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# Differential effects of progestins on the circulating IGF-I system

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## Abstract

**Objective:** Circulating insulin-like growth factor-I (IGF-I) is mainly produced by the liver under GH stimulation and is influenced by nutrition and insulin. IGF-I bioavailability is regulated by interactions with specific binding proteins (IGFBPs). The objective of this paper is to review available data on modifications of the IGF-I system in menopausal women during HRT, with particular attention on the differential effects of progestins. **Method:** All available reports on the effects of different forms of HRT have been taken into account. **Results:** Available data suggest that different kinds of HRT have different effect on the IGF-I system, depending on route of administration, oestrogen dose, basal IGF-I values and type of progestin. Oestrogen administration (oestrogen replacement therapy (ERT)) reduces circulating IGF-I mainly through a hepatocellular effect. The decrease is sharper when oral ERT is used (first pass hepatic effect) and in women with higher basal IGF-I levels. The progestins endowed with androgenic effects—the 19-nortestosterone derivatives and, to a lesser extent, medroxyprogesterone acetate (MPA)—tend to reverse the IGF-I decrease induced by oral oestrogens. In contrast, progestins devoid of androgen-like hepatocellular and metabolic actions (e.g. dydrogesterone) do not interfere with the IGF-I decrease induced by oral oestrogens. Data on the effect of ERT on IGFBP-3 level are not consistent. Oral ERT, via hepatocellular actions (amplified by the first pass hepatic effect) causes a two to three-fold increase in IGFBP-1 levels. Androgenic progestins oppose the IGFBP-1 increase induced by oral oestrogens. Data on the effect of ERT and different progestins on the level of free IGF-I are scant and inconsistent. **Conclusion:** Even if some aspects need clarification, available data demonstrate that different progestins have differential effects on the circulating IGF-I system. © 2003 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Progestins; Estrogens; HRT; IGF-I; IGFBP-1; IGFBP-3

## 1. Introduction

Insulin-like growth factor-I (IGF-I) is a polypeptide with structural homology to proinsulin. Its predominant effect is to promote cell growth in several tissues and cell lines, including malignant ones, through highly specific binding to the IGF-I receptor, which

has a key role in promoting cell proliferation [1]. IGF-I is widely present in the body; it is detected in several tissues following diffusion from the serum (where it is present in the highest concentration) or local production. Circulating IGF-I is mainly of hepatic origin. Its production is stimulated by GH, to which it is linked by a feed-back mechanism, and is influenced by nutrition and insulin level [2]. Circulating IGF-I levels may vary in adults from 50 to 300 ng/ml. IGF-I bioavailability is regulated by interactions with specific binding proteins (IGFBPs) [3]. The most important of these, IGFBP-3, is produced by the liver under GH stimulation and its

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