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ORIGINAL ARTICLE

Epidemiologic survey: reference ranges of serum insulin-like growth factor 1 levels in Caucasian adult population with immunoradiometric assay

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Abstract Gender, age adjusted, population based reference ranges are necessary to use insulin-like growth factor 1 (IGF-1) as a diagnostic marker or for therapeutic monitoring in growth hormone (GH) related diseases. The aim of the present study was to describe the serum IGF-1 distribution and to calculate age and gender specific reference values for Caucasian adult population. A representative sample of 1002 male and 1039 female, totally 2041 participants aged above 18 years old was examined. The subjects suffering from diabetes mellitus, renal diseases, liver diseases, cancer, or diseases of pituitary gland were excluded by medical history, physical examination, and laboratory tests. The subjects were not using any drug that could affect IGF-1 levels. Body mass index (BMI) >30 or <18 kg/m^2 were excluded. Serum IGF-1 concentrations were determined by immunoradiometric assay (IRMA). Serum IGF-1 concentrations were declined with age in both males and females after the age of 18. Males had significantly higher serum IGF-1 levels than females in the age groups 18–24, 50–69 ($P < 0.05$), but not in others ($P > 0.05$). The present study established age and gender specific reference ranges for serum IGF-1 levels calculated for Caucasian adult population with IRMA that could be used in medical practice.

Keywords Insulin-like growth factor 1 · Growth hormone · Immunoradiometric assay

Introduction

Circulating insulin-like growth factor 1 (IGF-1) is predominantly synthesized in the liver upon stimulation by growth hormone (GH) and mediates most of the endocrine actions of GH. IGF-1 is involved in cell replication and proliferation, protein synthesis, carbohydrate homeostasis, and bone metabolism. GH secretion follows a pulsatile pattern, however circulating concentrations of IGF-1 are stable during the day and therefore reflect the general long term status of GH secretion [1].

Analysis of IGF-1 in serum has become an integral component in the diagnosis of GH related disorders such as GH deficiency and excess. IGF-1 is also used for dose adjustment of GH replacement therapy and is suggested as the most reliable component for monitoring the success of therapeutic interventions in acromegaly [1, 2]. Moreover, IGF-1 represents an important prognostic factor for systemic diseases including cardiovascular disorders [3–5], cancer [6], and osteoporosis [7]. Lower IGF-1 levels are associated with increased risk of congestive heart failure [3], ischemic heart disease [4], and cardiovascular mortality [5]. Higher IGF-1 concentrations are related to prostate cancer, colorectal cancer, and premenopausal

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breast cancer [6]. The specific role of IGF-1 in the pathogenesis of osteoporosis is unclear [7].

Gender, age adjusted, geographical, ethnical, population based reference ranges are necessary to use IGF-1 as a diagnostic marker or for therapeutic monitoring in GH related diseases. The decline of the serum IGF-1 concentrations with advancing age and gender differences require gender and age specific reference ranges [1, 2, 8–10]. Currently available reference values of IGF-1 were calculated using non-representative samples for Caucasian adult population [1, 2, 8, 11]. Furthermore, the general concept of mean ± 2SD was often used for the calculation of reference values, which relies on the Gaussian distribution of the analyte under study. However many blood analytes are far from showing a Gaussian distribution and a 5% outliers may be misleading from the medical point of view. The standard non-parametric alternative is to give several age specific references [1]. Moreover, some problems exist for measuring IGF-1. There is no universal calibrator and no consensus for the method that should be used to measure IGF-1.

The aim of the present study was to describe the serum IGF-1 distribution and to calculate age and gender specific reference values for Caucasian adult population and by this way to get criteria for evaluation and follow up of patients with GH related disorders. Different from the previous studies held in restricted local populations, all the geographic regions of Turkey were included in this study.

Materials and methods

The Ethical Committee of the Ankara University Medical School and Ministry of Health approved the study. Informed consent was obtained from each participant.

This study was a cross-sectional survey conducted in the sixteen provinces from seven distinct geographic regions of Turkey, between March 2004 and May 2006. The sampling design was a multistage sampling. A representative sample of 1002 male and 1039 female, totally 2041 participants aged above 18 years old was examined. The subjects suffering from diabetes mellitus, renal diseases, liver diseases, cancer, or diseases of pituitary gland were excluded by medical history, physical examination, and routine laboratory tests. The subjects were not using any drug that could affect IGF-1 levels such as oral contraceptives or hormone replacement therapy. As an association between body mass index (BMI) and IGF-1 levels was suggested [12–16], we excluded BMI values >30 or <18 kg/m^2 with possible pathological background.

Blood samples for the determination of IGF-1 were taken in the morning after an overnight fast and were centrifuged at room temperature for 10 min at 3000 rpm. The sera extracted were stored in ice bags and placed into deep freezes at −70°C on the same day. Sera from all participants were studied in Ankara University Medical School Endocrinology Laboratory. Serum IGF-1 concentrations were determined by immunoradiometric assay (IRMA) (Immunotech SAS®; A Beckman Coulter Company, France) after separation of IGF-1 from IGF-binding proteins by acid-ethanol extraction and neutralization. The IGF-1 assay has been calibrated against the World Health Organization International Reference Reagent 1988, IGF-1 87/518. Analytical sensitivity was 2 ng/ml. The antibodies used in the immunoassay are highly specific for IGF-I. Extremely low cross reactivities were obtained against several molecules (insulin, proinsulin, IGF II, GH). The intraassay coefficient of variation (CV) was ≤6.3% whereas the interassay CV was ≤6.8%. The subjects were stratified according to their age as 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (mean ± SD) and median (25th and 75th percentiles). Construction of the centile curves (5th, 10th, 25th, 50th, 75th, 85th, 90th, and 97th) was performed with the LMS Chart Maker Pro version 2.3 software program (The Institute of Child Health, London), which fits smooth centile curves to reference data of serum IGF-1 using the LMS method. This method summarizes percentiles at each age based on the power of age-specific Box–Cox power transformations that are used to normalize data [17]. These three quantities depend on age. The final curves of percentiles were produced by three smooth curves representing *L* (Lambda; skewness), *M* (Mu; median), and *S* (Sigma; coefficient of variation). The Kruskall–Wallis variance analysis was used to compare age groups and different regions of Turkey while Mann–Whitney *U* test was used to compare male and female. Two-tailed *P*-values of <0.05 were considered to be significant.

Results

The mean age was 49.09 ± 14.7 (mean ± SD) years in males and 45.66 ± 15.1 (mean ± SD) years in females. The median serum IGF-1 level was 159.4 (min 101–max 234) for males and 154.8 (min 92–max 234) for females. Serum IGF-1 concentrations declined with age in both males and females after the age of 18. Males had significantly higher serum IGF-1 levels than females in the age groups 18–24, 50–69 ($P < 0.05$), but there was no

statistically significant difference of the serum IGF-1 levels between males and females in other age groups ($P > 0.05$). IGF-1 values were lower in Eagean Region and higher in Southeast Region than the other regions of Turkey (Table 1). The calculated percentiles (5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th) of serum IGF-1 and LMS values for male and female in age groups were given in Table 2.

The curves of 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles of serum IGF-1 were shown in Fig. 1a for males and in Fig. 1b for females.

Discussion

In the present study, we established age and gender specific ranges for serum IGF-1 levels measured by IRMA (Immunotech SAS®) in a population based sample of 2041 subjects from the seven geographic regions of Turkey. The two previous studies about serum IGF-1 reference ranges in Turkey were held in İstanbul, in a restricted region. Tiryakioğlu et al. studied 272 healthy subjects aged 15–75 years who were recruited among hospital stuff and by an advertisement in the village clinics and schools from İstanbul [10]. Bereket et al. studied serum IGF-1 levels of Turkish children during childhood and adolescence in 807 healthy children from 9 different schools in İstanbul [18]. Different from the previous studies held in restricted local populations, all the geographic regions of Turkey with higher number of subjects were included in this study.

For both males and females, an age related decrease in serum IGF-1 levels was demonstrated in the present study. These findings are in agreement with previous studies [8, 9, 19]. Concerning gender specific differences in serum IGF-1 levels, conflicting results were reported. In the German study [1] and Swedish study [9], it was found that the serum IGF-1 levels were lower in younger males (20–39 years of age), but higher in older males (≥65 years of age) compared to females of the respective age. In contrast, the Turkish study [10] found lower serum IGF-1 levels in males than in females and two other studies [8, 11] described similar levels of serum IGF-1 levels in males and females. In the present study, male had significantly higher serum IGF-1 levels than females in the age groups 18–24, 50–69, but there was no statistically significant difference of the serum IGF-1 levels between males and females in other age groups. These differences might be owing to different analytic systems to measure serum IGF-1 levels as well as to different study designs.

The reasons for the different levels of serum IGF-1 in females and males are not well known. However, these gender differences might be caused by different pattern of GH secretion in females and males. The major difference in the pattern of GH secretion appeared to reside in the trough concentration parameter, which was four times higher in females than males, whereas peak serum GH values were similar. GH was secreted in a more disorderly manner in females and at a slower and less well defined pulse periodicity. Serum IGF-I levels are mainly determined by peak GH concentrations, with the relationship set at a lower value in females [20].

Most assays for IGF-I are calibrated against the WHO International Reference Reagent (IRR) for IGF-I Immunoassays (87/518) as in our study. The protein content assigned to WHO IRR 87/518 was a consensus value from a multicenter collaborative study. Physicochemical analyses showed that WHO IRR 87/518 is Met(-1)-IGF-I of low purity (44%), and that the assigned protein content is higher than the value determined by quantitative amino acid analysis. Thus, assays that are calibrated against WHO

Table 1 The number of males and females, mean ± SD and mean *z*-score of IGF-1 levels of both genders included in different regions

Regions	Gender								Total
	Male				Female				
	Number	Serum IGF-1 (ng/ml)			Number	Serum IGF-1 (ng/ml)			
		Mean ± SD	Mean *z*-score	Median (25–75p)		Mean ± SD	Mean *z*-score	Median (25–75p)	
Mediterranean	231	173.8 ± 96.2	−0.005	156.9 (102–230)	236	172.6 ± 97.3	−0.0162	153.0 (97–235)	467
Central	140	176.3 ± 96.7	0.020	158.8 (107–212)	184	183.2 ± 101.9	0.088	165.7 (102–237)	324
Southeast*	100	238.7 ± 107.7	0.637	230.3 (155–307)	76	220.3 ± 93.1	0.456	219 (150–294)	176
Eagean*	127	113.9 ± 79.1	−0.597	96.5 (58–147)	132	130.3 ± 93	−0.0434	103.3 (52.5–200.6)	259
Marmara	190	180.9 ± 94.4	0.067	168.4 (107–239)	134	175.1 ± 111.9	0.009	151.0 (85–238)	324
Black Sea	144	171.8 ± 81.6	−0.039	170.2 (113–218)	162	163.5 ± 86.6	−0.0106	149.7 (97–211)	306
East	70	199.9 ± 120.5	0.254	191.4 (101–268)	115	182.8 ± 121.5	0.084	150.0 (84–267)	185
*P**				<0.05				<0.05	

* *P*; Kruskall–Wallis test, $z = (X_i - \bar{X})/\mathrm{SD}$

Table 2 The calculated percentiles of serum IGF-1 and LMS values for male and female in age groups: *L* (Lambda; skewness), *M* (Mu; median) and *S* (Sigma; coefficient of variation)

Age	*N*	*L*	*M*	*S*	(−1.64 SD) 5	(−1.28 SD) 10	(−0.67 SD) 25	(0 SD) 50	(0.67 SD) 75	(1.04 SD) 85	(1.28 SD) 90	(1.64 SD) 95	(1.88 SD) 97
Serum IGF-1 percentiles (male)													
18–24	45	0.78	288.36	0.39	118.93	153.38	218.23	288.36	366.25	409.70	439.73	485.10	515.09
25–29	51	0.69	228.24	0.45	80.51	108.96	164.97	228.24	301.06	342.64	371.73	416.19	445.89
30–34	82	0.60	193.96	0.50	62.08	86.10	135.53	193.96	263.83	304.77	333.81	378.76	409.16
35–39	93	0.53	177.38	0.53	54.85	76.25	121.69	177.38	246.16	287.39	317.00	363.37	395.07
40–44	122	0.48	167.77	0.55	51.25	71.01	113.87	167.77	235.99	277.60	307.78	355.48	388.38
45–49	155	0.44	159.74	0.56	48.53	66.94	107.57	159.74	227.16	268.91	299.45	348.13	381.98
50–54	101	0.40	152.29	0.58	46.12	63.33	101.85	152.29	218.73	260.48	291.27	340.77	375.44
55–59	89	0.36	144.73	0.59	43.62	59.67	96.11	144.73	210.04	251.69	282.67	332.89	368.36
60–64	84	0.33	135.78	0.61	40.50	55.28	89.37	135.78	199.50	240.80	271.82	322.58	358.76
65–69	65	0.29	123.57	0.63	36.02	49.24	80.28	123.57	184.50	224.74	255.30	305.87	342.29
≥70	115	0.26	108.01	0.66	30.37	41.74	68.98	108.01	164.46	202.54	231.80	280.81	316.51
Serum IGF-1 percentiles (female)													
18–24	71	0.83	255.93	0.48	72.07	109.14	176.06	255.93	340.37	387.27	419.61	468.32	500.43
25–29	81	0.73	220.34	0.50	63.50	93.58	150.06	220.34	297.26	340.97	371.45	417.89	448.82
30–34	120	0.63	193.17	0.52	57.11	81.90	130.27	193.17	264.79	306.57	336.13	381.77	412.54
35–39	132	0.53	176.63	0.54	53.13	74.57	117.86	176.63	246.34	288.17	318.24	365.36	397.59
40–44	135	0.45	161.23	0.57	48.41	67.13	106.11	161.23	229.33	271.41	302.14	351.06	385.03
45–49	101	0.37	144.75	0.60	42.70	58.88	93.61	144.75	210.58	252.49	283.63	334.05	369.61
50–54	106	0.31	129.82	0.63	37.48	51.53	82.51	129.82	193.14	234.62	265.96	317.56	354.53
55–59	79	0.26	119.15	0.65	33.80	46.39	74.68	119.15	180.57	221.78	253.37	306.11	344.42
60–64	67	0.23	110.83	0.67	30.97	42.45	68.67	110.83	170.63	211.57	243.34	297.04	336.53
65–69	55	0.20	103.89	0.69	28.66	39.24	63.72	103.89	162.17	202.80	234.66	289.13	329.61
≥70	92	0.18	98.07	0.71	26.76	36.61	59.64	98.07	154.94	195.23	227.13	282.22	323.58

IRR 87/518 will report IGF-I concentrations in excess of actual values. Some authors believe that calibration against WHO IRR 87/518 is the cause of the systematic discrepancy between the Genentech IGF-I assay normal range and most other normal ranges, and that much of the plasma IGF-I concentration data in the literature are of questionable accuracy [21].

There are several factors that affect IGF-1 levels; energy intake, BMI, physical activity but the intimate relationship among these variables restricts the identification of their independent effects. Dietary energy intake and nutritional status are critical regulators of IGF-1 level [22]. In case of protein calorie malnutrition, the IGF-1 levels decrease but with improvement in energy intake, levels increase [23]. Fasting also causes a decrease in IGF-1 levels [24] and the effect is smaller in obese subjects [25] plausibly of their less dependency on energy intake to maintain IGF-1 levels. On the other hand, over nutrition has been found to result in increased IGF-1 [26]. It has been seen that protein restriction reduces plasma levels of IGF-1 by inducing resistance to the action of GH in liver and increases the metabolic clearance rate of the growth factor [22, 27, 28]. Different studies conducted on the association between IGF-1 and BMI revealed different results. Some studies [29, 30] showed no association with total IGF-1 whereas others [31, 32] showed inverse association with total or with free IGF-1. Cross-sectional studies have shown no association between physical activity and IGF-1 levels [29, 30, 33, 34], positive association with leisure time exercise [34], general physical activity [35], physical fitness [36], and training [37]. IGF-1 values were lower in Eagean Region and higher in Southeast Region than the other regions of Turkey which may be related with economical, nutritional, or habitual differences in those regions. In Eagean region, vegetarian type diets with protein restriction are more popular and in Southeast region high protein intake is common. In this study, in order not to confuse with BMI and IGF-1 relationship, while we were trying to find out calculate age and gender specific reference values, we excluded BMI values >30 or <18 kg/m^2 with possible pathological background. We chose BMI values >30 kg/m^2 as a criteria because in a study where BMI < 30 kg/m^2, there was no correlation between BMI and IGF-1 [30].

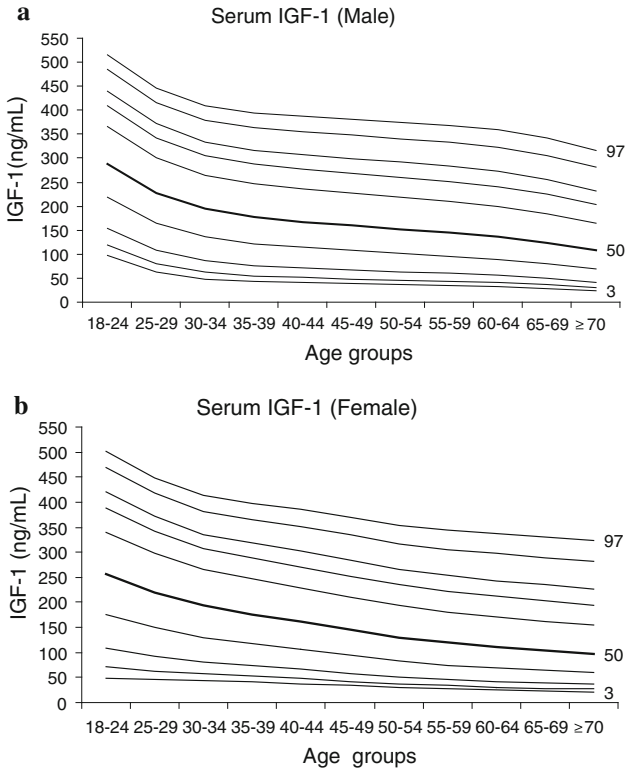

Fig. 1 The curves of 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles of serum IGF-1 for **a** males and **b** females

The major strength of our study is the use of data from a large population based sample of adults and the exclusion of the subjects with any known relevant disease. The present study established age and gender specific reference ranges for serum IGF-1 levels calculated for adult Caucasian population with IRMA that could be used in medical practice. In our best knowledge, this study is the largest population based study with the method of IRMA.

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