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IGF-1 Research Abstract

Prepared by the AARL Research Team

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Is IGF-1 the ONLY true marker of increased GH activity?

As members of the scientific community and a practitioner of AntiAging Research Science, We answer this resolution in the negative; no, IGF-1 is not recognized as the ONLY true marker for GH activity.

We will use scientific abstracts as our source of authority. They have the widest recognition and the highest level of respect among the scientific community and they are supported by the highest level of empirical data and research.

This resolution does not concern whether or not IGF-1 is useful as one of several markers for GH activity, which is widely known; it concerns IGF-1 as the ONLY marker for GH activity. The question is, is IGF-1 considered by science to be the ONLY marker for GH activity, not whether it is a marker or not.

This resolution also does not concern the way in which IGF-1 is used as a marker for GH activity.

Introduction

The usefulness of IGF-1 as an accurate and consistent measure of increased GH activity in the body has been hotly debated in recent journals. The growing body of evidence seems to suggest that IGF-1 is not the ONLY true marker of increased GH activity. In fact, it is becoming increasingly clear to biochemists and allopaths worldwide that IGF-1 may not even be a "dependable" marker in measuring GH activity since its production can be stimulated by factors other than GH production. In the following sections, we will show that IGF-1 can be effected by several events. Because of this, it is cautioned that anyone seeking to understand true levels of GH activity should follow a full blood panel protocol. Dependence on IGF-1 alone has been shown to give false markers.

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Is IGF-1 always increased by increases in GH production?

It is well documented that IGF-1 levels can and do decrease in many cases, even when GH activity increases. Please see the following medical journal excerpts.

Diagnosis of growth-hormone deficiency in adults.

Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KK
Garvan Institute of Medical Research, St Vincent's Hospital, Sydney, NSW, Australia.

"…There is no consensus as to the most appropriate method of diagnosing growth-hormone (GH) deficiency in adults. We have evaluated the relative diagnostic merits of measuring peak GH response to insulin-induced hypoglycaemia (insulin tolerance test), mean 24 h GH concentration derived from 20 min sampling, serum insulin-like growth factor I (IGF-I) concentrations, and serum IGF binding protein 3 (IGFBP-3) concentrations. These tests were undertaken in 23 patients considered GH deficient from extensive organic pituitary disease, and in 35 sex-matched normal subjects of similar age and body-mass index. Hypopituitary subjects had significantly lower stimulated peak GH, mean 24 h GH, IGF-I, and IGFBP-3 concentrations than normal subjects. The ranges of stimulated peak GH responses were clearly separated between the hypopituitary (< 0.2-3.1 ng/mL) and normal (5.3-42.5 ng/mL) groups, but mean 24 h GH, IGF-I, and IGFBP-3 concentrations overlapped. Mean 24 h GH concentrations were below assay sensitivity in 80% of hypopituitary subjects and 16% of normal subjects. 70% and 72%, respectively, of the IGF-I and IGFBP-3 values in hypopituitary subjects were within the range for normal subjects. We conclude that GH deficiency in adults is most reliably identified by stimulatory testing, and that IGF-I and IGFBP-3 are poor diagnostic tests of adult GH deficiency…"

Serum Levels of Insulin-like Growth Factor-I (IGF-I) and IGF Binding Protein-3 (IGFBP-3) in Idiopathic Tall Basketball Players

G. E. Krassas, L. M. S. Carlsson, C. Karlsson, N. Pontikides, Th. Kaltsas, R. Gunnarsson

"…On the basis of these results one can hypothesize that IGF-I levels appear to reflect high physical exercise and food intake rather than differences in GH secretion, while IGFBP-3 reflects most probably differences in GH secretion and food intake…"

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A five day treatment with daily subcutaneous injections of growth hormone-releasing peptide-2 causes response attenuation and does not stimulate insulin-like growth factor-I secretion in healthy young men.

Nijland EA; Strasburger CJ; Popp Snijders C; van der Wal PS; van der Veen EA
Department of Endocrinology, Free University Hospital, Amsterdam, The Netherlands.
Eur J Endocrinol, 1998 Oct, 139:4, 395-401

"…The synthetic hexapeptide growth hormone-releasing peptide (GHRP)-2 specifically stimulates GH release in man. To determine the effects of prolonged treatment and whether response attenuation occurs in man, we administered to nine healthy subjects a daily s.c. injection of 100 microg GHRP-2 over 5 days. Every day blood samples were taken to determine GH, IGF-I, IGF-binding protein (IGFBP)-3 and osteocalcin levels. On days 1,3 and 5, GH was measured at -20,0,20,40,60,90,120 and 180 min using an immunometric and an immunofunctional assay. Mean-/+S.D). peak GH concentrations were 83+/-31, 59+/-22 and 51+/-13 microg/l on days 1, 3 and 5 respectively. Mean+/-S.D. areas under the curve for days 1, 3 and 5 were 6366+/-2514, 3987 +/- 1418 and 3392+/-1215 mU/l per min. Despite the maintained GH release, analysis of variance revealed that significant response attenuation occurred (P < 0.01). Mean serum IGF-I concentration did not increase after a 5 day treatment with GHRP-2. Mean basal levels were 22, 25,23,25,23,24 nmol/l measured on days 1 to 6. However, osteocalcin, another serum marker of GH activity in tissue, increased significantly from 3.2+/-1.0 to 4.2+/-0.4 microg/l (mean+S.D.) (P< 0.01)…"

Defining growth hormone deficiency in adults.

Ho KK, Hoffman DM
Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, Australia.

"…The absence of a distinct clinical syndrome calls for a strategy to reliably identify patients with hyposomatotropism. However, there is no consensus as to the most appropriate method of defining growth hormone (GH) deficiency in adults. Since GH secretion falls with senescence and is also reduced by obesity, both of these factors must be controlled for in such an evaluation. We have investigated the relative diagnostic merits of measuring (1) peak GH response to insulin-induced hypoglycemia (ITT), (2) mean 24-hour GH concentration derived from 20-minute sampling (IGHC), (3) serum IGF-I levels, and (4) serum insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) levels. These tests were undertaken in 23 patients considered GH-deficient from extensive organic pituitary disease and in 35-sex-matched normal subjects of similar age and body mass index. The ITT was the only test capable of distinguishing patients

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with organic GH deficiency from matched normal subjects. The sensitivity of the GH radioimmunoassay (0.2 ng/mL) limited the utility of IGHC measurements, since many subjects from both groups had undetectable values. Using a GH assay with a 100-fold greater sensitivity, we found a better but still incomplete separation of values between the two groups. There was a significant overlap of IGF-I and IGFBP-3 values, with only a third of GH-deficient subjects having low IGF-I values. The limitation of IGF-I has been confirmed by others, although its sensitivity as a diagnostic test is greater in young adults. We conclude that organic GH deficiency in adults can be reliably diagnosed by the ITT…"

Association of insulin-like growth factor-I with body composition, weight history, and past health behaviors in the very old: the Framingham Heart Study.

Harris TB; Kiel D; Roubenoff R; Langlois J; Hannan M; Havlik R; Wilson P
National Institute on Aging, Epidemiology, Demography and Biometry Program, Bethesda, MD 20892-9205, USA.
J Am Geriatr Soc, 1997 Feb, 45:2, 133-9

"…CONCLUSION: Although IGF-I declined with age, these data from the Framingham Heart Study did not show expected cross-sectional associations of weight, body fat, and lean mass. The strongest associations were between IGF-I and nutritional indicators. These results suggest caution may be warranted with regard to use of IGF-I as an indicator of growth hormone…"

Insulin-like growth factor measurements in the evaluation of growth hormone secretion.

Furlanetto RW

"…However, IGF-I levels are age dependent and subject to regulation by other hormones and nutritional variables; these features complicate the interpretation of IGF-I levels in individual patients and limit the usefulness of these measurements, particularly for determining GH deficiency in young children. Circulating IGF-II levels are not GH dependent and, therefore, their measurement is of little clinical utility in assessing GH secretion…"

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IGF-I levels in different conditions of low somatotrope secretion in adulthood: obesity in comparison with GH deficiency.

Maccario M, Grottoli S, Aimaretti G, Gianotti L, Endrio Oleandri S, Procopio M, Savio P, Tassone F, Ramunni J, Camanni F, Ghigo E
Department of Internal Medicine, University of Turin, Italy.

"…CONCLUSIONS: In conclusion, present data confirm that IGF-I levels depends on GH secretion as well as on nutritional status, being negatively and independently correlated with age and BMI. IGF-I assay is not a reliable test for the diagnosis of GH deficiency in adulthood though it gives good discrimination between GHD and normal subjects up to 40 yrs of age. In spite of low GH secretion, IGF-I levels are only slightly reduced in obesity, probably as consequence of hyperinsulinism…"

Can IGF-1 production be stimulated by factors other than GH?

In this section, it will be shown that IGF-1 can indeed be stimulated by factors other than GH production even though among biochemists, it is used as the preliminary marker. However, the growing body of respected science is moving away from IGF-1 as a reliable marker of GH activity. Since the production of IGF-1 is "reactionary" to other processes in the body, it can be stimulated by several factors that are "mimetic." This means that if a substance that "mimes" GH is picked up by the receptor sites of the Liver, it can trigger a rise in IGF-1 production without triggering a rise in GH production and therefore would not give a reliable reading of increased GH production in those cases. Nutrition and Amino Acid supplementation, in addition to protein intake can stimulate the elevation of IGF-1 independent of GH increase. This may indicate why IGF-1 levels rise in subjects ingesting "Amino Acid" growth hormone products and this rise may not be indicative of actual GH rise. Some Amino Acid precursors to GH actually increase IGF-1 production directly without acting on GH.

The measurement of insulin-like growth factor I: clinical applications and significance.

Teale JD, Marks V

"…Apart from GH control, several other factors influence circulating IGF-I levels. Nutritional status can be assessed through reference to IGF-I analysis, overall catabolic or anabolic processes being associated with decreasing or increasing plasma IGF-I levels respectively…"

IGF-1 synthesis and release

Excerpted from the University of Virginia Endocrinology syllabus

"…nutritional status is the second most important regulator of IGF-1…" (GH release is the first)

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Feeding colostrum increases circulating insulin-like growth factor I in newborn pigs independent of endogenous growth hormone secretion.

Wester TJ, Fiorotto ML, Klindt J, Burrin DG
Children's Nutrition Research Center, ARS, USDA, Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA.

"…Our objective was to examine the influence of feeding and endogenous GH secretion on circulating IGF-I in colostrum-deprived newborn pigs fed colostrum (n = 4), formula (control, n = 4), or water (n = 4). In another four formula-fed pigs, GH was ablated (GRF-A) with two intravenous injections of a GH releasing-factor antagonist (N-Ac-Tyr1,D-Arg2)-GRF(1-29)-NH2. Blood was serially sampled in all pigs to measure plasma IGF-I and GH profiles. Feeding increased plasma IGF-I concentration two- to fourfold and decreased GH secretion. Despite a more than 80% decrease in the plasma GH in GRF-A pigs, the circulating IGF-I concentration was similar to that in control pigs. In colostrum-fed pigs, plasma IGF-I was higher than that in control pigs, <u>despite equal nutrient intake and lower circulating GH</u>. There were no differences in plasma IGF binding protein (IGFBP)-3 levels among the treatment groups. However, the relative abundance of plasma IGFBP-4 was lower, and that of IGFBP-1 higher, in unfed pigs than in any of the three fed groups. The plasma insulin concentration was not different among fed pigs, but it was lower in unfed pigs. <u>Our results indicate that the circulating IGF-I concentration is more dependent on nutrient intake than on GH</u> in newborn pigs, despite relatively high GH concentrations. However, because the nutrient content in the formula was designed to match that of colostrum, a factor other than nutrient intake and GH was responsible for the maximal increase in circulating IGF-I concentration observed in colostrum-fed pigs…"

Independent effects of food intake and insulin status on insulin-like growth factor-I in young pigs.

Taylor-Roth JL, Malven PV, Gerrard DE, Mills SE, Grant AL
Lilly Research Laboratories, Greenfield, IN 46140, USA.

"…Reduction of food intake was associated with decreased body weight gains, <u>decreased serum IGF-I concentrations, and increased serum GH concentrations</u>. Nutrient restriction also tended to decrease the relative abundance of IGF-I mRNA in liver and skeletal muscle…"

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Clinical utility of insulin-like growth factor assays.

Lee PD, Rosenfeld RG
Department of Pediatrics, Children's Hospital, Denver, Colo.

"…Insulin-like growth I and II (IGF-I and II) mediate many of the peripheral mitogenic actions of growth hormone (GH). The marked dependence of IGF levels on GH adequacy has led to the development of commercial immunoassays for IGF-I (somatomedin-C), and the widespread use of IGF-I levels in the evaluation of short stature. Proper interpretation of IGF-I levels requires consideration of assay methodology, age-related norms, clinical findings, nutritional status, and concurrent hormonal and disease processes. IGF-I levels alone cannot be used to predict stimulated GH response, but may have value in directing the clinical evaluation of a child with short stature. Low IGF-I levels may also be characteristic of a subpopulation of short children with neurosecretory GH deficiency. The role of IGF-II levels in the evaluation of short stature is uncertain, although the combination of low IGF-I and IGF-II levels is more specific for GH deficiency than either value alone. Other clinical applications for IGF assays in pediatrics are also reviewed…"

Nutritional regulation of insulin-like growth factor-I.

Ketelslegers JM, Maiter D, Maes M, Underwood LE, Thissen JP
Department of Internal Medicine, School of Medicine, Catholic University of Louvain, Brussels, Belgium.

"…Several lines of evidence indicate that in the human, insulin-like growth factor-I (IGF-I) is nutritionally regulated. Both energy and protein availability are required for maintenance of IGF-I. Measurements of serum IGF-I constitute a sensitive means for monitoring the response of acutely ill patients to nutritional intervention. Serum IGF-I may also serve as a marker for evaluation of nutritional status. Our findings and those of others in animal models suggest that nutrients influence synthesis and action of IGF-I and its binding proteins (IGFBPs) at multiple levels. In fasting, liver growth hormone (GH) binding is decreased, providing one explanation for decreased IGF-I. In protein restriction, GH receptors are maintained, but there is evidence for a postreceptor defects. The latter results from pretranslational and translational defects. Amino acid availability to the hepatocytes is essential for IGF-I gene expression. Protein malnutrition not only decreases IGF-I production rate, but also enhances its serum clearance and degradation. Finally, there is evidence for selective organ resistance to the growth-promoting effects of IGF-I in protein-restricted rats…"

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By what methods is IGF-1 measured?

Blood Panel

It is already widely known that a measure of serum IGF-1 can be accomplished by testing the blood. However, testing IGF-1 alone is thought by many biochemists to be inadequate in reflecting true GH levels.

Saliva

Salivary insulin-like growth factor-I originates from local synthesis.

Ryan J, Mantle T, McQuaid S, Costigan DC
Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland.

"…Insulin-like growth factor-I (IGF-I) is a GH-dependent growth factor found in its highest concentrations in plasma. It is also measurable in saliva. The origins of salivary IGF-I concentrations were studied. Intracardial administration of Sprague-Dawley rats with 125I-labelled IGF-I and subsequent analysis of plasma and saliva samples by exclusion gel chromatography and SDS-PAGE, followed by autoradiography, demonstrated the apparent inability of IGF-I to cross from the plasma pool through to saliva. 125I-Labelled IGF-I was not chromatographed immediately before injection, resulting in administration of free iodide along with the iodinated peptide. This free iodide was demonstrable in saliva, indicating that movement of substances from plasma to saliva was measurable using the levels of 125I activity administered. Free iodide in saliva was not contributed to by 125I-labelled IGF-I degradation since 125I-labelled IGF-I was shown to be stable in saliva over 24 h. These data indicated that IGF-I in saliva is produced locally. Identification of a 4.7 kb IGF-I mRNA transcript in rat parotid salivary gland was consistent with IGF-I synthesis within that tissue…"

normal population study of human salivary insulin-like growth factor 1 (IGF 1) concentrations from birth through puberty.

Ryan J, Mantle T, Costigan DC
Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland.

"…Insulin-like growth factor 1 (IGF 1) concentrations in mixed saliva samples, collected from a normal population (n = 327, ranging in age from birth to adolescence), were determined by RIA. Salivary IGF 1 concentrations remained steady over a 24-h period when collected at basal rates, but were diminished in saliva samples collected at a maximally stimulated flow rate. A similar pattern was observed for males and females, when IGF 1 levels in saliva were plotted as a function of age.

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The pattern was that of low levels in early childhood, rising with age, peaking in puberty and falling again in late adolescence. Salivary IGF 1 measurement differed from plasma measurement in three ways: 1) salivary IGF 1 concentrations (70 +/- 50 pM) were 100- to 200-fold less than plasma IGF 1 levels; 2) salivary IGF 1 levels in age-matched male and female samples were not different outside of pubertal influences; 3) salivary IGF 1 levels in neonates were highly variable with concentrations ranging up to pubertal concentrations. The study provides salivary IGF 1 reference data for a pediatric population…"

Free insulin-like growth factor I (IGF-I) and IGF-II in human saliva.

Costigan DC, Guyda HJ, Posner BI
Division of Endocrinology and Metabolism, Montreal Children's Hospital-Research Institute, Quebec, Canada.

"…We found that human saliva contains both insulin-like growth factor I (IGF-I) and IGF-II but no significant binding proteins, and that salivary IGF-I levels correlated with plasma GH levels. Mixed saliva had globular proteins precipitated by freezing/thawing. After centrifugation the clear supernatant was used directly in the IGF-I RIA (Van Wyk and Underwood antibody) and in a human placental membrane RRA for IGF-II. The lower limits of detection for IGF-I and IGF-II were 0.7 ng/mL (micrograms/L) and 1.2 ng/mL (micrograms/L), respectively. Iodinated IGF added to saliva was not degraded, as assessed by trichloroacetic acid precipitability and placental membrane binding. In saliva from 14 normal subjects, IGF-I was measurable in all. IGF-II was detectable only in 8 of 14 subjects; the mean value in these 8 subjects was 2.6 +/- 0.6 (+/- SE) ng/mL (micrograms/L). The mol wt of salivary IGF was similar to that of free plasma IGF after acid or neutral pH gel chromatography. Human saliva contained no significant IGF-binding protein. Eluates from neutral gel chromatography of concentrated (20-fold) normal saliva did not inhibit IGF-II binding to placental membrane receptors. Eluted proteins from saliva samples subjected to prior acid gel chromatography failed to bind radiolabeled IGF after neutralization. Saliva samples assayed for binding protein using an amniotic fluid binding protein RIA had values at or below the lower limit of detection [less than 0.06 micrograms eq/mL (mgeq/L)]. Salivary IGF-I concentrations did not change with increasing salivary flow rates above normal, with time of day, or with storage at room temperature for up to 24 h before freezing. The mean IGF-I concentration in mixed saliva from 14 normal young adults (8 men) was 2.3 +/- 0.3 (+/- SE) ng/mL (micrograms/L), and their mean plasma IGF-I level was 315 +/- 27 ng/mL (micrograms/L). Mean salivary IGF-I was significantly lower in 15 patients with GH deficiency [1.3 +/- 0.2 ng/mL (micrograms/L); P less than 0.01] and 8-fold higher in 5 acromegalic patients [17.2 +/- 6.3 ng/mL

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(micrograms/L); P less 0.01]. Removal of their GH adenomas led to a fall in salivary IGF-I to 5.6 +/- 1.3 ng/mL (micrograms/L); P less than 0.05). In summary, saliva contains free IGFs but no significant quantities of specific binding proteins. Salivary IGF-I levels reflect the GH status of the donor…"

Urine

Immunoreactive insulin-like growth factor II in urine.

Zumkeller W, Hall K
Department of Endocrinology, Karolinska Hospital and Institute, Stockholm, Sweden.

"…Insulin-like growth factor II and insulin-like growth factor binding protein-1 were identified and quantified in the urine of 23 healthy subjects between 17 and 76 years of age. IGF-II was measured after separation by gel chromatography at low pH and compared with IGF-I levels in the same samples, whereas IGF binding protein-1 was measured in dialysed urine. Urinary IGF-II was found at much higher concentrations than IGF-I (mean +/- SEM: 717 +/- 69 vs 110 +/- 5 ng/mmol creatinine). The chromatographic profile indicates that pro-IGF-II may also be present. The concentrations of IGF-II appear to be less variable than the other reported parameters. The mean IGF binding protein-1 concentrations in these urine samples was 414 +/- 83 ng/mmol creatinine. IGFs in the urine are in part bound to binding proteins..."

Urinary growth hormone excretion in post-menarcheal adolescent girls with type 1 diabetes.

Aman J, Kroon M, Jones I, Segnestam K, Snellman K
Department of Paediatrics, Orebro Medical Centre Hospital, Sweden.

"…The aim of the present study was to compare measurements of urinary growth hormone (GH), serum insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP3) between two groups of post-menarcheal girls, 13-18 y of age, one comprising 64 type 1 diabetic patients and the other 64 healthy girls matched for age and stage of puberty. GH was determined on two occasions in nocturnal urine samples by using a modification of an immunoradiometric method for serum. Significantly higher urinary GH concentrations but lower IGF-I and IGFBP3 levels were found in diabetic girls than in controls ($p < 0.001$). A significant correlation was found between urinary GH concentrations and the daily dose of insulin (U kg[-1]) ($r = 0.426$, $p = 0.003$). Urinary GH concentrations were also significantly related to HbA1c ($r = 0.380$, $p = 0.003$). In conclusion, disturbances of the GH-IGF-I axis may be evaluated by the use of non-

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invasive urinary GH measurements, which is a simple alternative to frequent sampling of serum GH. Increased GH secretion seems to be related to a great need for insulin and poor metabolic control. More knowledge about underlying causal factors in the disturbed GH-IGF-I axis is required…"

Changes in serum concentrations of growth hormone, insulin, insulin-like growth factor and insulin-like growth factor-binding proteins 1 and 3 and urinary growth hormone excretion during the menstrual cycle.

Juul A, Scheike T, Pedersen AT, Main KM, Andersson AM, Pedersen LM, Skakkebaek NE
Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

"…Few studies exist on the physiological changes in the concentrations of growth hormone (GH), insulin-like growth factors (IGF) and IGF-binding proteins (IGFBP) within the menstrual cycle, and some controversy remains. We therefore decided to study the impact of endogenous sex steroids on the GH-IGF-IGFBP axis during the ovulatory menstrual cycle in 10 healthy women (aged 18-40 years). Blood sampling and urinary collection was performed every morning at 0800 h for 32 consecutive days. Every second day the subjects were fasted overnight before blood sampling. Follicle stimulating hormone, luteinizing hormone (LH), oestradiol, progesterone, IGF-I, IGFBP-3, sex hormone-binding globulin, dihydroepiandrosterone sulphate and GH were determined in all samples, whereas insulin and IGFBP-1 were determined in fasted samples only. Serum IGF-I concentrations showed some fluctuation during the menstrual cycle, with significantly higher values in the luteal phase compared to the proliferative phase ($P < 0.001$). Mean individual variation in IGF-I concentrations throughout the menstrual cycle was 13.2% (SD 4.3; range 0.1-18.3%). There were no cyclic changes in IGFBP-3 serum concentrations and no differences in IGFBP-3 concentrations between the luteal and the proliferative phases. Mean individual variation in IGFBP-3 concentrations throughout the menstrual cycle was 8.8% (SD 2.7; range 3.2-14.1). IGFBP-1 concentrations were inversely associated with insulin concentrations, and showed a significant pre-ovulatory increase that returned to baseline at the day of the LH surge. Fasting insulin concentrations showed large fluctuations throughout the menstrual cycle without any distinct cyclic pattern. No cyclic changes in urinary GH excretion during menstrual cycle were detected. We conclude that, although IGF-I concentrations are dependent on the phase of the menstrual cycle, the variation in IGF-I concentrations throughout the menstrual cycle is relatively small. Therefore, the menstrual cycle does not need to be considered when evaluating IGF-I or IGFBP-3 serum values in women suspected to have GH deficiency…"

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(IGFs) and IGF binding protein 3 in healthy volunteers before and after stimulation with recombinant human growth hormone.

Tonshoff B, Blum WF, Vickers M, Kurilenko S, Mehls O, Ritz E
Department of Pediatrics, University Hospital of Heidelberg, Germany.

"…We examined excretion of urinary insulin-like growth factors I and II (IGF-I and IGF-II) and their major binding protein IGFBP-3 in comparison to their respective serum concentration in nine healthy female volunteers (median age 25 years, range 22-27) under baseline conditions and after stimulation with recombinant human growth hormone (rhGH), 4.5 IU twice daily subcutaneously for a period of 3 days. The IGFs were measured in unconcentrated urine by use of recently developed, highly sensitive radioimmunoassays. The IGFBP-3 was measured by a specific radioimmunoassay. The mean (+/- SD) urinary concentrations of IGF-I (0.08 +/- 0.07 micrograms/l), IGF-II (1.02 +/- 0.47 micrograms/l) and IGFBP-3 (19.1 +/- 6.9 micrograms/l) were two to three orders of magnitude lower than in serum. The ratio of IGF-II over IGF-I concentration in urine (13:1) was five times higher than in serum (2.5:1), and the ratio of IGFBP-3 over the sum of IGF-I and IGF-II in urine (17:1) was four times higher than in serum (4:1). Urinary excretion was 63.3 +/- 46.6 ng.m-2.24h-1 for IGF-I, 1002 +/- 598 ng.m-2.24h-1 for IGF-II and 18039 +/- 4983 ng.m-2.24h-1 for IGFBP-3. Using fast protein liquid exclusion chromatography, only immunoreactive IGFBP-3 components of less than 60 kD were detected in urine, with a major peak at 20 kD. Urinary IGFBP-3 excretion correlated with serum IGFBP-3 ($r = 0.61$, $p < 0.01$) and the glomerular filtration rate ($r = 0.56$, $p < 0.05$) measured by steady-state inulin infusion clearances…"

Cerebro Spinal Fluid

Specific assay for insulin-like growth factor (IGF) II using the IGF binding proteins extracted from human cerebrospinal fluid.

Binoux M, Lassarre C, Gourmelen M

"…A protein-binding assay for insulin-like growth factor II (IGF II) is described. The assay uses IGF binding proteins extracted from human cerebrospinal fluid which have selective affinity for IGF II. IGF I was 9 times less potent than IGF II in displacing [125I]IGF II, and when mixtures of the IGFs were assayed at IGF I/IGF II ratios of 2, 5, and 10, interference from IGF I in the assay was 0%, 5%, and 9%, respectively. Given the serum concentrations of IGF I and IGF II estimated by RIA and by this protein-binding assay, IGF I can be said to have had no cross-reaction when IGF II was assayed in human serum and at most 5% cross-

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reaction in the case of rat serum. After separation of IGFs from their binding proteins by acidic gel filtration, serum IGF II levels (mean +/- SE) measured by this method were 1322 +/- 66 ng/ml in normal adults, 500 +/- 65 ng/ml in patients with total GH deficiency, 1327 +/- 69 ng/ml in untreated acromegalic patients, and 1817 +/- 145 ng/ml in uremic patients undergoing chronic hemodialysis. In postpubertal young rats, the mean serum IGF II level was 43 +/- 2.6 ng/ml and after hypophysectomy it was 16 +/- 2.4 ng/ml. Although the IGF II levels in man and in the rat were different, they appeared to be similarly GH dependent, although less so than IGF I. In view of the sensitivity (0.03 ng IGF II) and the specificity of this assay, the small quantities of cerebrospinal fluid required (1 mu leq/assay tube) and its applicability for IGF II measurement in several species, the use of this assay for measuring IGF II in a variety of biological media can be envisaged…"

Amniotic Fluid

Insulin-like growth factors in amniotic fluid.

Merimee TJ, Grant M, Tyson JE

"…The concentrations of insulin-like growth factors I and II (IGF-I and IGF-II) in amniotic fluid were determined by specific immunoassays in 58 women. IGF-I concentrations were constant throughout gestation at approximately 20 ng/ml; the mean IGF-II concentration was 114 +/- 13 (+/- SE) ng/ml at the earliest period of gestation studied and remained unchanged at 26 to 33 weeks despite a greater than 50% decrease in amniotic fluid total protein. A precipitous decrease in IGF-II concentration occurred at term which was not explainable by alterations in total amniotic fluid protein concentration. The concentrations of IGF-I and IGF-II in amniotic fluid did not correlate with concentrations of these factors in maternal serum (r = 0.08 and 0.09, respectively). [125I]IGF-I and [125I]IGF-II, after incubation with amniotic fluid, bound to a 40-45 K protein (or proteins). A carrier protein of greater mol wt, as in serum, was not detected. These findings indicate that there is dynamic control of IGF in amniotic fluid during normal pregnancy…"

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Bile

Presence of insulin-like growth factor I but absence of the binding proteins in the bile of rats.

Kong W, Philipps AF, Dvorak B, Anderson GG, Lake M, Koldovsky O
Department of Pediatrics, Steele Memorial Children's Research Center, Furrow Research Laboratory, University of Arizona College of Medicine, Tucson 85724.

"…Whereas insulin-like growth factor I (IGF-I) has been found in various body fluids from different species, the presence or absence of IGF and associated binding proteins (IGFBPs) in bile has not been clearly defined. Bile concentration of IGF-I was measured in this study and found to be highest in the neonate and lowest in adult rats [133 +/- 15.9, 79.4 +/- 10.5, 45.3 +/- 12.7 ng/ml (mean +/- SE) in 12-day-old, 33-day-old, and adult rats, respectively]. When bile delivery rates of IGF-I (i.e., the product of IGF-I concentration in bile and the biliary flow rate) were calculated, IGF-I delivery was highest in weanling rats (469 pg.h-1.g body wt-1). When expressed as amount of IGF-I in bile delivered per day, however, delivery rates rose from 0.2 micrograms/day in the suckling and remained constant at 1.6-1.7 micrograms/day in both weanling and adult animals. Bile samples exposed to a placental membrane IGF receptor preparation showed significant dose-dependent inhibition of binding of native IGF-I. Because no IGF binding proteins were identified by Western ligand blot or by Sephadex gel chromatography, the results suggest the presence of biologically significant quantities of bioactive IGF-I in bile. We speculate that IGF-I in bile may play an important role in the growth of the gastrointestinal tract, both in the suckling as well as later in life…"

Can IGF-1 be too high?

Prostate Cancer Risk

Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study.

Wolk A, Mantzoros CS, Andersson SO, Bergstrom R, Signorello LB, Lagiou P, Adami HO, Trichopoulos D
Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden.
Alicja.Wolk@mep.ki.se

"…BACKGROUND: Recent epidemiologic investigations have suggested an association between increased blood levels of insulin-like growth factor 1 (IGF-1) and increased risk of prostate cancer. Our goal was to determine whether an association exists between serum levels of IGF-1 and one of its binding proteins, insulin-like growth factor-binding protein 3

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(IGFBP-3), and prostate cancer risk. METHODS: An immunoradiometric assay was used to quantify IGF-1 levels and IGFBP-3 levels in serum samples as part of a population-based, case-control study in Sweden. The study population comprised 210 patients with newly diagnosed, untreated prostate cancer and 224 frequency-matched control subjects. Data were analyzed by use of unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Reported P values are two-sided. RESULTS: The mean serum IGF-1 level for case patients (158.4 ng/mL) was significantly higher than that for control subjects (147.4 ng/mL) (P = .02); corresponding mean serum IGFBP-3 levels were not significantly different between case patients (2668 ng/mL) and control subjects (2518 ng/mL) (P =.09). We found a moderately strong and statistically significant (P = .04) positive association between serum levels of IGF-1 levels and risk of prostate cancer (OR = 1.51; 95% CI = 1.0-2.26 per 100 ng/mL increment); the association was particularly strong for men younger than 70 years of age (OR = 2.93; 95% CI = 1.43-5.97). No association was found between serum IGF-1 levels and disease stage. Serum IGFBP-3 levels were not significantly associated with increased risk of disease, and adjustment for IGFBP-3 had little effect on the association between IGF-1 levels and risk of prostate cancer. CONCLUSION: Elevated serum IGF-1 levels may be an important predictor of risk for prostate cancer. However, our results do not support an important role for serum IGFBP-3 as a predictor of risk for this disease…"

Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia.

Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO
Department of Epidemiology and Harvard Center for Cancer Prevention, Harvard School of Public Health, Boston, Massachusetts 02115, USA.

"…Blood samples were collected from 52 incident cases of histologically confirmed prostate cancer, an equal number of cases of benign prostatic hyperplasia (BPH) and an equal number of apparently healthy control subjects. The three groups were matched for age and town of residence in the greater Athens area. Steroid hormones, sex hormone-binding globulin, and insulin-like growth factor 1 (IGF-1) were measured in duplicate by radioimmunoassay in a specialized US centre. Statistical analyses were performed using multiple logistical regression. The results for IGF-1 in relation to prostate cancer and BPH were adjusted for demographic and anthropometric factors, as well as for the other measured hormones. There was no relation between IGF-1 and BPH, but increased values of this hormone were associated with increased risk of prostate cancer; an increment of 60 ng ml(-1) corresponded to an odds ratio of 1.91 with a

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95% confidence interval of 1.00-3.73. There was also some evidence for an interaction between high levels of testosterone and IGF-1 in relation to prostate cancer. This finding suggests that, in addition to testosterone, IGF-1 may increase the risk of prostate cancer in humans…"

Breast Cancer Risk

It has been consistently shown that sustained rises in IGF-1, rises like those claimed by amino acid based, IGF-1 stimulating HGH products, can contribute to a heightened risk of Breast, Colon and Pancreatic cancers among others. Please see the following abstracts.

The insulin-like growth factors and breast cancer--revisited.

Yee D
University of Texas Health Science Center at San Antonio, 78284-7884, USA.
yeed@uthscsa.edu

"…In 1992, a special issue of Breast Cancer Research and Treatment was devoted to the insulin-like growth factors and breast cancer. In that issue, identification of the key components of the IGF system was reviewed and their potential role in breast cancer growth was described. In this issue, we revisit the IGF system with particular attention to data that further supports their role in the growth regulation of breast cancer. Several new facets of the IGF system are described, and several laboratories have more clearly defined how each individual component of the IGF system may influence breast cancer biology…"

IGF-I physiology and breast cancer.

Pollak M
Department of Medicine, McGill University, Montreal, Quebec, Canada.

"…Recent studies imply that IGF-I levels vary greatly between normal women, and that premenopausal breast cancer risk is increased among women with higher IGF-I levels. It is known that tamoxifen lowers IGF-I levels, but further research is needed to determine whether antiestrogens will be of particular value in risk reduction for women with high IGF-I levels, and also to determine if IGF-I levels can indeed be used as an intermediate endpoint in risk reduction interventions. With respect to adjuvant therapy, we currently have convincing data that antiestrogens have moderate IGF-I lowering actions, but it remains unclear to what extent these contribute to the therapeutic effect of these compounds. Ongoing trials are addressing this question, as well as the hypothesis that interventions that increase IGF-I suppression will be associated with reduced relapse rates…"

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Circulating concentrations of insulin-like growth factor-I and risk of breast cancer.

Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M
Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA.

"…BACKGROUND: Insulin-like growth factor (IGF)-I, a mitogenic and antiapoptotic peptide, can affect the proliferation of breast epithelial cells, and is thought to have a role in breast cancer. We hypothesised that high circulating IGF-I concentrations would be associated with an increased risk of breast cancer. METHODS: We carried out a nested case-control study within the prospective Nurses' Health Study cohort. Plasma concentrations of IGF-I and IGF binding protein 3 (IGFBP-3) were measured in blood samples collected in 1989-90. We identified 397 women who had a diagnosis of breast cancer after this date and 620 age-matched controls. IGF-I concentrations were compared by logistic regression with adjustment for other breast-cancer risk factors. FINDINGS: There was no association between IGF-I concentrations and breast-cancer risk among the whole study group. In postmenopausal women there was no association between IGF-I concentrations and breast-cancer risk (top vs bottom quintile of IGF-I, relative risk 0.85 [95% CI 0.53-1.39]). The relative risk of breast cancer among premenopausal women by IGF-I concentration (top vs bottom tertile) was 2.33 (1.06-5.16; p for trend 0.08). Among premenopausal women less than 50 years old at the time of blood collection, the relative risk was 4.58 (1.75-12.0; p for trend 0.02). After further adjustment for plasma IGFBP-3 concentrations these relative risks were 2.88 and 7.28, respectively. INTERPRETATION: A positive relation between circulating IGF-I concentration and risk of breast cancer was found among premenopausal but not postmenopausal women. Plasma IGF-I concentrations may be useful in the identification of women at high risk of breast cancer and in the development of risk reduction strategies. Additional larger studies of this association among premenopausal women are needed to provide more precise estimates of effect…"

Insulin and related factors in premenopausal breast cancer risk.

Del Giudice ME, Fantus IG, Ezzat S, McKeown-Eyssen G, Page D, Goodwin PJ
Mount Sinai Hospital, Division of Clinical Epidemiology of the Samuel Lunenfeld Research Institute, Toronto, Ontario, Canada.

"…BACKGROUND: Insulin and insulin-like growth factor I (IGF-I) are important mitogens in vitro and in vivo. It has been hypothesized that these factors may play an important role in the development of breast

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cancer. METHODS: A case-control study comparing plasma insulin levels in 99 premenopausal women with newly diagnosed node-negative invasive carcinoma of the breast and 99 age-matched controls with incident biopsied non-proliferative breast disease (NP) was conducted. Women with known diabetes were excluded. RESULTS: For the entire study group, mean age was 42.6 +/- 5.1 years and mean weight was 62.9 +/- 10.3 kg. After adjustment for age and weight, elevated insulin levels were significantly associated with breast cancer, Odds Ratio (OR) for women in the highest insulin quintile versus the lowest quintile = 2.83 (95% Confidence Interval [CI] 1.22-6.58). There were no statistically significant differences between cases and controls for IGF-I and IGFBP-1 levels. However, after adjustment for age, the association between plasma levels of insulin-like growth factor binding protein 3 (IGFBP-3) and breast cancer approached statistical significance; OR for highest quintile versus lowest quintile of IGFBP-3 being 2.05 (95% CI, 0.93-4.53). All results were independent of diet and other known risk factors for breast cancer. CONCLUSION: Circulating insulin levels and possibly IGFBP-3 levels are elevated in women with premenopausal breast cancer. This association may reflect an underlying syndrome of insulin resistance that is independent of obesity…"

rBGH, IGF-1, and Cancer

(Think Before You Drink, by Ben Davis, Conscious Choice, November/December 1995)

"…In addition to the unusual growth patterns IGF-1 seems to promote, there is strong evidence of a cancer risk from IGF-1. Science Magazine recently reported that IGF-1 increases the malignancy of human breast cancer cells, including their invasiveness and ability to spread to distant organs. A study in the New England Journal of Medicine confirmed that growth factors such as IGF-1 are responsible for the promotion of breast cancer cells. IGF-1 has been similarly linked with colon cancer." "A leading British medical journal recently reported that the breast cells of fetuses and infants are particularly susceptible to hormonal influences. Such imprinting by IGF-1 may increase future breast cancer risks, and may also increase the sensitivity of the breast to subsequent unrelated risks such as mammography and the carcinogenic and estrogen-like effects of pesticide residues in food, particularly in pre-menopausal women…" "…Excessive IGF-1 also wreaks havoc on the gastro-intestinal tract. A recent study on acromegaliacs--people who suffer from excessive growth of the their head, hands, face, and feet--shows that they have a higher incidence of tumors in the colon (a portion of the intestines). Acromegaly is caused by

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an excessive amount of natural IGF-1 in the human body. In another recent study, IGF-1 was exposed to human cells taken from the human gut. The study reported that IGF-1 promoted cell division." "Another recent study published in Cancer Research shows clearly that IGF-1 is required for the establishment and maintenance of tumors. This study found that IGF-1 protects the cells from programmed cell death. IGF-1 was shown to accelerate tumor growth and effect the aggressiveness of tumors. As IGF-1 levels were decreased, cell death took place…"

Insulin-like growth factor-I in relation to premenopausal ductal carcinoma in situ of the breast.

Bohlke K, Cramer DW, Trichopoulos D, Mantzoros CS
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

"…We evaluated the association of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) with risk of breast cancer in a study of 94 cases of premenopausal ductal carcinoma in situ and 76 controls. Compared with women in the lowest tertile of IGF-I, women in the upper two tertiles of IGF-I had an elevated risk for ductal carcinoma in situ. Conversely, compared with women in the lowest tertile of IGFBP-3, women in the upper two tertiles of IGFBP-3 had a decreased risk for ductal carcinoma in situ. After grouping women on the basis of both IGF-I and IGFBP-3, women in the highest two tertiles of IGF-I and the lowest tertile of IGFBP-3 were at notably higher risk than women in the lowest tertile of IGF-I and the highest two tertiles of IGFBP-3 (odds ratio = 3.7; 95% confidence interval = 1.1-12.2). We conclude that the combination of high IGF-I and low IGFBP-3 may increase the risk of premenopausal ductal carcinoma in situ…"

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Other Important Blood Panel biomarkers for GH production

Sex Hormones

Osteocalcin

BP3/BP2 Ratios (IGF-Binding Proteins)

DHEA

Pregnenolone

Thyroid Stimulating Hormone

Thyroid, free T3

Thyroid, free T4

FSH

LH.

Is Oral Growth Hormone Real or Rip-Off?

Orally active growth hormone secretagogues: state of the art and clinical perspectives.

Ghigo E, Arvat E, Camanni F
Department of Internal Medicine, University of Turin, Italy.

"…Growth hormone secretagogues (GHS) are synthetic, non-natural peptidyl and nonpeptidyl molecules with potent stimulatory effect on somatotrope secretion. They have no structural homology with growth hormone-releasing hormone (GHRH) and act via a specific receptor, which has now been cloned and is present at both the pituitary and hypothalamic level. This evidence strongly suggests the existence of a still unknown natural GHS-like ligand. Several data references favor the hypothesis that GHS could counteract somatostatinergic activity at both the pituitary and hypothalamic level and/or, at least partially, via a GHRH-mediated mechanism. However, the possibility that they act via an unknown hypothalamic factor remains open. GH-releasing peptide-6 (GHRP-6) is the first hexapeptide studied extensively in humans. More recently, peptidyl superanalogues GHRP-1, GHRP-2 and hexarelin, and nonpeptidyl mimetics, such as the spiroindoline derivative MK-677, have been synthesized and their effects have been studied in humans. The GH-releasing activity of GHS is marked, dose related and reproducible after

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intravenous, subcutaneous, intranasal and even oral administration. The effect of GHS is partially desensitized but prolonged, intermittent oral administration increases insulin-like growth factor I (IGF-I) levels. The GH-releasing effect of GHS undergoes age-related variations; it increases from birth to puberty, remains similar in adulthood and decreases with ageing. The effect of GHS on GH release is synergistic with that of GHRH, while it is only partially refractory to inhibitory influences, which nearly abolish the effect of GHRH. GHS maintain their GH-releasing activity in some somatotrope hypersecretory states such as acromegaly, anorexia nervosa, hyperthyroidism and critical illness. The GH response to GHS has been reported clear although reduced in GH deficiency, obesity and hypothyroidism, while it is strongly reduced in patients with pituitary stalk disconnection or Cushing's syndrome. In short children, elderly subjects, critically ill patients and even in adult patients with GH deficiency an increase of IGF-I has been shown after GHS treatment. These data indicate that treatment with orally active GHS in humans enhances the activity of the GH-IGF-I axis and could be clinically useful…"

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Pregnenolone_____

Thyroid Stimulating Hormone _____

.....Thyroid, free T3 _____

.....Thyroid, free T4_____

Testosterone (total) _____ug/dl

.....Testosterone (free)_____

Estradiol_____ug/dl (women;week before menstruation)

FSH_____

LH.. _____

Somatomedin C (IGF-1) (Corning Lab,CA.) _____

Osteoporosis Screen (Dual Photon Densitometry) (optional) _____

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