Insulin-like growth factor-I (IGF-I) and clinical nutrition

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Abstract
IGF-I (insulin-like growth factor-I) is a peptide hormone, produced predominantly by the liver in response to pituitary GH (growth hormone), which is involved in a wide variety of physiological processes. It acts in an endocrine, paracrine and autocrine manner to promote growth. The production of IGF-I signals the availability of nutrients needed for its anabolic actions. Recently, there has been growing interest in its role in health and disease. IGF-I has long been known to be regulated by nutrition and dysregulated in states of under- and over-nutrition, its serum concentrations falling in malnutrition and responding promptly to refeeding. This has led to interest in its utility as a nutritional biomarker. A considerable evidence base supports utility for measurement of IGF-I in nutritional contexts. Its concentration may be valuable in providing information on nutritional status, prognosis and in monitoring nutritional support. However, it is insufficiently specific for use as a screening test for under nutrition as its serum concentration is influenced by many factors other than nutritional status, notably the APR (acute-phase response) and endocrine conditions. Concentrations should be interpreted along with clinical findings and the results of other investigations such as CRP (C-reactive protein). More recently, there has been interest in free IGF-I which holds promise as a nutritional marker. The present review covers nutritional regulation of IGF-I and its dysregulation in disease, then goes on to review recent studies supporting its utility as a nutritional marker in clinical contexts. Although not currently recommended by clinical guidelines, it is likely that, in time, measurement of IGF-I will become a routine part of nutritional assessment in a number of these contexts.

Key words: clinical nutrition, free insulin-like growth factor-I (free IGF-I), insulin-like growth factor-I (IGF-I), malnutrition, obesity

INTRODUCTION
Experiments in the 1950s on the action of GH (growth hormone) to enhance sulfate incorporation into epiphyseal cartilage indicated that its action required a circulating factor, initially called ‘sulfation factor’ [1]. In 1972, this was given the term ‘somatomedin C’, reflecting its ability to mediate the action of GH [2]. Finally, in 1978, it was named IGF (insulin-like growth factor)-I, having been characterized and found to resemble insulin in its structure and metabolic functions. The original somatomedin hypothesis proposed that pituitary GH stimulated hepatic IGF-I production, which brought about the growth-promoting effects of GH. This hypothesis was later modified when it emerged first that GH had direct growth-promoting effects and secondly that IGF-I, produced locally in most tissues, also acted in an autocrine and paracrine manner [3]. Since then, there has been a debate about the relative importance of hepatic IGF-I and locally produced IGF-I in the regulation of growth [4]. Following the discovery of the IGFBPs (IGF-binding proteins), it became clear that the system was considerably more complex than originally thought. Interest in IGF-I as a nutritional marker began in 1973 when its serum concentrations were observed to fall in malnutrition [5]. The purpose of the present review is to provide readers with a perspective and update on IGF-I as a nutritional marker.

Abbreviations: ALS, acid-labile subunit; APR, acute-phase response; BMD, bone mineral density; BMI, body mass index; BMR, basal metabolic rate; BV, biological variation; CF, cystic fibrosis; CHD, coronary heart disease; CRP, C-reactive protein; CV, coefficient of variation; DEXA, dual-energy X-ray absorptiometry; GH, growth hormone; IF, intestinal failure; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IGF-1R, type 1 IGF receptor; IGF-2R, type 2 IGF receptor; IL, interleukin; IR, insulin receptor; KIRA, kinase receptor activation assay; LBM, lean body mass; LOS, length of stay; NEFA, non-esterified (‘free’) fatty acid; NGR, nutritional growth retardation; NICE, National Institute for Health and Clinical Excellence; PEM, protein energy malnutrition; PN, parenteral nutrition; RBP, retinol-binding protein; rGH, recombinant human GH; RI, refeeding index; RS, refeeding syndrome; RTK, receptor tyrosine kinase; SBS, short bowel syndrome.

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NUTRITIONAL ASSESSMENT

Research studies have increasingly linked malnutrition and obesity to the development of disease, but both conditions are still under-diagnosed and under-treated. Malnutrition is particularly prevalent in hospital patients, in whom it increases the risk of adverse outcomes such as post-operative complications or delayed recovery [6]. This increases the LOS (length of stay) for patients, in turn increasing healthcare costs. Once diagnosed, however, malnutrition can be treated with nutritional support. This can buy time for other therapeutic interventions to aid recovery, thereby reducing morbidity and mortality [7]. Early detection of malnutrition is therefore vital in order that nutritional support can be commenced. In this context, we should distinguish between nutritional assessment and nutritional screening. The former is generally considered to indicate a relatively detailed evaluation, carried out by a professional trained in clinical nutrition, to help to decide on appropriate therapeutic interventions [8]. Traditionally, it involves a combination of history taking, physical examination, anthropometric measurements and laboratory tests. Nutritional screening, on the other hand, is a quick and initial means of determining whether potentially malnourished or overweight patients require in-depth nutritional assessment. It is usually carried out by a non-expert. Nutritional screening of hospital patients has been advocated by professional bodies as a means of facilitating the detection of malnutrition, which may otherwise be easily overlooked [9]. At present, it is carried out using screening tools such as the MUST (malnutrition universal screening tool) [10].

Once the decision has been taken to provide nutritional support, the individual’s nutritional requirements should be met if the full benefit is to be realized. Energy requirements can be estimated based on body weight and age using a method such as the Schofield equation to determine the BMR (basal metabolic rate) [11,12]. Likewise, protein requirements can be estimated from body weight. It should be emphasized that these methods only provide approximate values. Requirements can be significantly altered in, for example, critical illness and it should be remembered that the final arbiters of the success of nutritional support are weight restoration and recovery. Patients should therefore be closely monitored for evidence of nutritional repletion, and, if they are not recovering, consideration needs to be given to adjusting the nutritional support. Nutritional support can be delivered orally, enterally or parenterally depending on the clinical situation, the first two routes being the more physiological. PN (parenteral nutrition) is reserved for patients with IF (intestinal failure) where the gut is either dysfunctional or inaccessible. The provision of nutritional support requires careful monitoring to enable the early detection of complications. NICE (National Institute for Health and Clinical Excellence) provides guidance on the monitoring of patients [13]. This includes anthropometric and laboratory measurements.

Biomarkers of protein energy status can be useful adjuncts to nutritional assessment, with their attraction being their objectivity. As such, they can complement clinical nutritional assessment, which is in part subjective. This has prompted researchers to identify novel markers. However, the diagnostic performance of biomarkers is difficult to assess as there is no universal ‘gold standard’ method for nutritional assessment against which they can be compared. If a novel biomarker is to be of value, its result should lead to clinical action, potentially improving the outcome for the patient. Biomarkers can be considered as having three potential roles: namely diagnosis of malnutrition and micronutrient disorders, monitoring of therapeutic interventions and providing information on prognosis, i.e., predicting outcome. The latter can assist the clinician in deciding whether to intervene therapeutically. Biomarkers currently available are transferrin, pre-albumin and RBP (retinol-binding protein), all of which may exhibit reduced serum concentrations in malnutrition (Table 1). Although they are sensitive tests for the detection of malnutrition, their diagnostic specificity is too low for use in screening. Their main role in clinical practice is in monitoring nutrition support. However, their clinical utility is debated and current NICE guidelines do not advocate their measurement [13].

THE IGF AXIS

The IGF system consists of the peptide hormones IGF-I and IGF-II, their cell-surface receptors and IGFBPs. IGF-I and IGF-II are 7.5 kDa peptides consisting of 70 and 67 amino acid residues respectively. Both have biological roles during development and in adulthood and circulate in considerably higher concentrations.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Molecular mass (kDa)</th>
<th>Half-life</th>
<th>Reference range</th>
<th>Positive confounders</th>
<th>Negative confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (total)</td>
<td>150 (ternary complex)</td>
<td>10–16 h</td>
<td>Age-related</td>
<td>Acromegaly</td>
<td>APR, LD, GH deficiency, hypothyroidism, zinc deficiency</td>
</tr>
<tr>
<td>Transferrin</td>
<td>80</td>
<td>10 days</td>
<td>2.15–3.65 g/l (M) 2.50–3.80 g/l (F)</td>
<td>Iron deficiency</td>
<td>APR, LD</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>50</td>
<td>2 days</td>
<td>0.20–0.50 g/l</td>
<td>Hypothyroidism, CKD, pregnancy, steroids</td>
<td>APR, LD</td>
</tr>
<tr>
<td>RBP</td>
<td>21</td>
<td>12 h</td>
<td>20–40 mg/l</td>
<td>CKD</td>
<td>APR, vitamin A deficiency, zinc deficiency, hyperthyroidism</td>
</tr>
</tbody>
</table>

Table 1 Nutritional biomarker proteins

CKD, chronic kidney disease; F, female; LD, liver disease; M, male.
Various regulatory mechanisms regulate the release of IGFs from complexes increasing interaction with receptors [25]. First, the proportions of the different IGFBPs in serum may be important. The levels of IGFBP-1 and -2, although constituting a small proportion of the total IGFBP pool, are thought to have a role in regulation of free IGF-I. Conditions influencing their levels can alter free IGF-I concentrations without affecting total IGF-I [20]. Proteases and matrix metalloproteinases can fragment IGFBPs, thereby reducing their affinity for IGFs and enhancing IGF release [20]. A variety of catabolic states, namely critical illness, post-surgery and malignancy, are known to be accompanied by increased IGFBP-3 proteolysis [26–28]. It is also increased in maternal serum during pregnancy [29]. This may be an adaptive process in these conditions which enables IGFs to be mobilized from their vascular store, making them available to extravascular tissues. However, it may be maladaptive in some situations. IGFBP-3 protease activity released by breast cancer cells acts as a tumour-growth stimulator by increasing local IGF availability [30]. PAPP-A (pregnancy-associated plasma protein A), is a locally acting IGFBP-4 protease released from cells which is thought to increase local bioavailability of IGF-I [31]. This is thought to be activated by the pro-inflammatory cytokines TNFα (tumour necrosis factor α), IL (interleukin)-1β and IL-6 [32]. Inhibitors of IGFBP protease expression include N-acetylcysteine and antioxidants [33]. Release of IGFs from complexes is also regulated by IGFBP phosphorylation and cell-surface association via the extracellular matrix [34].

PHYSIOLOGICAL EFFECTS OF IGF-I

IGF-I has a wide variety of effects, but, essentially, these can be divided into acute metabolic effects and longer-term growth-promoting effects [15]. The acute actions of IGF-I overlap with those of insulin on carbohydrate and protein metabolism to promote energy storage. They include stimulation of amino acid uptake into skeletal muscle and stimulation of peripheral glucose uptake [35]. Its long-term effects are on cell proliferation, differentiation and anti-apoptosis [36,37]. IGF-I is a potent mitogen of muscle growth helping to maintain skeletal muscle mass by increasing DNA synthesis and accelerating cell-cycle progression [36,38]. IGF-I is essential for the attainment of normal body size during fetal development, peak bone mass during puberty and optimal fecundity during the reproductive period.

Briefly, the growth-promoting actions of IGF-I on individual tissues are summarized as follows. It is the most important mediator of muscle growth helping to maintain skeletal muscle mass by stimulating protein synthesis [39,40]. It induces an increase in expression of oxidative enzymes which promote fatigue resistance [41]. In brain, IGF-I is a potent neurotrophic and neuroprotective factor [42]. It is a critical promoter of brain development and neuronal survival influencing cognitive function. IGF-I has a role in regulation of β-cell mass and the regulation of insulin secretion and sensitivity [43]. It is also considered to have a physiological
role in maintaining the function of the immune system [44]. Locally produced IGF-I is responsible for much of the growth in the body, but it is considered to be unable to replace liver-derived IGF-I for mediating certain GH actions, namely regulation of cortical bone mass, GH secretion and insulin sensitivity [45].

REGULATION OF IGF-I

A wide variety of factors influence serum IGF-I concentrations, namely age, gender, genetic factors, nutritional status and disease. IGF-I levels are low at birth and increase to the age of 20 years, thereafter declining gradually [46]. This decline appears to be entirely physiological occurring independently of malnutrition and inflammatory processes [47]. Genetic factors have a significant influence on its expression accounting for up to 50% of serum concentrations under physiological circumstances [48,49]. Other hormones influence GH-stimulated hepatic IGF-I secretion. Thyroxine and androgens enhance IGF-I secretion, whereas oestrogens antagonize IGF-I secretion [50]. The production of hepatic IGF-I in response to pituitary GH is acutely regulated by a negative-feedback loop. Factors causing serum IGF-I concentrations to fall reduce feedback inhibition, resulting in increased GH levels. This increase is directly related to the reduction in free IGF-I which has led to the belief that it is the free component which regulates pituitary GH secretion [51,52]. By suppressing GH secretion, hepatic IGF-I indirectly enhances insulin sensitivity. The bioactivity of IGF-I is regulated at the level of its expression, binding to IGFBPs and by IGF resistance. Factors that regulate IGFBPs, particularly IGFBP-3, have a major influence on free IGF-I concentrations in serum, in turn influencing IGF-I signalling [25]. Tissue sensitivity to IGF-I can be regulated by tissue-specific expression of receptor numbers or by factors influencing the intracellular signalling pathways [53].

Nutritional regulation of IGF-I

Growth is a complex process driven by genes, but dependent on many other factors. It is an energy-demanding process which, in addition, requires plentiful substrate for cellular proliferation. Since IGF-I is responsible for physiological up-regulation of protein synthesis, it is logical that its release should be linked to sufficient substrate availability, indicating that the individual is nutritionally replete. Hepatic IGF-I synthesis also requires portal insulin, the presence of which signals sufficient carbohydrate intake [54]. Insulin stimulates IGF-I gene transcription and peptide synthesis independently of GH, but also regulates GH receptor density [55,56]. It inhibits synthesis of IGFBP-1 and -2 in the liver, both of which are thought to have inhibitory actions on IGF-I bioactivity by reducing free IGF-I concentrations. In this way, insulin enhances both IGF-I levels and bioactivity [57,58]. Both the IGFs and insulin are therefore part of an energy-sensing mechanism linking nutrition and growth.

During malnutrition, adaptation is necessary so that metabolic resources normally used for growth can supply the immediate energy needs of the individual. Starvation, semi-starvation, fasting and caloric restriction all result in lowering of serum IGF-I concentrations, the physiological purpose of which is to divert substrates towards these energy needs [59]. Low IGF-I concentrations favour protein catabolism in skeletal muscle, mobilizing amino acids for hepatic gluconeogenesis, a process in which simultaneously occurring low insulin concentrations are permissive. This process is assisted by the relatively insulin-resistant state which exists in starvation. Gluconeogenesis maintains glucose levels needed to supply glycolytic tissues such as brain. The decrease in circulating IGF-I concentrations also results in enhanced GH secretion. However, there is also a state of relative GH insensitivity in which the liver does not respond normally to the elevated GH, resulting in persistently low IGF-I concentrations [60–62]. This favours lipolysis in adipose tissue making NEFAs [non-esterified (‘free’) fatty acids] available as an energy source [63]. GH also enhances hepatic gluconeogenesis by antagonizing insulin’s suppressive action and by providing amino acids from muscle. Thus GH has an anti-insulin effect increasing the availability of glucose and NEFAs.

The mechanism of the decline in serum IGF-I during fasting has been studied extensively in animal models, but less in humans [64]. The relative resistance to GH action on liver in malnutrition results in a block in hepatic IGF-I secretion. In severe dietary restriction, there is reduced expression of hepatic GH receptors, whereas protein restriction alone is associated with a post-receptor defect in GH action [65]. The decline also reflects the general decrease in hepatic protein synthesis which accompanies malnutrition, caused in part by reduced availability of amino acids. Other factors contributing to the decline are nutritionally induced hormonal changes, namely reduced concentrations of insulin, as discussed above, and tri-iodothyronine. During dietary restriction, there is also increased clearance and degradation of serum IGF-I mediated by changes in concentrations of circulating IGFBPs. IGFBP-1 and -2 levels rise early during malnutrition, possibly to limit the amount of bioactive IGF-I as a means of preventing hypoglycaemia. IGFBP-3 levels fall if malnutrition is prolonged.

As noted above, IGF-I was observed to be dysregulated in malnutrition shortly following its discovery. The decline in its concentrations was greater in those with PEM (protein energy malnutrition) compared with protein malnutrition alone [66,67]. Of the two factors, protein appears to be the more important in determining circulating IGF-I concentrations. Where energy restriction is moderate and long-term, this does not reduce serum IGF-I, but concentrations fall significantly in moderately protein-restricted subjects [68]. In terms of the response of IGF-I levels to nutritional support, it appears that optimal intakes of both protein and energy are required for their restoration [64]. The dietary essential amino acid intake is also critical for IGF-I restoration following fasting. A diet in which the protein content is low in essential amino acids (80% non-essential amino acids) attenuates the return of IGF-I to normal [69]. Serum IGF-I also appears to be sensitive to both the amount and type of fat provided in nutritional support. Fish oil and low fat solutions were significantly correlated to serum IGF-I, appearing to promote a more rapid recovery of its concentrations [70]. Figure 2 illustrates the main regulatory influences upon production of IGF-I and its action.
Dysregulation of IGF-I in disease

Critically ill patients with sepsis, injury and burns are in a negative nitrogen balance, a state which occurs independently of total body protein status and irrespective of whether the patient is receiving adequate nutritional support [71]. These patients also exhibit a state of GH resistance in which there is a reduction in both circulating and locally produced IGF-I, analogous to that observed in malnutrition [72–75]. The mechanism of the decrease is incompletely understood, but pro-inflammatory cytokines such as IL-1 and IL-6 act to inhibit IGF-I expression in liver and skeletal muscle [76,77]. In some conditions, reduced IGF-I concentrations are in part due to decreased IGFBP-3 concentrations resulting from increased proteolysis [78]. Whatever the mechanism, IGF-I concentrations tend to be inversely related to those of APR (acute-phase response) markers such as CRP (C-reactive protein) [79]. Studies have also provided evidence that cytokines induce IGF resistance without influencing expression of IGF-1R [80,81]. They appear to block post-receptor intracellular signalling. This may contribute to the inability of nutrient supplementation to promote gain of LBM (lean body mass) in acutely ill patients [82]. IGF-I concentrations measured in the post-acute stage of critical illness appear to have prognostic value. A prospective observational study of 102 critically ill ICU (intensive care unit) patients observed higher IGF-I levels in the survivors [83].

These responses probably developed as an adaptation to regulate utilization of limited resources [53]. During acute illness, the immediate survival of the organism demands that growth and energy storage are restricted. In the short term, it is therefore important that amino acids continue to be mobilized from muscle to fuel gluconeogenesis. By inhibiting the anabolic effects of IGF-I, cytokines and glucocorticoids enable energy to be provided for the immune system [44,53]. Glucocorticoid hormones also promote protein catabolism by antagonizing the anabolic actions of IGF-I at the molecular level. Although the basis of these responses is adaptive, there are pathological consequences. Sustained cytokine action leads to a reduction in skeletal muscle mass which can prolong mechanical ventilation [84]. Cytokines also induce sickness behaviour such as malaise, fatigue, reduction in appetite and change in sleep patterns [85].

The findings of low IGF-I levels in critical illness stimulated interest in therapeutic use of rhGH (recombinant human GH). Treatment did result in increased IGF-I concentrations with nitrogen retention and decreased LOS. However, two large trials in 1999 reported increased mortality associated with infection and organ dysfunction [86]. Smaller clinical trials have re-examined rhGH treatment in prolonged critical illness, demonstrating increased IGF-I and IGFBP-3 concentrations. In a recent trial of 30 multiple trauma patients with prolonged critical illness, pulsatile rhGH delivered intravenously normalized IGF-I concentrations [87]. Recombinant GH supplementation may be safer and more efficacious in some critically ill patients, but the subgroup likely to benefit needs to be defined. A clearer understanding of the GH resistance present in critical illness should lead to the development of new therapies to restore the anabolic effects of GH and IGF-I. Current guidelines recommend against therapeutic use of rhGH in critical illness [88].

Dysregulation of the IGF axis is implicated in the adverse effects of aging [89]. The decline in IGF-I concentrations which occurs with age is associated with reduced muscle mass and strength, reduced protein synthesis and increased cellular apoptosis [90]. As well as a decline in concentrations, there appears to be an impairment of intracellular signalling which contributes to age-related loss of muscle and bone mass [91]. During aging, individuals can develop visceral adiposity, a pro-inflammatory state associated with impairment of IGF-I action. These changes are accompanied by a decline in the concentrations of other anabolic hormones, namely DHEAS (dehydroepiandrosterone sulfate) and testosterone. In contrast, there is a relative abundance of catabolic hormones such as thyroid hormones and cortisol. This catabolic milieu is associated with frailty, cognitive decline and mortality in the elderly [92]. The changes in IGF-I appear to influence survival. A prospective study in elderly men observed that higher circulating IGF-I bioactivity was better associated with overall survival. Those in the lowest quartile had 1.8-fold increased mortality risk compared with the highest quartile [93]. It has been recognized for many years that the decline in the IGF-I axis which occurs with aging may be linked to cognitive deficits and...
These findings led researchers to consider possible clinical utility for measurement of IGF-I in nutritional contexts. As a marker of nutritional status, IGF-I is more sensitive and specific than prealbumin, transferrin and RBP [59,119]. Its shorter serum half-life, indicative of high turnover, renders it more sensitive to changes in nutritional status, an attribute which increases its value in monitoring compared with previous markers [120]. The findings of studies on IGF-I in under-nutrition and obesity are discussed below.

**Anorexia nervosa**

As in other situations where there is malnutrition, GH levels are high in patients with anorexia nervosa, following the reduction in negative feedback on GH secretion [121]. Likewise, suppressed IGF-I reflects the GH resistance present as part of the adaptive response to malnutrition [122]. Since increases in GH and IGF-I during puberty are essential for increased bone formation, these changes do have pathological consequences. In patients with anorexia nervosa, low BMD (bone mineral density) can occur [123]. In addition to changes in the IGF axis, patients with anorexia nervosa often have multiple other endocrine abnormalities, including amenorrhea, hypothyroidism and hypercortisolism [124]. These are not hallmarks of anorexia nervosa itself, but occur secondarily to malnutrition as they are also observed in starvation states accompanying other conditions such as catabolic states and liver disease. They return to normal upon weight restoration [125].

During recovery, IGF-I has an active role in regenerative processes. Since its serum concentrations respond to nutritional support, it has been investigated as an indicator of nutritional status in these patients [99]. Total serum IGF-I concentrations are closely related to BMI, body fat and body muscle mass, reflecting the severity of nutritional depletion [98]. During nutritional rehabilitation, IGF-I increased in parallel with the BMI S.D. score, a measure of leanness. The authors of this study concluded that IGF-I can be considered an indicator of nutritional status which is sensitive to short-term weight changes. The increase in serum IGF-I which occurs with weight gain predicts increases in markers of bone formation and BMD [126,127].

Following recovery, a possible use for IGF in the context of anorexia nervosa is in prediction of relapse. This is an important issue as patients who appear clinically recovered still have a high rate of relapse. In this situation, body weight alone may be misleading as a parameter of energy balance because it reflects extracellular fluid as well as body cell mass. Weight measurements alone may therefore underestimate the risk of relapse. Monitoring of IGF-I may help avoid this problem. Investigation of this would require the IGF-I concentration to be studied prospectively to assess whether its decline precedes that of significant loss of LBM, as assessed by an imaging technique such as DEXA (dual-energy X-ray absorptiometry) scanning. Monitoring of IGF-I as a marker of repletion during artificial nutrition support may also potentially help to avoid overfeeding of patients and the adverse consequences thereof.

**Paediatrics**

Many diseases can present with growth failure in childhood. These include coeliac disease, renal disease, HIV infection and

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**Table 2** Pathophysiological influences on total serum IGF-I concentrations

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on serum IGF-I</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>U/↑↓</td>
<td>[48,49]</td>
</tr>
<tr>
<td>Age</td>
<td>↑ until 20 years ↓ until 50 years</td>
<td>[96]</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>↑ as pregnancy progresses</td>
<td>[97]</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>↓</td>
<td>[98,99]</td>
</tr>
<tr>
<td>Obesity</td>
<td>U/↑/↓</td>
<td>[100–107]</td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>↓</td>
<td>[108]</td>
</tr>
<tr>
<td>Chronic wasting conditions</td>
<td>↓</td>
<td>[109]</td>
</tr>
<tr>
<td>Catabolic conditions</td>
<td>↓</td>
<td>[76]</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>↓</td>
<td>[110]</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>↓/U</td>
<td>[111,112]</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↓</td>
<td>[50,113]</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>↓</td>
<td>[114]</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>↑</td>
<td>[114]</td>
</tr>
</tbody>
</table>

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Alzheimer’s disease [42]. Loss of IGF-I also has pathological effects on the immune system [53]. There is a paradox in the actions of IGF-I in that some are potentially harmful. Whereas the growth factor and anti-apoptotic effects of IGF-I are beneficial in physiological proportions, persistently elevated IGF-I bioactivity and hyperinsulinaemia appear to be detrimental, increasing the risk of age-related diseases [94]. There is epidemiological evidence to suggest that excess IGF-I has a role in the development of some cancers, Type 2 diabetes and atherosclerosis. Patients with IGF-I concentrations in the upper quartile of normal have an increased incidence of cancers, whereas low serum IGF-I concentrations are associated with diminished tumour growth and metastasis [95]. IGF-I also promotes tumour growth and metastasis in pre-existent cancers. Pathophysiological factors influencing total serum IGF-I concentrations are summarized in Table 2.

**CLINICAL UTILITY OF IGF-I IN NUTRITIONAL CONTEXTS**

Currently, the principal utility of serum total IGF-I measurements is in the assessment and monitoring of GH status in deficiency and acromegaly, which have been reviewed elsewhere [114]. At present, NICE guidance does not recommend measurement of IGF-I in the context of clinical nutrition [13]. However, there is abundant evidence from studies supporting its measurement. The serum IGF-I concentration has long been recognized to reflect nutritional status, declining during starvation and responding to refeeding [59,115–117]. During nutritional support, concentrations have been observed to rise incrementally in relation to weight gain, correlating with anthropometric indices such as BMI (body mass index) and the levels of other biomarkers [59,116–118]. These findings led researchers to consider possible clinical utility for measurement of IGF-I in nutritional contexts. As a marker of nutritional status, IGF-I is more sensitive and specific than prealbumin, transferrin and RBP [59,119]. Its shorter serum half-life, indicative of high turnover, renders it more sensitive to changes in nutritional status, an attribute which increases its value in monitoring compared with previous markers [120]. The findings of studies on IGF-I in under-nutrition and obesity are discussed below.
cystic fibrosis [128]. Malnutrition is the common factor underlying growth failure in patients with these conditions, but catch-up growth can usually be achieved with appropriate nutritional intervention. Serum IGF-I concentrations, along with those of IGFBP-3, are regulated by nutritional intake, with their regulatory patterns being similar to those observed in adults. It has therefore been suggested that their measurement may indicate adequacy of nutrient intake [129]. When used in the assessment of growth in malnourished children, the IGF-I concentration correlates strongly with height S.D. score, suggesting that it is a useful indicator of growth and nutritional status [130].

Serum IGF-I has been extensively studied as a marker of LBM in children with medical disorders. In CF (cystic fibrosis), it correlated with LBM, as evaluated by DEXA scanning, independently of weight [131]. The significance of this is that reduced LBM can impair respiratory function, worsening the clinical outcome in these patients. IGF-I could therefore be used to identify patients at risk of deteriorating respiratory function. In a separate study of children with CF, decreased IGF-I was observed to reflect growth retardation [132]. It was also used as a marker of LBM in a recent study of children starting antiretroviral therapy for HIV infection [133]. During treatment, improved muscle mass, but not linear growth, was associated with IGF-I concentrations returning to normal. In children with congenital heart disease, the presence of cyanosis was the most important factor influencing serum IGF-I. Concentrations were significantly lower in cyanotic compared with acyanotic patients [134]. The authors suggested that chronic hypoxia has a significant role in the pathogenesis of malnutrition, reflected by serum IGF-I concentrations. In addition, the loss of the growth-promoting effect of IGF-I in these patients may be directly responsible for the decrease in left ventricular mass.

Prolonged suboptimal energy intake can result in NGR (nutritional growth retardation), a condition which is easily overlooked. It can be detected by monitoring body weight over time. In contrast with children with PEM, these patients do not appear wasted and IGF-I concentrations, in common with RBP, prealbumin and transferrin, do not distinguish them from patients with constitutional short stature. This is because these patients have adapted to reduced nutritional intake to conserve energy. They have a reduced BMR due to reduced Na+/K+-ATPase activity [135], reduced protein synthesis, which accounts for 10–15% of the BMR, and a reduction in body temperature [136]. The essential needs of metabolism are still met, but with less energy available for growth.

**SBS (short bowel syndrome)**

IGF-I measurement has been used in the context of research studies to monitor PN where changes in its concentrations have been observed to correlate with changes in protein metabolism [137]. It has also been studied in children with SBS receiving PN. Levels improved in line with nitrogen balance, suggesting that it may be of value, along with other measurements, in assessing protein nutritional status of these children [138]. Not all children with SBS respond equally to standard nutritional support, and it is important to identify those who may respond poorly. There is evidence supporting IGF-I measurement as an index of IF in children with SBS who merit more aggressive therapeutic intervention [139]. Utility has been suggested in children with IF undergoing intestinal transplantation. Transplantation can potentially free these patients from long-term PN, but it is often difficult to achieve satisfactory growth post-transplant. Low pre-transplant concentrations of IGF-I predicted negative linear growth velocity [140]. Pre-transplant IGF-I concentrations may therefore be useful in identifying those patients requiring more intensive nutritional support post-transplant. rhGH is another treatment that may reduce the amount of PN required in patients with SBS. When this was recently trialled in PN-dependent children, they remained on PN, but significantly more nutrition could be delivered enterally [141]. This paralleled an increase in their energy balance over a 12-month period during which serum IGF-I concentrations increased significantly. There may therefore be a place for monitoring IGF-I in the context of rhGH treatment.

**RS (refeeding syndrome)**

RS, the hallmark of which is hypophosphataemia, can occur as a complication following the commencement of nutrition support in malnourished patients [142,143]. Although there are recommendations on how to recognize patients at risk of RS [13], prediction is difficult in practice. Many at-risk patients do not suffer refeeding complications. Conversely, some patients who develop complications are not identified as being at-risk. In practice, NSTs (nutrition support teams) adopt a cautious approach of initially underfeeding most patients. Although this minimizes complications, it has the consequence that many patients are underfed unnecessarily. The availability of reliable objective markers or RS risk would enable these patients’ nutritional needs to be met at an earlier stage, thereby promoting their recovery. A recently published study on patients receiving PN examined three parameters as potential predictors of RS, namely serum IGF-I measured before commencement of PN, the leptin concentration and an RI (‘refeeding index’) derived from the other two values [144]. Although the RI predicted a fall in the serum phosphate concentration more sensitively and specifically than the other two parameters, IGF-I was a better predictor of mortality. Such prognostic value is useful as it indicates to the clinician the need for cautious calorie delivery. Aside from IGF-I, there is potential for other markers of the IGF system, or composite indices thereof, to assist in prediction of refeeding risk. The reported effects of under-nutrition and obesity on the levels of IGF axis components other than IGF-I are shown in Table 3. Proposed clinical utility of IGF-I measurement in endocrine and nutritional contexts is summarized in Table 4.

**Obesity**

Studies on the effects of obesity on the IGF system have observed changes, but these are less consistent than in malnutrition. There is considerable overlap in serum IGF-I concentrations between obese and lean subjects. When assessed in large population groups, total concentrations follow an inverted U-shaped distribution curve, maximal at a BMI of 30–35 kg/m², although the changes are relatively small [152]. Obesity is associated with hyposecretion of GH, the mechanistic basis of which is incompletely understood [153]. Its reversibility upon weight reduction
suggestions that it is an adaptive change to excess energy provision favouring energy storage.

Various studies have investigated the effect of therapeutic interventions on IGF-I concentrations in obesity. These have fairly consistently observed a reduction in concentrations in response to various approaches, namely caloric restriction [107], physical activity [154], combinations of dietary restriction and exercise training [155], and gastric banding [156]. In the case of dietary restriction, the duration and extent of the calorie restriction appear to be important. In obese subjects subjected to short-term calorie restriction, serum IGF-I fell less readily than in subjects of normal weight, particularly where protein intake was sufficient. During 3 weeks on a low-energy diet (445 kcal; 1 kcal = 4.184 kJ), but with adequate protein (50 g), total serum IGF-I did not change in obese subjects [157]. This and other studies suggest that, in obesity, the maintenance of serum IGF-I concentrations is less dependent upon energy intake, providing that protein intake is adequate. Presumably this is because these subjects are able to utilize energy stores to maintain hepatic protein synthesis.

Although the research findings in obesity are interesting, measurement of IGF-I in this context does not currently appear to be of value in guiding clinical management. There is an increasing interest in the link between obesity and cancer, and it has been suggested that dysregulation of the IGF system plays a major role in this link [158]. Research in this area will continue to seek the underlying mechanisms, but it remains to be established whether measurement of IGF-I is of clinical value in predicting or monitoring mortality risk.

The metabolic syndrome
Numerous studies have observed an inverse relationship between IGF-I and CRP concentrations in subjects with the metabolic syndrome [159–161]. The number of metabolic syndrome features increase with declining IGF-I and increasing CRP. A population-based study on elderly subjects observed that this inverse association between IGF-I and inflammatory markers persisted in individuals with hsCRP (highly sensitive CRP) below 3.0 mg/l, i.e. within the population reference range [162]. The population-based CARDIA (Coronary Artery Risk Development in Young Adults) male hormone study investigating healthy young black males and white males observed a correlation between the two variables which was confined to black male smokers [163]. The causal nature of the association was unclear, but the elevated CRP is indicative of chronic subclinical inflammation which, along with insulin resistance, is implicated in atherogenesis. Both factors are related to CHD (coronary heart disease) risk which may have implications for preventative strategies. There are extensive data from studies to demonstrate that IGF-I is a metabolic biomarker associated with health outcomes [164]. A study of 846 healthy young men provided outcomes and IGF-I data [165]. IGF-I was positively associated with improved aerobic fitness and muscular endurance in these subjects. IGF-I may have utility in assessing cardiovascular risk associated with metabolic syndrome, but it is not clear at present what value it would provide over existing approaches.

**FREE IGF-I**

Total serum IGF-I suffers from the drawback that its concentration does not necessarily reflect IGF-I bioactivity. Consequently, interest has increased in measurement of free IGF-I as a biologically and potentially more clinically relevant parameter. Since 1994, assays have been available for free IGF-I enabling it to be studied in clinical context [166]. It is usually estimated by measurement of IGF-I immunoreactivity following extraction of IGFBPs, which is a technically simple method. When measured
in malnourished patients, free IGF-I concentrations have been observed to fall in common with total IGF-I [147,167]. It has been reported to be more sensitive than total IGF-I as a marker of short-term nutritional status [57]. In a study on healthy fit young men exposed to 8 days of energy deficit, the authors reported that concentrations of all ternary complex components followed the loss in body mass more closely than transferrin or RBP [148]. Free IGF-I measured by immunoradiometric assay in this study was more closely associated with changes in LBM than the other IGF system parameters. The authors concluded that free IGF-I along with other parameters of the system had utility in assessing the severity of an energy deficit and changes in body composition. In studies on obese subjects, free IGF-I concentrations have been reported as normal [105], high [106,145,146] or low [115], although most suggest high concentrations. An increase in free IGF-I may be explained by decreases in levels of IGFBP-1 and -2 which have been described in obesity as a consequence of chronic hyperinsulinaemia [168,169]. However, this elevation of free IGF-I may be confined to non-diabetic subjects because obese Type 2 diabetic subjects had free IGF-I concentrations which were not significantly elevated compared with lean controls. Subjects with Type 1 diabetes had a marked reduction (>50%) in free IGF-I [106].

Different assay methods for free IGF-I yield different results. Consequently, there has been a debate over how best to measure it. Although results obtained by immunoreactivity are valid in many cases, they may not closely reflect IGF-I bioactivity in all conditions [57]. In addition, immunoreactivity does not take into account the effects of IGFBPs or their proteases on the interaction of IGF-I with receptor. A novel KIRA (kinase receptor activation assay) has been described which measures the ability of serum to activate IGF-1R autophosphorylation [170]. It can be argued that KIRA provides the most relevant measurement available as it measures IGF-I available to its receptor and so accounts for the effects of IGFBPs and proteases. Age-specific normal values for IGF-I bioactivity as measured by KIRA have been reported which show it to decline with age as for total IGF-I [171]. In order to assess the nutritional information provided by bioactivity, a study was carried out comparing RTK activation to total IGF-I in patients with anorexia nervosa [147]. Both parameters were significantly reduced and closely related, suggesting that total IGF-I may be considered a surrogate marker for IGF-I bioactivity in these patients at least. In a study on malnutrition in patients receiving continuous ambulatory peritoneal dialysis, IGF-I bioactivity measured by KIRA was observed to fall during the APR regardless of the nutritional state [71,72,175,176]. Inevitably, this is most problematic in hospitalized patients who are acutely ill. The serum IGF-I concentration correlates strongly with negative nitrogen balance in these patients [177]. In subjects with malignancy who have an active systemic inflammatory response, IGF-I is limited as a marker of nutritional status [174]. The influence of these factors may not be possible to separate from that of malnutrition. These are discussed below.

As discussed above, hepatic IGF-I expression is reduced in acute illness due to the influence of cytokines. This causes serum IGF-I, in common with the concentrations of other biomarkers, to fall during the APR regardless of the nutritional state [71,72,175,176]. Inevitably, this is most problematic in hospitalized patients who are acutely ill. The serum IGF-I concentration correlates strongly with negative nitrogen balance in these patients [177]. In subjects with malignancy who have an active systemic inflammatory response, IGF-I is limited as a marker of nutritional status [174]. Where there is acute inflammation, methods detecting changes in body composition, performance or physical activity may be better options for evaluating nutritional support.

### FACTORS INFLUENCING IGF-I INTERPRETATION

#### Confounding factors

It is worthwhile considering the characteristics of the ideal nutritional biomarker which would be unaffected by limitations (Box 1). Although there is no ideal biomarker currently available, this list should be kept in mind when considering the merits of novel markers. IGF-I meets the first four criteria but, in common with other biomarker proteins in current use, suffers from the limitation that factors other than nutritional status influence its serum concentration [174]. The influence of these factors may not be possible to separate from that of malnutrition. These are discussed below.

As discussed above, hepatic IGF-I expression is reduced in acute illness due to the influence of cytokines. This causes serum IGF-I, in common with the concentrations of other biomarkers, to fall during the APR regardless of the nutritional state [71,72,175,176]. Inevitably, this is most problematic in hospitalized patients who are acutely ill. The serum IGF-I concentration correlates strongly with negative nitrogen balance in these patients [177]. In subjects with malignancy who have an active systemic inflammatory response, IGF-I is limited as a marker of nutritional status [174]. Where there is acute inflammation, methods detecting changes in body composition, performance or physical activity may be better options for evaluating nutritional support.

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8. Measurement is simple, cheap and available locally
In this situation, systemic inflammation is inversely correlated with survival. Systemic inflammation is best assessed by measurement of CRP. Rather than considering IGF-I as a nutritional marker, it can be considered primarily a marker of short-term changes in hepatic protein synthesis on which both nutritional status and the APR have an impact. From this perspective, the APR is not a confounding factor in IGF-I interpretation, but a principal determinant of concentrations. Effectively, IGF-I, like albumin, can be considered a negative acute-phase marker and may have value as such.

The IGF-I concentration is also lowered in disease of the liver, its main site of synthesis [110], and can be normal or lowered in renal disease due to changes in IGFBP concentrations [111,112] (see also Table 2). IGF-I concentrations have been reported to be low in patients with untreated severe hypothyroidism, reflecting the regulatory influence of thyroxine on IGF-I [113]. These increased significantly following thyroxine replacement. It may therefore be advisable to assess thyroid function when interpreting IGF-I concentrations. In patients with NGR due to chronic energy deficit, adaptations enable homeostasis to be maintained and so IGF-I concentrations tend not to be deranged as in overt malnutrition [135]. Until more sensitive biochemical tests are available, the detection of NGR requires careful serial weight monitoring.

IGF-I also has limitations as a marker of malnutrition in obese subjects. A common scenario encountered in hospitals is an obese patient who has lost weight due to chronic illness or post-operatively. In this situation, it is important that nutritional needs are fully met in order to hasten recovery, e.g. by promoting wound healing. Under-provision of nutrition support will favour catabolism. In this context, it should be borne in mind that serum IGF-I concentrations do not fall readily in energy restriction where protein intake has been maintained [157]. Pregnancy can also be considered a confounding factor as IGF-I concentrations rise as pregnancy progresses, particularly in the third trimester. However, this does not necessarily preclude it as a nutritional biomarker in this situation. In malnourished pregnant women, IGF-I concentrations correlate with the degree of negative nitrogen balance, suggesting that it may be of use as a biomarker of under-nutrition in pregnancy [97].

As with older biomarkers, the many confounding factors influencing IGF-I concentrations in hospital patients result in too low a specificity for it to be suitable as a screening test. Biochemical tests appear unlikely to replace nutritional screening tools in the foreseeable future. Clearly when used in monitoring, IGF-I concentrations should be interpreted in a clinical context, taking the disease state into account. This includes seeking features suggesting recovery and anabolism, namely weight restoration, recovery of appetite, reduction in oedema, mobilization and general clinical recovery. Biochemically, there may be fall in CRP concentrations and a rise in concentrations of albumin and other biomarkers. In view of the limitations discussed, IGF-I may find greater use in out-patients or in hospitalized patients who are relatively well, particularly when used serially to assess the adequacy of the regimen. There may be value in concurrent measurement of inflammatory markers, such as CRP, in an effort to exclude inflammatory disease. Authors of research studies have also measured liver function tests and thyroid function tests in an effort to exclude confounding factors [178].

Variation

BV (biological variation) of analyte concentrations encompasses intra-individual and inter-individual variation. Data on BV enable derivation of reference ranges and data of use in interpreting serial results. As is the case for other hormones, normal values for IGF-I vary significantly between individuals. Reported values for inter-individual variation of IGF-I range from 27.0 to 45.4 % [179]. This largely reflects the genetic factors influencing the physiological set-point across the population. Consequently, the population reference ranges for IGF-I are relatively wide compared with intra-individual variation [88]. Another consequence of the large inter-individual variation is that it may be unclear what should be considered the target value indicative of recovery in an individual. A value towards the lower end of the reference range, for example, may be normal for one individual, but not for another. Given that intra-individual variation is relatively small around the physiological set-point, a pre-morbid value for the individual, if available, could be used as the target. In the absence of a pre-morbid value, an alternative approach may be to observe the fold response over the baseline concentration, as it has been suggested that relative changes in IGF-I may be more useful than absolute values [98]. In monitoring nutritional rehabilitation of chronically malnourished patients, a 2.6-fold increase in serum IGF-I concentrations was observed compared with much smaller increases in transferrin [66]. This change correlated with changes in nitrogen balance. It may therefore be useful to know that the concentration is improving from baseline.

When interpreting apparent changes in consecutive results, the clinician needs to know whether these are of sufficient magnitude to represent a real change or are small enough to be accounted for by sources of variation. This principle is of relevance to IGF-I as its concentrations are likely to be interpreted in serial samples. Data on intra-individual variation have clinical utility in assessing the significance of differences between consecutive results obtained from an individual [180]. It can be described by the CVi (coefficient of variation) (S.D./mean expressed as a percentage) derived from measurements at intervals. In a recent small study on healthy subjects, the CVi for IGF-I was reported to be low at 9.4 % [179]. From these data, the authors calculated that a change of 8.4 nmol/l between two samples had a 95 % chance of being significant. A study on pre-pubertal children reported a CVi of 13.9 % [181]. This higher value may reflect the sensitivity of the IGF-I concentration to short-term change in LBM in growing children [58].

The problem with carrying out such studies on normal volunteers is that variation, particularly for hormone concentrations, may be higher in subjects who are unwell [182]. Changes in concentrations of the analyte sufficient to represent real changes under physiological circumstances may not represent real changes in patients who are clinically unwell. Ideally, intra-individual variation of IGF-I should therefore be studied in subjects with the relevant clinical condition. There is a need for studies to assess intra-individual variation for IGF-I in malnourished and hospitalized patients. As a biomarker, IGF-I has the advantage that there
is minimal circadian alteration in its levels throughout the day. A specimen taken at any time of day is therefore a valid measure of its status [62]. It should be noted that, although analytical imprecision is a source of variation, its contribution in practice is sufficiently small to be ignored, provided that assay performance is satisfactory. IGF-I concentrations are also influenced by the assay used [183]. It is therefore preferable to use assay-specific reference data in any given situation. During research on IGF-I, care should be taken to use the same assay throughout the study.

**FUTURE CONSIDERATIONS**

Advances in basic research will continue to improve our understanding of this complex system, no doubt further refining the somatomedin hypothesis. In terms of future research, the importance of paracrine and autocrine IGF-I in nutrition is relatively poorly understood and demands further study. In addition, the dysregulation of free IGF-I in malnutrition and its potential utility in clinical nutrition need to be examined further. More information is needed on BV of IGF-I concentrations during illness so that changes can be meaningfully interpreted by the clinician. Clinical research also needs to be extended to other components of the IGF system which have potential utility in clinical nutrition. The findings from further studies will, in turn, lead to a greater appreciation of how biomarkers of the IGF system can be used in clinical contexts as well as suggesting possible therapeutic interventions. At the present time, the main role for IGF-I measurement would appear to be in monitoring nutritional support, especially in malnourished patients in whom acute illness and liver disease can be excluded.

To date, serum IGF-I is the best-studied biomarker of protein-energy status. Although much potential utility has been defined for its measurement in nutritional contexts, this alone will not guarantee its place in the clinical laboratory repertoire. Aside from the limitations discussed, barriers remain to the routine assessment of IGF-I in nutritional contexts. Its measurement will first have to be recommended by clinical guidelines. Even then, logistical factors such as cost and availability of the assay may mitigate against its adoption by clinical laboratories. At present, IGF-I is a relatively expensive test, compared with many other analytes, its analysis being carried out in a few specialist laboratories. Requesting practices therefore tend to be confined to those treating acromegaly and GH deficiency, situations in which its clinical utility is well established. In order for any biochemical test, including IGF-I, to have utility in monitoring nutritional support, it is essential that results are available the same day as they are requested so that the nutritional regimen can be modified appropriately. This would necessitate assays being both rapid and available on site which is not currently the case in most hospitals. These logistical problems are likely to be overcome in time as IGF-I assays become cheaper and easier to automate, possibly even available as near patient tests. The measurement of IGF-I in nutritional contexts may help inform the management of patients, but, as with all biochemical tests, its concentration must, in the end, be considered in the context of other clinical findings and the results of other laboratory investigations.

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