGF-I signaling, a significant reduction in pro-aging signaling, cancer, and type 2 diabetes [39]. Serum from subjects with the Laron syndrome induced in vitro a reduced number of DNA breaks but increased apoptosis in human mammary epithelial cells treated by hydrogen peroxide [39]. Moreover, serum from subjects with the Laron syndrome also caused reduced expression of rat sarcoma virus (RAS), PKA (protein kinase A), and mTOR (target of rapamycin) and up-regulation of superoxide dismutase 2 in treated cells [39]. All these changes promote normal cellular

protection and life-span extension in model organisms and provide a possible explanation for the observed low incidence of cancer in subjects with the Laron syndrome in the study by Guevera-Aguire et al. [39]. Moreover, individuals with the Laron syndrome showed reduced insulin concentrations (1.4 μU/mL versus 4.4 μU/mL in unaffected relatives) and a very low HOMA-IR (homeostatic model assessment-insulin resistance) index (0.34 versus 0.96 in unaffected relatives), indicating that higher insulin sensitivity could provide a possible (alternative) mechanism explaining the reduced prevalence of type 2 diabetes and cancer observed in subjects with the Laron syndrome [39]. Thus Laron syndrome, an experiment of nature, showed that in humans, low(er) activity of the insulin/IGF-I signaling pathway and high insulin sensitivity may play a crucial role in the protection from diseases typically related to Western civilization, such as type 2 diabetes and cancer [40].

## 5. The Activity of the Insulin–IGF-I Signaling Pathway and Longevity

Disruption of genes in the insulin–IGF-I signaling pathway that share similarities with those in humans can significantly extend life span in diverse species, including yeast, worms, fruit flies, and rodents [41]. It has therefore been suggested that reducing the activity of the insulin–IGF-I signaling pathway plays a key role in delayed aging and prolonged longevity [42]. A point to emphasize here, and in favor of this suggestion, is that all long-lived mutants, ranging from yeast to mice, share some important phenotypic characteristics, including reduced insulin signaling, enhanced insulin sensitivity, and reduced IGF-I plasma levels [41].

Laboratory animals fed ad libitum have relatively low levels of physical activity and therefore show similarities to humans with a Western (sedentary) lifestyle, who are at high risk for hyperinsulinemia, obesity, and insulin resistance [43]. Caloric restriction counteracts the general trend for laboratory animals to progressively increase fat mass during aging [43]. Restriction of the number of calories consumed lowers the incidence of age-related loss of functions and disease and increases life span in a wide variety of animals [43][44]. It has been further suggested that many of the beneficial effects of caloric restriction on lifespan are mediated, at least in part, by down-regulation of the insulin/IGF-I signaling pathway activity [45]. In support of this latter option is the observation that caloric restriction in rodents decreases activity of the insulin/IGF-I signaling cascade and postpones or attenuates cancer, immunosenescence, and inflammation without irreversible side effects [43].

Nutrients and insulin both activate the mTOR pathway and this pathway is involved in cellular senescence and age-related diseases [45][46][47]. Overnutrition increases insulin secretion, increases IGF-I bioactivity and hyperactivates the mTOR pathway [47] (**Figure 1**A). Hyperactivation of the mTOR pathway induces insulin receptor resistance which blocks insulin-mediated glucose uptake and results in elevated glucose levels [47]. The elevated glucose levels induce a further increase in insulin secretion, which will, in turn, further deteriorate insulin sensitivity [45]. In contrast, lifespan-extending caloric restriction without malnutrition, decreases the activity of the mTOR pathway: this improves insulin receptor sensitivity and secondarily reduces plasma glucose levels, insulin levels and IGF-I bioactivity [45][46] (**Figure 1**B).

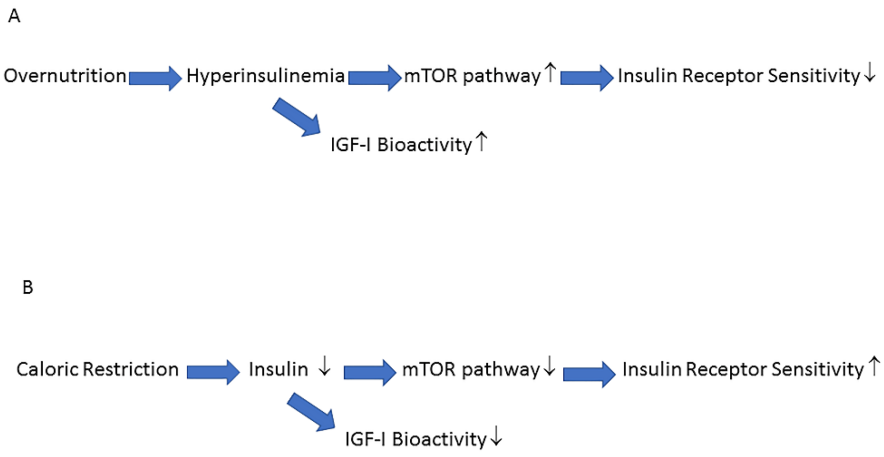


**Figure 1.** Nutrients and insulin activate the target of rapamycin (mTOR) pathway and increase IGF-I bioactivity. (**A**) Overnutrition increases insulin levels, IGF-I bioactivity and hyperactivates the mTOR pathway. Hyperactivation of the mTOR pathway induces insulin resistance and blocks insulin-mediated effects on glucose metabolism, resulting in elevated plasma glucose levels. (**B**) Caloric restriction (without malnutrition) reduces insulin levels, IGF-I bioactivity, and the activity of the mTOR pathway. The reduced activity of the mTOR pathway improves insulin receptor sensitivity and insulin-mediated effects on glucose metabolism, resulting in lower plasma glucose levels. ↑ increased, ↓ decreased.

Healthy centenarians are often considered the best living model of successful human aging and therefore often used to study healthy longevity [48]. Interestingly, it has been found that in healthy centenarians, fasting insulin levels, glucose tolerance, glucose-stimulated insulin secretion, and insulin sensitivity, are low and comparable to those found in healthy subjects aged 50 years or younger [49]. Thus healthy centenarians have preserved insulin actions comparable to subjects aged 50 years or younger, again suggesting that hyperinsulinemia, age-related insulin resistance and reduced insulin actions are not an obligatory finding in the elderly [50].

Parr previously hypothesized that low(er) insulin levels due to increased insulin sensitivity might provide healthy centenarians with a well-balanced insulin–GH–IGF-I axis, which may induce a slower loss of physiologic reserves, thereby permitting better conditions for a longer life span [48]. In addition, healthy centenarians usually show significantly less oxidative stress and greater plasma antioxidant defenses than aged subjects [51]. It has further been clearly shown that oxidative stress is a precursor to insulin resistance [52]. Due to the vicious circle occurring between insulin and oxidative stress, it has been proposed that low insulin (and IGF-I) levels with preserved insulin sensitivity are important factors responsible for the observed higher insulin sensitivity and lower oxidative stress in healthy centenarians compared with aged subjects [50].

## 6. How to Halt the Negative Impact of the Western Lifestyle on the Insulin/IGF-I System and the Prevalence of the Metabolic Syndrome

The increasing prevalence of the metabolic syndrome seems primarily driven by changes in diet and increasingly sedentary lifestyles [53]. Due to the Western dietary pattern of frequent snacking and frequent consumption of sucrose-containing soft drinks, insulin levels are elevated most of the day [54][55]. The changes in dietary habits, adopted by the Western world over the past 100 years, appear to have made an important contribution to the increasing prevalence of the metabolic syndrome and its consequences—coronary artery disease, hypertension, diabetes, and some cancers. These conditions have only emerged in the past century but were virtually absent in hunter-gatherer populations following a traditional hunter-gatherer (or paleolithic) diet and lifestyle [56]. However, genetic make-up of humans is still, at present, best adapted to the low-glycemic and low-insulinemic hunter-gatherer (paleolitic) diet, and it therefore has been suggested that, although we are people living in the 21st century, genetically we are still citizens of the Paleolithic era [54][57].

As discussed previously, the “modern” Western diet and lifestyle, by exerting negative (i.e., stimulating) effects on the activity of the insulin–IGF-I system, may play an important etiological role in the pathogenesis of the metabolic syndrome. Interventions that normalize/reduce activity of the insulin–IGF-I system might therefore play a key role in the prevention and treatment of the metabolic syndrome and its consequences. Primary prevention of the metabolic syndrome (i.e., before it starts) is probably the only effective and cost-effective approach, counterbalancing the environmental roots of the increased prevalence of the metabolic syndrome. Some advocate that we should turn to the paleolithic diet and lifestyle when seeking solutions for the increased prevalence of hyperinsulinemia, insulin resistance, obesity, and type 2 diabetes, which have emerged in many populations worldwide after switching to the Westernized way of life [56].

Modifications of our diets and lifestyle, in accordance with our genetic constitution-formed in adaptation to Paleolithic diets and lifestyles during a period of several million years of human evolution—may help prevent or limit the development of the metabolic syndrome. Translating this insight into clinical practice, however, requires not only individual changes in our food and lifestyle and the early start and adoption of healthy habits at a young age in pediatric populations, but also requires fundamental changes in our health system and food industry.

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