Syndrome X: Just the tip of the hyperinsulemia iceberg?

By

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Introduction:

When body tissues become resistant to insulin the pancreas is frequently able to maintain normal glucose tolerance by sustaining a relative degree of compensatory hyperinsulinemia. The onset of impaired glucose tolerance or type 2 diabetes marks a failure of the pancreas to maintain this state of compensatory hyperinsulinemia. Compensatory hyperinsulinemia is not necessarily benign and underlies several of the most common and deadly chronic diseases in western, industrialized nations. Hypertension, abnormal glucose tolerance, type 2 diabetes, dyslipidemia [increased plasma triacylglycerol, decreased high density lipoproteins, and smaller, denser low density lipoproteins] , coronary artery disease (CAD), and obesity, are all linked to insulin resistance and have been collectively termed syndrome X (1,2). Abnormalities of fibrinolysis and hyperuricaemia also appear to be members of the cluster of maladies comprising syndrome X (2). Because insulin resistance is such a common phenomenon (afflicting at least 25 %) of the population, it has been suggested that the various facets of syndrome X are involved to a substantial degree in the cause and clinical course of the major diseases of Western civilization (2).

In the past 2 years emerging evidence suggests that the web of diseases and abnormalities associated with insulin resistance may extend far beyond the common maladies (obesity, type 2 diabetes, hypertension, dyslipidemia and CAD) that frequently present themselves concurrently in patients. Such diverse abnormalities and illnesses as polycystic ovary syndrome (PCOS), acne, myopia, epithelial cell cancers (breast, prostate and colon), reduced age of menarche and the secular trend for increased stature

are all linked to the compensatory hyperinsulinemia of insulin resistance by hormonal interaction.

Compensatory Hyperinsulinemia and Insulin Like Growth Factor

The metabolic ramifications of chronic hyperinsulinemia are diverse and complex. Recently it has been demonstrated 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 (3,4). The increase in circulating levels of insulin and IGFBP-1 vary inversely throughout the day, and the suppression of IGFBP-1 by insulin (5), and hence elevation of free IGF-1, may be maximal when insulin levels exceed 70 to 90 pmol/L (6). Additionally, growth hormone (GH) levels fall via negative feedback of free IGF-1 on GH secretion, resulting in reductions in IGFBP-3 (4). These experiments show that both acute (4) and chronic (3,4) 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 (7). Hence, elevated plasma concentrations of IGF-1 induced by hyperinsulinemia have a high potential for stimulating growth in a wide variety of tissues throughout the body.

Compensatory Hyperinsulinemia and Retinoid Receptors

Retinoids are natural and synthetic analogues of vitamin A that are inhibitors of cell proliferation and promoters of apoptosis (programmed cell death) (8). The body's natural retinoids (trans retinoic acid 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 homodimers to retinoic acid response elements located in the promoter regions of target genes whose function is to limit growth in many cell types (9). It has recently been demonstrated that IGFBP-3 and RXR alpha bind one another in the nucleus and that IGFBP-3 enhances RXR-RXR homodimer mediated signaling (10). Consequently, low plasma levels of IGFBP-3 induced by hyperinsulinemia reduce the effectiveness of the body's natural retinoids to activate genes that limit cell growth and promote apoptosis.

Hyperinsulinemia, IGF-1, Retinoid Receptors and Unregulated Tissue Growth

Figure 1 schematically demonstrates how insulin resistance may promote unregulated and enhanced tissue growth resulting in such diverse abnormalities as PCOS, acne, myopia, epithelial cell cancers (breast, prostate and colon), reduced age of menarche and the secular trend for increased stature. Although these conditions and illnesses may appear to be seemingly unrelated, they all are characterized by enhanced or unregulated tissue growth mediated directly by elevations in IGF-1, reductions in IGFBP-3 and/or reductions in retinoid receptor activity.

Early Menarche and Increased Stature

Free IGF-1 is a potent mitogen for virtually all of the body's tissues (7), as well as a stimulant for increased growth velocity during puberty (11). Numerous studies have confirmed that low levels of IGF-1 are associated with reduced stature (12,13) and conversely high levels are known to result in increased stature (13-15). Human recombinant IGF-1 therapy has also been shown to improve linear growth (16). Further, hyperinsulinemic subjects with elevated levels of free IGF-1 are more sexually mature than subjects with superior insulin sensitivity (17,18), and recombinant IGF-1 therapy accelerates

the tempo of puberty in a primate model (19). Wong et al. (17) have provided metabolic evidence showing that Black American girls were more advanced in their pubertal development and taller than a comparable group of White girls. Further, 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-I production – increase in circulating free IGF-I –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 puberty.

Breast, Prostate and Colon Cancers

Although the etiology of cancer almost certainly involves multiple environmental elements interacting with genetic susceptibility, there is an emerging body of evidence indicating that elevated plasma IGF-1 and reduced IGFBP-3 is a substantial risk factor for epithelial cell cancers (breast, colon and prostate) (20). IGF-1 may be an important factor in carcinogenesis because of its direct mitogenic effect on neoplastic cells or as an anti-apoptotic agent (20). IGFBP-3 has been shown to directly induce apoptosis in prostate cancer cells, breast cancer cells and other cell types (21,22). Hence low plasma levels of IGFBP-3 would promote oncogenesis by permitting cancer cells to survive. Low plasma concentrations of IGFBP-3 may not only directly influence oncogenesis via apoptosis, but it may also operate indirectly by its influence upon retinoid receptors. Prostate and breast cancer cell growth have been consistently shown to be growth inhibited by retinoids (23,24). Thus, the hyperinsulinemia induced reduction in nuclear retinoid receptor activity augments the stimulatory effects of IGF-1 and further facilitates unregulated tissue growth.

Increased stature (25), an early age of menarche (26), and insulin resistance (27) are all well established risk factors for breast cancer. Increased adult stature has long been recognized as an independent risk factor for many cancers (28). Therefore, diet induced insulin resistance and its subsequent elevation of IGF-1, reduction in IGFBP-3 and reduction in retinoid receptor activity may represent the common hormonal pathway responsible for the association among these variables.

Juvenile Onset Myopia

Myopia or nearsightedness 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 (29). 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) (30). Because of the unique physical characteristics of the printed page (a narrow range of luminance, achromaticity of text, 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 (31). 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 been recently shown to be retinoic acid synthesized by both the retina and choroid (32,33). 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 reduces retinoid receptor activity via reductions in plasma IGFBP-3 then the retinoid acid signal is reduced further, thereby augmenting the increase in scleral tissue growth initially caused by form deprivation. As was the situation with cancer patients, myopes are both taller and have an earlier age of menarche when compared to non myopes (34-37), and diets that are known to improve insulin sensitivity have been shown to slow the progression of myopia (38).

Acne and Polycystic Ovary Syndrome

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(39). Retinoids are frequently prescribed for the treatment of acne vulgaris because of their powerful anti-proliferative effects that act to normalize desquamation and proliferation of the follicular epithelium (40). Because compensatory hyperinsulinemia reduces the retinoid receptor activity (Figure 1), then the uptake of endogenous retinoids are likely reduced in follicular epithelial cells, which may in turn be partially responsible for the abnormal desquamation of the follicular epithelium. Additionally, androgen induction of follicular epithelial cell growth is mediated by IGF-1 (41), and hyperinsulinemia is known to promote hyperandrogenism (42) . Therefore, hyperinsulinemia mediated impaired uptake of endogenous retinoic acid by follicular epithelial cells along with elevated plasma concentrations of free IGF-1 likely cause unregulated proliferation of follicular epithelial cells, while elevated plasma insulin levels accelerate sebum production via increases in circulating testosterone concentrations.

In support of this hormonal cascade is the observation that direct injections of recombinant IGF-1 results in acne (43), and women with post adolescent acne frequently have elevated levels of IGF-1 (44) and show insulin resistance (45). Abusers of anabolic steroids have a hypersecretion of sebum and concurrently develop acne (46), and exogenous administration of testosterone and testosterone derivatives elevates IGF-1 concentrations (47). Acne is a major symptom in PCOS patients who also are frequently hyperinsulinemic (48) and have elevated levels of androgens and IGF-1 (49). Both acne and Syndrome X symptoms are often alleviated when PCOS patients are put on diets or drug therapy that control their hyperinsulinemia (50).

Finally, women with persistent adult acne are at increased risk for breast cancer (51). Consequently, diet induced insulin resistance and its subsequent elevation of IGF-1 and reduction in retinoid receptor activity may represent the common hormonal pathway responsible for the association between acne and breast cancer.

Summary

Compensatory hyperinsulinemia is a well recognized metabolic disturbance that is at the root cause of diseases and maladies of syndrome X (hypertension, type 2 diabetes, dyslipidemia, CAD, obesity, abnormal glucose tolerance). Abnormalities of fibrinolysis and hyperuricaemia also appear to be members of the cluster of maladies comprising syndrome X. Recent evidence indicates that compensatory hyperinsulinemia causes a shift in a number of endocrine pathways that favor growth. Specifically, chronically elevated plasma insulin levels result in increased circulating concentrations of IGF-1 and reduced concentrations of IGFBP-3. Because circulating IGFBP-3 upregulates retinoid receptor activity, hyperinsulinemically mediated reductions in IGFBP-3 will reduce transcription of

antiproliferative genes in a variety of cells. These endocrine shifts (elevations of free IGF-1, reductions in IGFBP-3 and reductions in retinoid receptor activity) favor cellular proliferation and growth in a variety of tissues whose clinical course may result in PCOS, acne, epithelial cell cancers, myopia and the secular trends for increased stature and reductions in the age of menarche. Consequently, these illnesses and maladies may, in part, have compensatory hyperinsulinemia at their root cause and therefore should be classified as diseases of syndrome X.

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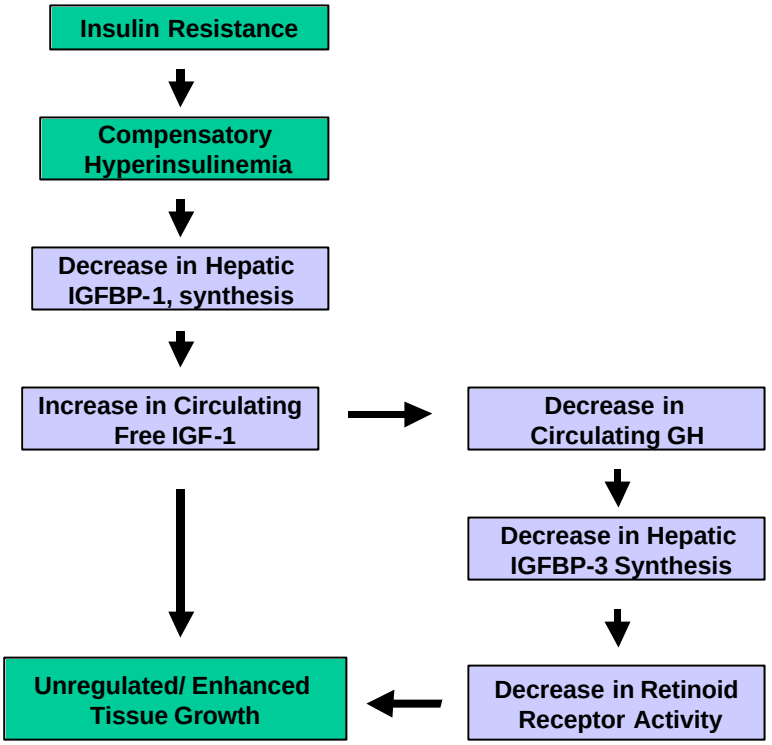
Figure Legends:

Figure 1. Schematic representation of hormonal events induced by insulin resistance leading to enhanced and unregulated tissue growth. (IGF-1 = insulin like growth factor 1, IGFBP-1 = insulin like growth factor binding protein 1, GH = growth hormone, IGFBP-3 = insulin like growth factor binding protein 3.


Insulin Resistance
Compensatory Hyperinsulinemia
Decrease in Hepatic IGFBP-1, synthesis
Increase in Circulating Free IGF-1
Decrease in Circulating GH
Decrease in Hepatic IGFBP-3 Synthesis
Decrease in Retinoid Receptor Activity
Unregulated/ Enhanced Tissue Growth