# Metabolic Actions of Insulin-Like Growth Factor-I in Normal Physiology and Diabetes

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**KEYWORDS**

• Fat metabolism • Growth • Insulin resistance • Growth hormone

**KEY POINTS**

- Insulin-like growth factor-I (IGF-I) is an important stimulant of protein synthesis in muscle but it also stimulates free fatty acid uptake and metabolism.
- IGF-I actions are regulated by IGF-binding proteins; in obesity and metabolic syndrome, there is a major dysregulation of IGF-binding protein secretion resulting in alterations in the concentration of free IGF-I and IGF-I actions.
- In Type 1 diabetes, IGF-I synthesis is markedly impaired; in Type 2 diabetes, multiple changes occur in IGF-I actions, including sensitization to its mitogenic actions in some target tissues.

## INTRODUCTION

Insulin-like growth factor-I (IGF-I) has significant structural homology with proinsulin. IGF-I, IGF-II and proinsulin evolved from a single precursor molecule approximately 60 million years ago. The function of that single precursor molecule was to provide a chemical signal for cells within primitive organisms to establish that adequate nutrient was present not only for basal metabolic needs but also for protein synthesis and cell proliferation. At the time vertebrates appeared, this system evolved into one with more complexity to be able to store calories as fat. At that time, insulin diverged from IGF-I and the pituitary gland appeared along with growth hormone (GH). The function of these 3 hormones was linked to be able to regulate both nutrient availability during periods of starvation and repletion as well as continuing to provide adequate signals and substrate for growth. As such, the regulation of synthesis and the secretion of these 3 hormones are directly linked to nutrient intake. Because insulin, IGF-I, and IGF-II evolved from a single precursor, they continue to share significant structural homology; however, there are also distinct differences. The primary domains within

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IGF-I and insulin that determine receptor binding have significant amino acid differences that account for major differences in affinity for their respective receptors.[1] Similarly, the IGFs have the unique characteristic of being able to bind to IGF-binding proteins (IGFBPs), which is determined by a specific amino acid sequence in positions, 3, 4, 15, 16 of N terminus of IGF-I molecule and homologous substitutions in IGF-II.[2] These structural differences provide an important distinction for the regulation of IGF-I and insulin bioavailability and, thus indirectly regulate their effects on metabolism.

IGF-I and insulin have distinct receptors. Both receptors are tyrosine kinase–containing receptors and they show 48% amino acid sequence homology.[3] Despite these similarities, the ligand-binding specificity is strict. The affinity of the IGF receptor is 1000 times greater for IGF-I than insulin, and the insulin receptor has a 100-fold greater affinity for insulin compared with IGF-I. Insulin and IGF-I receptor densities vary widely among cell types (ie, mature differentiated hepatocytes and adipocytes have abundant insulin receptors, whereas they have almost no IGF-I receptors). Conversely, cell types, such as vascular smooth muscle cells, have abundant IGF-I receptors and minimal insulin receptors. This difference in receptor distribution accounts for many of the differences in insulin and IGF-I actions. GH has an entirely different structure and its receptor belongs to the cytokine receptor family.[4] GH has a major regulatory influence on the metabolic actions of both IGF-I and insulin and functions in several important ways that are distinct from insulin and IGF-I to modulate nutrient availability that is necessary for both balanced tissue growth and the maintenance of normal intermediary metabolism. Therefore, coordinated regulation of the metabolic actions of these 3 hormones provides an important basis for understanding their individual effects on intermediary metabolism and how they function coordinately to maintain nutrient balance.

## NUTRIENT REGULATION OF IGF-I SECRETION

As can be predicted from the phylogenetic development of IGF-I, the primary variable regulating plasma IGF-I concentrations is nutrient intake. Both total caloric and protein intake are important regulatory variables.[5] The effect of caloric intake is such that if caloric intake is reduced by approximately 50%, there is a significant reduction in IGF-I secretion. The effects of protein are more graded in that even small reductions result in changes in IGF-I.[6] For each 25% reduction in protein intake, there is an equivalent reduction in IGF-I. Most IGF-I in plasma (estimated at 80% based on mouse genetic manipulation studies) is derived from hepatic synthesis.[7] Both protein and energy participate in the regulation of hepatic synthesis, with energy regulating IGF-I gene transcription and protein functioning primarily to regulate mRNA stability and translation. A concomitant effect of changes in carbohydrate intake is the indirect effect that occurs as a result of changes in insulin secretion. If carbohydrates are provided at a level of less than the equivalent 700 kcal/d, then even supplemental fat intake will not restore a normal IGF-I. This is because IGF-I synthesis in the liver is also regulated by insulin,[8] which is best demonstrated by measuring serum IGF-I concentrations in untreated patients with Type I diabetes. When they receive insulin they have a substantial increase in serum IGF-I.[9] Studies in experimental animals have also shown that blocking insulin action in the liver lowers serum IGF-I. Therefore, carbohydrate intake functions not only to increase the total amount of energy that is available, thereby increasing IGF-I synthesis, but also by a direct effect of insulin on IGF-I gene transcription, particularly the ability of GH to stimulate IGF-I gene transcription.[8]

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