Circulating IGF-I: New Perspectives for a New Century
Clifford J. Rosen and Michael Pollak

Insulin-like growth factor I (IGF-I) is a ubiquitous endocrine, paracrine and autocrine polypeptide, which influences cell proliferation and differentiation in many tissues. Classically, IGF-I has been tied to growth hormone (GH) and has often been considered a surrogate marker of overall GH status. The advent of recombinant technology has made possible studies of GH and IGF-I for the treatment of chronic diseases (such as diabetes mellitus, osteoporosis and muscle atrophy) as well as to forestall the aging process. Examples of currently active areas of research include efforts to define the involvement of IGF-I physiology in bone remodeling, atherosclerosis and neoplasia. Recent epidemiological evidence suggests that individuals with IGF-I levels in the 'high normal' range have increased risk of common cancers relative to individuals with levels in the 'low normal' range. These findings have focused renewed attention on the genetic and non-genetic determinants of serum IGF-I levels. It is unlikely that the serum IGF-I level itself is related directly to risk of neoplasia, but it may serve as a surrogate for a variable that is important in epithelial cell carcinogenesis, such as rate of epithelial cell proliferation. We review relatively new data suggesting that adult serum IGF-I levels are under the control of heritable factors apart from GH. Such factors may influence tissue expression of IGF-I as well as serum IGF-I levels, and influence a number of clinically important outcomes, including bone density and risk of neoplasia. The concept that there is little physiological importance in the heterogeneity between individuals regarding IGF-I levels within the broad 'normal' range may require re-assessment.

It has been more than four decades since Salmon and Daughaday made the seminal observation that the action of growth hormone (GH) on cartilage is mediated through a factor absent in hypophysectomized animals\(^1\). Over the ensuing years, discoveries concerning the identity of insulin-like growth factors (IGFs), their receptors, various IGF-binding proteins (IGFBPs) and a host of tissue-specific IGFBP proteases have occupied investigators in several areas of endocrinology\(^2\). The advent of recombinant peptide technology made possible preclinical research and clinical trials of GH as well as IGF-I, not only for various GH deficiency states, but also for heart failure, neurological conditions, diabetes mellitus, muscle disorders, various catabolic states, stress syndromes, sarcopenia and osteoporosis\(^3\). At the same time, improved assay methodology has led to more widespread utilization of serum IGF-I as an indicator of GH status in both adults and children.

There is little doubt these advances are important for endocrine researchers and clinicians. GH replacement is now an approved and widely accepted treatment for growth hormone deficiency (GHD) states. The diagnosis of severe GHD is straightforward, but uncertainty remains regarding interpretation of serum IGF-I levels after midlife, where distinguishing between the 'normal' age-related decline in IGF-I levels and GHD is more controversial. Although trials with GH and/or IGF-I have been undertaken in a number of therapeutic contexts, there is some concern about lack of data relating to possible adverse effects of these agents with respect to neoplasia, particularly if superphysiological IGF-I serum levels are achieved and maintained over decades.

Advances in our understanding of regulatory pathways that control IGF-I expression, independent of GH, have been made recently. These developments have led investigators to 'revisit' some of the basic tenets of IGF-I physiology established nearly four decades ago. In this paper, we will highlight several areas of investigation that might have a major impact on the diagnostic and therapeutic arenas of the 21st century.

- **Circulating IGF-I and its Regulation**

  **Circulating IGF-I**

  IGF-I is a ubiquitous peptide that has characteristics of both an endocrine hormone and a tissue growth factor. The IGF-I gene is expressed in many tissues but liver and, to a lesser extent, bone are the primary sources of circulating IGF-I. Serum IGF-I levels peak at puberty and decline with age\(^4\). In all extracellular tissues, IGF-I is bound to a family of IGFBPs (Ref. 2). More than 75% of circulating IGF-I is carried in a trimeric complex composed of IGFBP-3, the largest molecular weight IGFBP, and a liver-derived glycoprotein known as the acid-labile subunit (ALS)\(^5\). ALS is a member of a leucine-rich repeat family of proteins that is important for binding to the C-terminal domain of IGFBP-3. All three components of the trimeric complex are induced by GH and therefore are affected by states of GH deficiency or excess\(^6\). Recently, it has been reported that IGFBP-3 can form ternary circulating complexes with ALS and IGF-I (Ref. 6). The other IGFBPs are considerably smaller than IGFBP-3 and can traverse the capillary membrane. In
serum, IGFBPs provide binding capacity for IGFs in excess of their usual serum concentrations. This extends their half-life and forms a circulating reservoir. A very small proportion of serum IGF-I is unbound in healthy individuals, but the physiological role of 'free' IGF-I has not been defined.

Tissue IGF-I bioactivity represents the integrated effect of complex interactions involving endocrine, autocrine and paracrine sources of IGFs, IGFBPs and IGFBP proteases. Pathological conditions of growth hormone deficiency and excess suggest that the serum IGF-I level might represent a valid surrogate for tissue IGF bioactivity under certain circumstances. If one assumes that the pathological sequelae of acromegaly and GHD are related to increased and decreased tissue IGF-I bioactivity, respectively, then it follows that circulating IGF-I level and tissue IGF bioactivity are regulated in parallel.

Regulation of Circulating IGF-I

Many factors determine the concentration and availability of circulating IGF-I (Table 1). First, changes in the relative proportion or concentration of the six circulating IGFBPs can alter the transport of IGFs within the extracellular space. Second, the relative amount of IGF-I bound to the ternary complex (IGFBP-3 or IGFBP-5) versus the proportion of IGF-I bound to low molecular weight IGFBPs is crucial for tissue bioactivity. Third, changes in the binding affinity of ALS for IGFBP-3 in comparison to its binding to the binary complex (IGF-I:IGFBP-3 or IGF-I:IGFBP-5) are also important. Fourth, the degree of serine phosphorylation of IGFBP-1, -3 and -5 influences the affinity of IGFBP for IGF-I and therefore can regulate IGF-I dissociation or activity. In particular, the highly phosphorylated form of IGFBP-3 predominates in the circulation, thereby increasing binding affinity but effectively blocking circulating IGF-I from exerting any biological activity. Finally, the degree of proteolytic cleavage of the IGFBPs might define how the IGF-I receptor can be occupied by the IGFBPs for ligand occupancy. There are several IGFBP-specific proteases that catalyze proteolysis, some of which are tissue specific and some of which are active in the circulation. Prostate-specific antigen (PSA) is the best known example of a kallikrein enzyme with specificity for IGFBP-3.

Hormonal and Genetic Factors

GH is the principal regulator of circulating IGF-I. However, poor nutritional status can override growth hormone regulation by impairing hepatic GH induction of IGF-I (Ref. 12). Aging is also associated with a decline in serum IGF-I, in part as a result of reduced GH secretion. Even when these three factors are controlled, there still remains significant interindividual heterogeneity in adult serum IGF-I levels. This has led several investigators to postulate that genetic determinants might regulate circulating IGF-I. Evidence to support this idea comes from several sources. First, two twin and several population studies have demonstrated that serum IGF-I is a heritable phenotype. Second, Rosen et al. showed that among healthy inbred strains of mice of the same body weight and length, and similar GH levels, serum IGF-I levels differed by nearly 30% (Ref. 15). Finally, Rosen et al. have also shown recently that a polymorphic microsatellite within the IGF-I gene is associated with differences in serum IGF-I levels in several cohorts, even after correction for age and sex. These lines of evidence suggest that there are strong heritable determinants of the IGF-I phenotype and that these unknown factors might be crucial in defining adult levels of IGF-I independent of GH. Apart from polymorphic variations in the IGF-I gene itself suggested by a recent report, there is a long list of candidate genes that might be subject to subtle polymorphic variation between individuals (with respect to function or level of expression), and these variations could influence IGF-I levels. These include, for example, genes encoding somatostatin, GH-releasing hormone, GH and the receptors for these hormones.

- Tissue Responsiveness to IGFs

The Role of the IGF Receptor

While IGF-I can bind under certain conditions to the IGF-II receptor (IGF-IIIR), the insulin receptor and hybrid receptors, the actions of IGF-I as a potent mitogen, anti-apoptotic factor and modulator of differentiation are mediated mainly through the IGF-IR (Ref. 2). IGF-II can also act as the ligand for the IGF-IR. Evidence that the IGF-IIR does not transduce a mitogenic signal, but rather acts as a 'sink' for IGF-II by sequestering this ligand away from the IGF-IR is provided by experiments showing that deletion of the IGF-IIR is associated with increased growth. A functional IGF-IR is not an absolute necessity for cell proliferation in vitro and in vivo, but it may be required for optimal growth. Overexpression or

<table>
<thead>
<tr>
<th>Major direct determinants of circulating IGF-I levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Protein-calorie intake</td>
</tr>
<tr>
<td>Catabolic stressors</td>
</tr>
<tr>
<td>Illnesses</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Anorexia/bulimia nervosa</td>
</tr>
<tr>
<td>Thyroid hormones</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Binding affinity of the acid-labile subunit (ALS) for IGFBP-3/IGF-I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect determinants operating through the GH-IGF-I axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Body fat (?leptin)</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>?Adrenal androgens (such as DHEA)</td>
</tr>
<tr>
<td>?Inflammatory cytokines</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other determinants that could affect circulating IGF-I directly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
</tr>
<tr>
<td>PTH-related peptide (PTHrp)</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>Adrenal androgens</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
</tr>
</tbody>
</table>

| IGF-I, insulin-like growth factor I; IGFBP-3, IGF-binding protein 3; DHEA, dehydroepiandrosterone. |

Table 1. Factors that affect circulating IGF-I concentrations
constitutive activation of the IGF-IR can lead to ligand-independent cell growth and the establishment of a transformed phenotype. On the other hand, targeted disruption of the IGF-IR results in cell refractoriness to viral and cellular oncogenes, increases the probability of apoptotic cell death and can inhibit neoplastic proliferation. There are many examples of the anti-apoptotic actions of the IGF-IR, including protection from the sequelae of exposure to cytotoxic agents, such as etoposide or tumor necrosis factor.

The dominant source of ligand for the IGF-IR may vary among different tissues. In bone, IGF-I and -II are stored in the matrix, bound to IGFBP-5, and released during active bone resorption. Newly released IGF-I can then recruit osteoblasts to the cell surface and thereupon play an important role in bone remodeling and in the establishment of skeletal metastases. Hence, autocrine and extracellular matrix are key sources of IGF-I for the osteoblast, while circulating levels of IGF-I appear to be less crucial. In contrast, there is evidence that paracrine sources of IGF-I are important in the breast and prostate, and that breast epithelial cell proliferation rate is correlated with (or even determined by) circulating IGF-I (Ref. 23).

Alternative IGF Regulatory Pathways

Recent studies have demonstrated the importance of the IGF regulatory system in the ultimate fate of cells through an IGF-IR-independent pathway. p53 is a tumor suppressor protein and cell cycle regulator that is essential in safeguarding the replication and propagation of intact DNA (Ref. 24). In response to DNA damage, p53 can induce cell cycle arrest or trigger signals for programmed cell death. Recent evidence suggests that IGFBP-3 is involved in one of the several mechanisms of action of p53 (Ref. 24). Two distinct p53 response elements have been identified in the first and second intron of the IGFBP-3 gene, and IGFBP-3 transcripts are rapidly induced in response to p53 activation or genotoxic stress, concomitant with accumulation of IGFBP-3 in the extracellular fluid. This IGFBP-3 can significantly impair the mitogenic activity of IGF-I. In addition, it has been shown that p53 may downregulate expression of the IGF-IR gene in hematopoietic cells. Finally, several lines of evidence suggest that several cell types, including breast cancer cells, exhibit specific cell surface IGFBP-3-binding sites. There is evidence that free IGFBP-3 can bind to these IGFBP-3 receptors and inhibit monolayer growth in vitro. This direct IGFBP-3 inhibitory action can be attenuated by IGFs, as IGF-IGFBP-3 complexes have reduced affinity for the putative IGFBP-3 receptor.

Recent evidence also emphasizes the importance of interactions between steroid hormones and IGFs. The antiproliferative action of antiestrogens is correlated with suppression of circulating IGF-I levels and upregulation of IGFBP-3 (Ref. 29) and IGFBP-5 (Ref. 30) production by cell types that are inhibited by antiestrogens. In tissues where estrogen stimulates proliferation, it inhibits IGFBP synthesis. Similarly, the apoptosis induced in the prostate after androgen deprivation is associated with significant upregulation of several IGFBPs (Ref. 30). Transdermal estrogen replacement therapy (ERT) is associated with increases in serum IGF-I levels, while oral ERT is associated with decreased serum IGF-I levels. This may be related to direct suppression of hepatic IGF-I synthesis by pharmacological doses of estrogens reaching the liver via the portal circulation. More information is needed on the effect of ERT on tissue IGF bioactivity: the demonstration that both oral and transdermal ERT increase IGF bioactivity would imply an exception to the generalization that serum IGF-I levels are a surrogate for tissue IGF bioactivity.

- Serum IGF-I and Chronic Disease States

**Overview**

Very high levels of serum IGF-I are pathognomonic of acromegaly, whereas very low circulating IGF-I concentrations can result from numerous conditions, including GHD, malnutrition, sepsis, drug abuse and cachexia associated with malignancies. Recently, studies have been undertaken to explore links between serum levels of IGF-I and several chronic diseases, including atherosclerosis, osteoporosis, and risk of future development of certain cancers. These studies are grounded in the basic physiology of IGF-I. Clearly, a certain level of this growth peptide is crucial for maintenance of muscular mass, vascular integrity and cardiovascular function, and chronic deficiency states (such as GH-deficient adults) are characterized by impaired motor function, increased atherosclerotic risk and reduced bone mass.

Although Rudman was the first to suggest that low serum IGF-I levels could be related to muscle dysfunction in elderly men, and that GH replacement could restore bone and lean mass, numerous other investigators have subsequently proposed that the characteristic decline in serum IGF-I during aging is strongly and causally linked to osteopenic and sarcopenic disorders. Until recently, however, less attention has focused on the other side of the equation — the possibility that there might be some disease associations with high (but sub-therapeutic) serum levels of IGF-I. Yet, as noted above, the IGF regulatory system is involved intimately in the regulation of proliferation and apoptosis, so the possibility of a relationship between IGF-I levels and neoplasia deserves study. In this section, we will review two very different disorders that are common in the elderly and for which evidence is emerging that interindividual heterogeneity in IGF-I levels may be important.

**IGF-I and Osteoporosis**

Evidence concerning the relationship between IGF-I and osteoporosis is conflicting. In some but not all cross-sectional studies, serum IGF-I correlates to a modest extent with bone mineral density. However, in a recent evaluation of women in the Framingham heart study, the highest serum IGF-I by quartiles could be related to the highest bone density at the spine, hip and wrist. Moreover, in the study of osteoporotic fractures, the
lowest quartile of serum IGF-I was associated with a nearly twofold greater risk of hip fracture, even after controlling for bone mineral density (D. Bauer, pers. commun.). Clearly, further prospective studies are required to define the precise relationship between this peptide and fracture risk.

On the other hand, despite great expectations and very promising clinical studies of recombinant human GH (rhGH) in GH deficiency states, trials with rhGH and IGF-I in patients with primary osteoporosis have been somewhat disappointing. Although exogenous GH and IGF-I can raise serum IGF-I levels and increase markers of bone formation, the changes in bone mass are relatively small and, in the best of studies, only comparable to those seen with antiresorptive therapies such as alendronate or estrogens. In part, this can be attributed to the capacity of skeletal IGF-I to stimulate both bone resorption and bone formation, thereby causing little change in overall bone mineral density. More studies need to be undertaken to determine how GH or IGF-I can be utilized, if at all, in osteoporotic states.

Of great interest in the present context is the negative association between osteoporosis and the risk of breast cancer. This relationship implies that factors that contribute to high bone density may also contribute to risk of breast cancer. While it has been widely speculated that estrogen exposure explains the relationship, this may not be the only factor involved, because the strength of the negative association between osteoporosis and breast cancer exceeds the strength of the positive association between estrogen exposure and breast cancer. Studies to determine whether IGF-related factors are involved in these relationships are under way.

IGF-I and Neoplasms

Although it has been known for several decades that acromegaly is at increased risk for colon neoplasms, interest in the association between serum IGF-I and cancer risk has increased with reports that individuals with higher IGF-I levels (or lower IGFBP-3 levels) have a broad normal range between acromegaly and GHD, have increased risk of prostate, colon and breast cancer. In one study, Chan et al. demonstrated that among a nested cohort of men in the physician's health study, the highest quartile of plasma IGF-I levels was associated with a 4.3-fold relative risk of prostate cancer compared with the lowest quartile. This association was independent of baseline PSA levels and suggested that IGF-I might be an independent predictor of prostate cancer risk. The major findings of this study were subsequently confirmed by Wolk et al. In a separate study of similar design utilizing women in the nurses' health study, Hankinson et al. noted that among premenopausal women less than 50 years of age, there was a 4.5-fold relative risk of breast cancer in the highest quartile of plasma IGF-I compared with the lowest quartile. Adjustment for IGFBP-3 increased the predictive value of IGF-I in two of these studies. Indeed, IGFBP-3 was shown to be related inversely to risk, while IGF-I was positively related to risk. This relationship was particularly strong in a study concerning the predictive value of IGF-I and IGFBP-3 with respect to colon cancer. The inverse relationship of IGF-I to IGFBP-3 with respect to the risk of neoplasia deserves comment. Normally, both IGFBP-3 and IGF-I are regulated by GH and therefore these two peptides exhibit a strong and direct correlation in the serum. Conceivably, certain individuals might have polymeric variations in the promoter regions of the genes encoding IGF-I and/or IGFBP-3 that lead to the lack of coordination of expression of IGF-I and IGFBP-3. Such variants might be linked to high IGF-I to IGFBP-3 ratios, increased cellular proliferation, and hence to increased accumulation of somatic cell mutations and cancer risk. Acromegalics may have a subtle (rather than extreme) increased cancer risk because in this condition, both IGF-I and IGFBP-3 are elevated, and changes in the IGF-I to IGFBP-3 ratio are subtle.

Other studies, some of which have utilized anti-neoplastic drugs, have provided further indirect evidence that the IGF regulatory system is involved in the pathobiology of neoplasia, both in terms of the risk of cancer and the behavior of cancers. Only a few of many examples are listed here. With respect to risk, it is highly relevant that a positive correlation between GH level (or IGF-I level) and breast epithelial cell proliferation was seen in an aged rhesus monkey model. With respect to neoplastic behavior, tumor growth in IGF-I-deficient mice is reduced relative to control mice. Furthermore, it has recently been shown that fenretinide, a synthetic retinoid with antitumor activity, reduced plasma IGF-I levels and increased IGFBP-3 concentrations, especially among premenopausal women. Also, tamoxifen has been shown to decrease IGF-I serum levels and to downregulate IGF-I induction of tyrosine phosphorylation of the IGF-1R and inhibit IRS-1 signaling in MCF-7 cells. Dunn et al., utilizing a p53-deficient mouse model, demonstrated that, as expected, dietary restriction lowered serum IGF-I, and that this was associated with increased apoptosis and decreased tumor progression. Furthermore, IGF-I administration to these diet-restricted mice increased cell proliferation and blocked the inhibitory effect of dietary restriction to tumor growth. Taken together, these and other experimental data suggest that the IGF-I system is involved in tumor development and progression. However, there are many unanswered questions. For example, it has not been established that the relationship between IGF-I levels and cancer risk is causal. Perhaps dietary factors are crucial, and influence both IGF-I and risk. More work is also needed to reconcile the observation that although IGF-I levels appear to be related to risk of cancer, in advanced cancers, autocrine IGF-II loops are common and may render circulating IGF-I irrelevant (and invalid as surrogates for IGF bioactivity).

- **Summary and Future Directions**

It has been recognized for some time that acromegaly and GHD are conditions related to obviously abnormal IGF-I serum levels, and that
successful treatment is correlated with normalization of IGF-I serum levels. Relatively little attention was given to variability of IGF-I within the broad normal range. The possibility that variability in IGF-I levels is related to other disease states, probably in a more subtle fashion than it is related to acromegaly or GHD, is now under active investigation. Such studies are justified by recent progress in cell biology that has emphasized the important role played by IGF-I in the regulation of cell proliferation and cell death. Also under study are various pharmacological approaches to modulate IGF physiology for therapeutic purposes.

Several preliminary conclusions can be drawn with respect to the relationship between serum IGF-I levels and chronic diseases. First, circulating IGF-I is a complex factor regulated by multiple influences, including both environmental and heritable determinants. Second, it is likely that the serum IGF-I level is positively related to muscle and bone mass, although the association with specific musculoskeletal disorders of aging remains uncertain. Third, emerging data suggest that serum IGF-I level is positively associated with the risk of a subsequent diagnosis of malignancy. Fourth, it is established that GH therapy can raise serum IGF-I levels, but there is uncertainty with respect to the long-term safety and efficacy of such treatment for conditions other than frank GHD.

There is considerable interest in both short-term and long-term therapeutic modulation of IGF physiology. Potential indications for GH or IGF-I therapy (apart from GHD) include various chronic neurological conditions, diabetes, osteoporosis, renal failure, congestive heart failure and the changes of body composition associated with aging. Several multicenter, randomized, controlled trials with rhGH and/or IGF-I in elderly individuals, sponsored by the National Institutes of Aging (NIA), are currently being completed in the USA. These studies were designed to address the issue of whether growth factor therapy can improve functional outcomes as well as designated end points such as bone density, lean body mass and lipids. These trials, however, have limited power to detect long-term (greater than two years) adverse effects, such as increased risk of cancer.

At this time, there is no conclusive evidence that growth factor therapy will alter functional outcomes in frail elders. For example, after six months of rhGH administration to elderly subjects, Papadakis et al. reported a marked increase in serum IGF-I but only a marginal increase (<1%) in bone mineral content, and no change in any functional parameter. Marcus has also shown that the combination of rhGH and calcitonin, or rhGH alone, offered little additional benefit over conventional antiresorptive treatment, at least with respect to bone mineral density. Others have shown that exercise can improve muscle function to the same extent as rhGH therapy and at far less cost, and have reported that among frail elders, serum IGF-I level is not related to indices of physical performance, body mass index or lean body mass.

Further research will be needed to determine whether ‘treatment’ of the ‘somatopause’ is indicated for any particular group of individuals. It is practical to raise IGF-I levels with GH, and oral therapies might be developed if it becomes clear that such treatments are worthwhile. However, before such therapy is endorsed, more data concerning both benefits and risks are needed. Postmenopausal estrogen therapy for the menopause provides an interesting precedent: it is now clear that such treatment is associated with excess breast cancer, but for many women the risks of this form of replacement therapy are offset by benefits in terms of overall mortality, cardiovascular disease and bone density.

It is possible that certain individuals will be found to benefit from specific kinds of therapeutic interventions that target the GH-IGF-I axis, and others will not benefit from any manipulation. Those with IGF-I levels at the low end of the normal age, no cancer risk factors and congestive heart failure might (or might not) be shown to benefit from measures that raise IGF-I levels to the mid-normal range. Conversely, those with IGF-I levels at the 90th centile for their age, and other independent risk factors for breast, prostate or colon cancer, might benefit from interventions that reduce IGF-I levels to the low normal range. Clinical research to address these issues will be challenging but important. New information concerning both the determinants of IGF-I serum levels and the physiological parameters that vary with the IGF-I serum level are likely to be forthcoming and will guide clinical research.

Acknowledgements
The authors would like to thank Majeed Majeed for assistance with manuscript preparation. Supported in part by grants from the NIH (AR 45433-01) to CJR and from the National Cancer Institute of Canada and the National Breast Cancer Foundation to MP.

References
late a growth inhibitory insulin-like growth factor binding protein 3 (IGFBP-3). Stability of the IGFBP-3 is associated with increased bone turnover and increased risk of breast cancer.


34 Hankinson, S.E. et al. (1998) Circulating concentrations of IGFBP-3 and the risk of breast cancer. Cancer Res. 58, 1593-1596


49 Jul, A., Kain, K., Blum, W., Lindholm, J., Ranke, M.B. and Skakkebaek, N.E. (1994) The ratio between serum levels of insulin-like growth factors (IGF-I and IGF-II) and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acomagrelic patients. Clin. Endocrinol. 41, 85-93


53 Dunn, S.E. et al. (1997) Dietar restription reduces IGFBP-3 levels which modulates apoptosis, cell proliferation and tumor progression in IGFBP-3 deficient mice. Cancer Res. 57, 4667-4672


