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GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR-I IN SYMPTOMATIC AND ASYMPTOMATIC PATIENTS WITH DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)

Charles W. Denko, Betty Boja and Charles J. Malemud

Departments of Medicine and Anatomy, Case Western Reserve University School of Medicine, and The Research Institute of University Hospitals of Cleveland, Cleveland, Ohio 41106-4946

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1. ABSTRACT

Basal serum growth hormone (GH) and insulin-like growth factor-I (IGF-I) concentration was measured by radioimmunoassay in patients with diffuse idiopathic skeletal hyperostosis (DISH) with muscle and joint pain and stiffness (symptomatic group) and in DISH patients without these constitutional clinical symptoms (asymptomatic group), but with persistent radiographic evidence of DISH. Serum GH and IGF-I was also measured in normal volunteers (control group) matched for gender and age to patients with DISH. Symptomatic male and female DISH patients had elevated serum GH and IGF-I concentration when compared to the control group. Asymptomatic DISH patients had serum GH levels that were significantly lower than their symptomatic counterparts. Clinical improvement did not alter serum IGF-I concentration. We conclude that serum GH concentration could be employed to monitor clinical remission in DISH.

2. INTRODUCTION

Growth hormone (GH), a neuropeptide of 191 amino acids is primarily a promoter of skeletal long bone growth and development and chondrocyte maturation (1, 2). However, there is increasing clinical and experimental evidence suggesting that GH also plays a key role in inflammation as well. Muscle and joint pain with stiffness and swelling in rheumatic disorders such as osteoarthritis (OA) and diffuse idiopathic skeletal hyperostosis (DISH) are characterized by elevated serum GH levels (3-6). Altomonte *et al.* (7) reported that while basal serum GH values were similar in DISH patients and controls, intravenous insulin resulted in a significant increase in serum GH after 30 min. and 45 min. in DISH patients when compared to controls.

Additional clinical evidence points to a role of GH in clinical symptoms in the rheumatic disorders. For example, patients exhibiting persistent radiographic evidence consistent with OA but no clinical symptoms of disease (asymptomatic OA) had serum GH levels in the normal range (8). Furthermore, the constitutional symptoms of hypertrophic pulmonary osteoarthropathy, a condition resembling rheumatoid arthritis, were relieved when agents that inhibited GH were employed (9). In acromegaly, late-stage arthopathy resembles a pattern seen in OA (10). In patients with acromegalic arthritis, muscle and joint pain with stiffness improved only when medical therapy reduced elevated serum GH levels to normal levels (11). Spine and heel entheses and new bone formation in the skull in patients with acromagaly satisfied accepted criteria for

DISH (12), suggesting that a common metabolic defect may be responsible for both acromegaly and DISH.

The clinical evidence suggesting a role for GH in arthritis is bolstered by experimental evidence which also links GH to manifestations of symptomatic arthritis and inflammation. Thus, Reinhart and Li could experimentally-induce arthritis by injecting rats with hypophyseal GH (13). The induced arthritis resembled both OA and rheumatoid arthritis. Furthermore, Berczi *et al*. (14) could not induce arthritis with adjuvant in hypophysectomized rats unless GH or prolactin was added to the induction protocol. In this regard, GH and prolactin appear to have a similar metabolic action on cartilage in that they both promote incorporation of radioactive sulfur into proteoglycans (15).

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by atypical florid proliferation of bone with large spurs or marginal osteophytes in the form of anterior osseus ridges (16, 17). Spinal stiffness is a common manifestation of DISH although in many clinical presentations spinal movement and pain is minimal and joint symptoms often extend to peripheral joints other than the spine which may include elbows, hips, knees and ankles among other joints (18). Although older studies suggested that serum GH and IGF-I were normal in patients with DISH (19, 20), more recent studies indicated that serum GH and IGF-I concentration were elevated in patients with clinical symptoms of DISH consisting primarily of muscle pain and joint stiffness (6). Elevated GH levels could be consistent with a pathogenetic contribution of GH to inflammation and aberrant bone growth in DISH.

The present study was conducted to determine whether serum GH and IGF-I which are metabolically linked in an autocrine/paracrine axis (21, 22) and which are elevated in DISH patients with clinical symptoms (6) become comparable to serum GH and IGF-I concentrations in age-and gender-matched control groups when DISH patients become clinically asymptomatic. This was accomplished by comparing patients with DISH who exhibited muscle and joint pain to patients with radiographically persistent DISH whose clinical symptoms had subsided in the course of normal care in the clinic and after medical therapy with steroids and/or non-steroidal anti-inflammatory drugs (NSAIDs).

3. MATERIALS AND METHODS

3.1. Patient Recruitment and Assignment to Group

This study was performed over several years in the Arthritis Clinics of University Hospitals of Cleveland and the Veterans Administration Medical Center (Wade Park Division, Cleveland, Ohio). The study protocol was approved by the Institutional Review Board of both hospitals. All participants were volunteers who gave informed consent.

Patients with DISH met the following criteria for inclusion in the study. All DISH patients were 45 years or older with symptoms of pain in the spine and characteristic radiological changes in the involved areas consisting of widened intervertebral disk space and exuberant osteophytoses (18).

Patients with DISH had inflammation as defined by a biochemical test, namely synthesis of acute phase reactants as well as by eliciting pain by pressing on the affected joints with restricted range of motion. In addition to these mandatory criteria for inclusion, many DISH patients also exhibited enlarged peripheral joints and exostoses of hands and to a lesser extent, feet. Radiographic evidence of osteophytes and joint space narrowing were evaluated at the time of entry into the study.

Patients with DISH were routinely treated with corticosteroids or with various NSAIDs such as ibuprofen, ketoprofen, diclofenac, naproxen, indomethacin, sulindac, tolmetin, piroxicam or salicylates for various periods of time. Steroids or NSAIDs reduced joint pain and stiffness in many patients to whom they were administered. Patients used these medications as long as symptoms persisted or until pain disappeared and function improved. Patients were routinely questioned at each clinic visit about muscle and joint pain and range-of-motion. As there are no published quantitative criteria for improvement in the activities of daily living in patients with DISH, these subjects were routinely evaluated during clinic visits and any changes in range-of-motion, gait and ability to stand from a chair noted. The steroid or NSAID dose effective in controlling pain and/or joint stiffness was discussed with patients. Any changes in NSAID dose and frequency of use required to control pain was routinely evaluated and adjustments in dosage made during the course of study. An overall assessment of clinical status was performed by both patient and physician using standard criteria for clinical improvement. These criteria included, an assessment of range of spinal motion, grip strength, palpation of involved joints for pain, swelling of peripheral joints, and x-ray changes, especially those involving joint space in the spine and radiographic evidence of osteophytes.

DISH patients were considered asymptomatic if their clinical status improved during customary care in the clinic after follow-up. These patients were maintained on NSAIDs. If they were asymptomatic, they exhibited no muscle pain or joint pain and stiffness as measured by an improvement in spinal range-of-motion. X-ray was employed to determine whether spine, hands or feet continued to show evidence of exostoses, if osteophytes had resorbed or if narrowing of the joint space had ceased to progress.

A control group consisting of normal visitors to the hospitals and hospital personnel were matched for gender and age to the DISH patients. All persons assigned to the control group were evaluated by a physician to avoid including any persons with underlying rheumatic disorders. Relatives of DISH patients were excluded from the study to avoid including persons with genetic predisposition to develop DISH.

3.2. Serum GH, IGF-I and Glucose assays

3.2.1. Blood Collection

Blood was drawn by venipuncture, clotted at room temperature, centrifuged and serum removed. Serum aliquots were produced and stored at -70C until assayed.

Table 1. Hand and Feet Exostoses in Symptomatic DISH patients

Gender	Patient	Extraspinal Exostoses	
		Hands	**Feet**
Male	C.L.	Yes	No
	G.M.	Yes	No
	M.P.	Yes	No
	V.S.	Yes	No
	L.M.	Yes	No
	F.K.	Yes	No
	E.M.	Yes	No
	T.K.	†	Yes
	F.S.	†	No
	J.J.	†	†
	C.C.	†	No
	B.O.	†	†
	J.M.	†	No
	R.P.	No	†
	M.H.	†	†
Female	R.S.	Yes	No
	E.D.	No	†
	S.G.	†	†
	M.W.	†	†
	C.S.	†	No

All patients showed evidence of exostoses in the spine. In some cases X-rays of the hands, wrist or feet were then examined for exostoses. The presence (Yes) or absence (No) of exostoses in hands and/or feet is indicated. In several cases (†) confirmation of exostoses in spine precluded further examination of hand or feet x-rays.

Blood from DISH patients and from controls were treated in an identical manner. Blood samples were included in the study if the blood glucose level was in the euglycemic range, i.e. 65-130 mg/dl. This basal metabolic state for glucose was attained after an overnight fast of 4 hrs. or more. Hyperglycemic and hypoglycemic samples were excluded because these variations might affect GH levels. Indeed, DISH is associated with adult onset type II diabetes (23).

3.2.2. Serum GH Radioimmunoassay (RIA)

The GH assay is a disequilibrium RIA employing the serum sample and guinea pig anti-human serum followed by incubation as previously reported (4-6). After the initial incubation, ^{125}I-GH was added and the incubation continued. This was by addition of precipitation complex, second antibody and polyethylene glycol (PEG) as recommended by the manufacturer (INCSTAR, manual for human GH, No. 07130). Because serum GH levels fluctuate, the basal physiologic level was defined by the normoglycemic state (24). Nearly all blood samples were collected between 9:30AM and 12:30AM. A fasting blood specimen is recommended by INCSTAR, but is not required. In the normal fasting individual, the baseline value for GH approaches zero. In the GH RIA employed in this study, the assay was modified for low GH values (predicted in the control group) by plotting the standard curves on log-logit paper which produces a straight line and by employing a Beckman 5500 ?-counter and associated computer which computes the lowest detectable values for each serum sample.

Standard control sera were provided with each assay kit to ensure validation of the GH RIA. The INCSTAR Quality Control Laboratory has determined the range for normal individuals calibrated against the World Health Organization standard 66/127. These values are included on the quality control graph included with each kit. The evaluation for GH for low to medium values gave the following data: intrakit coefficient of variation (CV) for 10 assays, 6.8%; interkit CV for 10 assays, 10.5%. Cross-reactivity of the anti-GH antibody was 0.8% with each of the following human peptides: insulin, prolactin, ß-endorphin, follicle-stimulating-hormone, leuteinizing hormone, thyroid stimulating hormone, chorionic gonadotropin, placental lactogen and adrenocorticotropin. The minimal detectible GH level was 0.4 ng/ml.

3.2.3. Serum IGF-I RIA

The IGF-I RIA employed a double antibody disequilibrium assay which included an octadecasilyl-silica column extraction of the serum sample prior to assay (4-6). After extraction, the RIA was performed by adding the serum sample to rabbit anti-IGF-I antibody followed by incubation for 2 hrs. The ^{125}I-IGF-I tracer pre-precipitated tracer was added for 20 hrs. followed by goat anti-rabbit precipitating complex with PEG, all added in one step (INCSTAR, manual for IGF-I, No. 53065). After 2 hrs. at 4C, the sample was centrifuged, the supernate discarded and the precipitate counted in a Beckman 5500 ? counter.

Quality control studies gave the following results: intrakit CV, 10 assays, 8%; interkit CV, 10 assays, 5.6%. The sensitivity of the method was defined as the apparent concentration at 3 standard deviations at maximum binding. The anti-IGF-I antibody cross-reacted with other peptides as follows: 1% with IGF-II, human GH, fibroblast growth factor, transforming growth factor and platelet derived growth factor. The minimum detectable IGF-I concentration in serum was 2 nmols/L.

3.2.4. Serum Glucose Assay

Serum glucose was measured by the hexokinase method (Sigma, St. Louis). Other hexoses, e.g. fructose and mannose are detected but are only present in trace amounts. Quality control evaluation gave the following results: intrakit CV, 10 assays, 8%; interkit CV, 10 assays, 8%.

3.3. Statistical Evaluation

For evaluation of data, we employed a standard technique comparing groups of different sizes, the one-tailed Student's t test, using the mean and standard deviation (4-6). A p-value = 0.05 was considered significant.

4. RESULTS

4.1. X-ray Evidence of Exostoses in DISH Patients

Exostoses, a pathological characteristic of DISH was confirmed by examining x-rays of the spine, hands and feet (Table 1). Among the male DISH patients, exostoses was found in thoracic (6/15), cervical (6/15) and lumbar/sacral (3/15) spine. Two male patients (M.P. and L.M.) presented with exostoses in the spine, hands and feet whereas 5 males had exostoses in the hands only (Table 1).

Table 2. Serum Growth Hormone (GH) and Serum Insulin-like Growth Factor-I (IGF-I) in Controls and Symptomatic and Asymptomatic DISH Patients

Female	**Control (C)**	**Symptomatic (S)**	**Asymptomatic (A)**
GH (ng/ml)[1]	1.2 ± 0.36	1.7 ± 0.53 [2]	0.74 ± 0.18 [6]
IGF-I (nmol/L)[1]	16.9 ± 5.0	21.0 ± 6.0 [3]	19.6 ± 6.0
N	15	15	10
Male	Control (C)	Symptomatic (S)	Asymptomatic (A)
GH (ng/ml)[1]	0.83 ± 0.42	1.2 ± 0.20 [4]	0.57 ± 0.18 [7]
IGF-I (nmol/L)[1]	19.3 ± 5.0	24.9 ± 9.0 [5]	21.0 ± 7.0
N	17	14	11

[1] Mean ± S.D., [2] p = 0.01 (C v. S), [3] p = 0.05 (C v. S), [4] p= 0.002 (C v. S), [5] p= 0.02 (C v. S), [6] p = 0.001 (S v. A), [7] p= 0.0005 (S v. A), Basal serum GH and IGF-I concentrations were measured by RIA (see text for details).

In all, 7/15 males had confirmed exostoses in either hands, feet or both. In a smaller series of female DISH patients, 4/5 had confirmed spine exostoses, but only 1/5 female DISH patients had hand exostoses which involved the wrist.

4.2. Serum GH and IGF-I concentration in age- and gender-matched normal controls and in patients with symptomatic and asymptomatic DISH

Baseline values for serum GH and IGF-I concentrations in an age- and gender-matched control group were obtained for comparison to patients with DISH (Table 2). Control group values were comparable to values obtained in previous studies (5, 6). As previously reported (5, 6), both female and male patients with symptomatic DISH had significantly elevated serum GH and IGF-I levels compared to controls (Table 2), By contrast, female and male DISH patients classified as asymptomatic by rehabilitation and other objective clinical criteria had a significantly lower serum GH concentration than the symptomatic DISH patients (Table 2). However, while female asymptomatic DISH patients had significantly lower serum GH levels compared to either female symptomatic DISH patients or female controls, male asymptomatic DISH patients tended to have lower serum GH levels, but this did not reach significance (Table 2). Asymptomatic DISH patients failed to show a reciprocal change in serum IGF-I concentration when compared to symptomatic DISH patients, where serum IGF-I concentration was comparable to the values in the control group (Table 2).

Several patients with DISH were studied longitudinally over several months duration. Patient J.P. was studied over a period of 23 months. A representative pattern of changes in serum GH concentration was seen in this patient. J.P. initially presented with constitutional symptoms of DISH and a serum GH concentration of 1.5 ng/ml. J.P.was maintained on NSAIDs and intra-articular steroids and 9 months later was considered to be free of muscle pain and joint symptoms. At that time, the serum GH was 0.86 ng/ml and 3 months later, 1.2 ng/ml. During this entire period of study, there was no change in the serum IGF-I concentration.

4.3. Radiography of asymptomatic DISH patients

It was not possible to obtain satisfactory radiological imaging to determine whether or not sufficient changes had occurred in our DISH patients to warrant the conclusion that joint space narrowing progression was suppressed as a consequence of improvement in clinical status. However, osteophytes persisted in the asymptomatic DISH patients.

6. DISCUSSION

Tissue homeostasis is maintained by complex and interactive biochemical alterations occurring at the molecular, cellular and tissue levels which involves specific metabolic regulators, and in many cases, acute phase reactants, largely formed in the liver under the control of GH and other stimuli (25). A common pathway by which GH induces inflammation is illustrated by the presence of elevated GH concentration in synovial fluid removed from patients with painful and swollen knees due to OA, gout, pseudogout, rheumatoid arthritis and DISH (5). Elevated GH concentration in the synovial fluid must be derived from a site within the joint space since the concentration of GH in synovial fluid exceeded that found in the peripheral blood (5). We have previously postulated that elevated serum GH represents potentially toxic levels which inhibit cartilage metabolism and form the basis for considering changes in GH as the underlying metabolic disturbance in OA among other rheumatic disorders (3). The significantly higher serum GH concentration seen in clinically symptomatic OA patients also results in elevated GH concentration in erthyrocytes (3, unpublished data). This provides a putative mechanism for increasing the concentration of GH in the peripheral circulation, and if GH is effectively transported into the synovial space, could result in elevated GH.

DISH patients who became asymptomatic used NSAIDs and/or steroids and their clinical status improved during continuity of care in the clinic. These patients exhibited no muscle pain or joint pain with stiffness (as measured by improved spinal range of motion). The time course to reach this clinical outcome was variable. DISH patients who remained symptomatic also were routinely treated with NSAIDs, but their clinical symptoms did not resolve over the same time period as those DISH patients who became asymptomatic.

Clinically, the asymptomatic state in DISH patients was determined in a manner similar to a previously reported assessment of clinical remission in OA (8). As noted, DISH patients required a variety of medicines, including salicylate as aspirin, NSAIDs and analgesics.

DISH patients who became asymptomatic had been taking these medications previously, but when the serum GH levels were obtained, required no medication. Thus, NSAID use gradually diminished over time and patients were re-evaluated in the medical clinic for continuity of medical care. As noted, serum GH concentration was significantly lower in asymptomatic DISH patients when compared to the DISH patients who remained symptomatic (Table 2). The reason(s) why all DISH patients did not respond to NSAID or other therapies in a similar fashion with concomitant changes in other clinical measurements was not clear. This could simply be a measure of responders and non-responders to NSAID therapy which may be typical of the rheumatic disorders, or other factors which contribute to the persistence of clinical symptoms in DISH. Whether clinical remission in DISH was brought about only via NSAID inhibition of cyclooxygenase or other pathways related to eicosanoid synthesis which are pro-inflammatory must also be considered. However, to our knowledge no direct link between inhibition of cyclooxygenase I/II and effects on GH synthesis patterns has been established.

In the previously published study which compared symptomatic and asymptomatic OA patients (8), serum GH concentration was comparable to a control group after symptoms of OA characterized as joint pain and stiffness subsided. In symptomatic OA patients (n=24; mean age ± S.D., 66 ± 11), serum IGF-I concentration was lower than in an aged-matched control population (n=24; mean age ± S.D., 63 ± 10) employed for comparison with the OA patients at that time (8). Hochberg *et al*. (26) could not confirm a reduced serum IGF-I concentration in clinically-active knee OA which was also stratified according to the Kellgren-Lawrence scoring system (27) and after adjustment for age-related changes in IGF-I were taken into account. The reasons for the discrepancy between that study and previously reported studies from this laboratory (4-6) remain unclear, but do not appear to represent a failure to include age as a potential confounder (28,29) in this and past analyses.

Schouten *et al*. (29) studied serum IGF-I in patients with radiographic OA and found that serum IGF-I correlated best with osteophyte growth and overall disease progression. In the present study of patients with DISH, patients with symptoms had both elevated serum GH and IGF-I concentrations compared to the control group suggesting an important difference between serum GH and IGF-I responses in symptomatic OA and symptomatic DISH which confirms previous studies (6). Of note, in asymptomatic DISH patients, serum IGF-I concentration was not significantly lower that serum IGF-I concentrations in the symptomatic DISH patients (Table 2). This result suggested that differences between DISH and OA exist as patients with these disorders respond to medical interventions and become asymptomatic.

DISH patients in this series had confirmed exostoses in spine and several patients had exostoses in the hands and feet by x-ray. Objective clinical criteria defined DISH patients who were classified as asymptomatic. However, exostoses persisted in the asymptomatic group. The radiographic pattern of spinal involvement of the thoracic, cervical and lumbar sacral regions in the present study was typical of the variable presentation of spinal involvement in DISH patients reported by el Miedany *et al*. (30) although the relative distribution of upper vis-à-vis lower spine involvement was somewhat higher in the present group of DISH patients.

Elevated GH could contribute to osteophytoses typical of exuberant bone formation in many joints of DISH patients (17, 18). Several lines of evidence have indicated that GH stimulates the proliferation and differentiated function of osteoblasts. This could occur via specific GH-binding sites and stimulation of IGF-I/II (22). The symptomatic DISH patients had elevated serum GH and IGF-I levels when compared to the control group which could account for the sustained x-ray findings of hyperostosis even after DISH patients become pain-free. In this regard, recent studies have indicated that IGF-I regulates direct anabolic effects on osteocytes *in vivo* (31). Additional regulatory steps controlling bone cell matrix formation relates to the GH-dependent effects on IGF-binding proteins (IGFBP), especially IGFBP-3 (32, 33). In the present study as well as the previously reported study on DISH patients (6), serum GH and IGF-I levels were both increased when compared to the age and gender-matched control group (Table 2). These results are quite different than those reported in OA patients where serum GH levels were elevated, but IGF-I levels were not (4, 5). The reason for the discrepancy in the GH/IGF-I patterns between DISH and other rheumatic disorders such as OA remains to be established. Recent studies have shown that GH and IGF-I do not induce expression of identical mRNAs in human osteoblasts (34), a result that appears germane to the present study.

Elevated serum GH concentration found in female patients with DISH and other rheumatic disorders (compared to males age-matched to the female group) could account for increased chemokine activity, as well as an increased incidence of arthritis among females (35). In the present study of symptomatic male and female DISH patients, female DISH patients had about a 45% increase in serum GH concentration when compared to the male DISH patients (Table 2). When both female and male DISH patients became asymptomatic, asymptomatic female DISH patients still showed a persistently higher serum GH concentration (about 30%) when compared to their male counterparts (Table 2).

These results suggest that DISH patients who undergo customary care resulting in a clinical resolution of symptoms have a lower serum GH concentration than DISH patients with persistent symptoms and that changes in serum GH probably contributes to the reduction in muscle and joint pain and swelling. However, the fact that DISH patients also had elevated serum IGF-I concentrations unrelated to clinical remission suggested that IGF-I contributed mainly to the pathological findings in DISH. Thus, routine monitoring of serum GH concentration (with the recognition that time of day will play a role in these measurements as a result of episodic

fluctuations in GH levels) (3) could serve as a useful surrogate measurement for determining the effectiveness of medical therapy relieving the clinical symptoms in DISH and perhaps other rheumatic disorders as well.

Finally, symptomatic patients with DISH differ from those that become asymptomatic. The fact that DISH causes symptoms through a putative mechanism involving increased serum GH suggests that GH contributes to disease progression, but does not rule out other mechanical alterations contributing to restricted range of motion. However, the results of the present study suggest that DISH is an endocrine disorder involving GH. Proof of this concept will require additional understanding of how GH contributes to the progression of DISH symptoms and provides an impetus for determining whether anti-GH strategies can result in successful alternative outcomes to those which commonly employ a battery of available anti-rheumatic agents.

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Send correspondence to: Charles J. Malemud, Ph.D., Department of Medicine/Division of Rheumatic Diseases, Biomedical Research Bldg. Rm. 1021, Case Western Reserve University School of Medicine, Cleveland, OH 44106-4946, Tel: 216-368-1372, Fax: 216-368-1332, E-mail: cjm4@po.cwru.edu