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Insulin Like Growth Factor-I and IGF-Binding Protein-3 Levels in A Healthy Adult Turkish Population

Yetişkin Sağlıklı Bir Türk Toplum Örnekleminde İnsülin-Benzeri Büyüme Faktörü-I ve IGF-Bağlayıcı Protein-3 Seviyeleri

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ABSTRACT Objective: Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) levels are important markers in diagnosis of growth hormone (GH) related disorders. The normal levels of IGF-I and IGFBP-3 vary among different ethnic groups, and using the references derived from different populations may sometimes be misleading during diagnosis, treatment and follow-up. We examined the levels of IGF-I and IGFBP-3 in healthy adult Turkish population. **Material and Methods:** Eight hundred and thirty-three subjects (512 females, 321 males) were enrolled in the study. Serum IGF-I and IGFBP-3 levels were measured by immunoradiometric assay in all participants. The study population was divided into age groups (18-20, 21-23, 24-25, 26-30, 31-40, 41-50, >50 years of age) and gender groups (females and males separately in the population ≤ 30 years of age, combined in age groups over 30 years of age) according to the references defined by the kit manufacturer and the results were compared to the reference values provided by the manufacturer that represents a reference population. **Results:** Serum IGF-I levels were statistically higher than the reference levels in all age groups of women ≤ 30 years of age ($p< 0.05$). In men, IGF-I levels were significantly higher ($p< 0.05$) only in 26-30 years age group. In gender-combined groups over 30 years of age, IGF-I levels were statistically higher than the reference levels ($p< 0.05$). Serum IGFBP-3 levels were significantly lower than the reference values in 24-25 years age group in both genders and in 18-20 years of age in males ($p< 0.05$). Serum IGFBP-3 levels were significantly higher in 26-30 years age group in males and in all gender-combined groups > 30 years of age ($p< 0.05$). **Conclusion:** Serum IGF-I concentrations of our study population are generally higher than the reference values of the commercial kit. Centers dealing with GH disorders might benefit from defining their own population's normal values for IGF-I and IGFBP-3 to overcome possible diagnostic and follow-up pitfalls.

Key Words: Human insulin-like-growth-factor-I (21-40); IGFBP3 protein, human; Turkey; population; sex

ÖZET Amaç: İnsülin benzeri büyüme faktörü-I (IGF-I) ve IGF-bağlayıcı protein-3 (IGFBP 3) seviyeleri büyüme hormonu (GH) ilişkili hastalıkların tanısında önemli belirteçlerdir. Normal IGF-I ve IGFBP- 3 seviyeleri farklı etnik gruplar arasında değişkenlik göstermektedir ve farklı populasyonlara göre belirlenenen referanslar bazı tanı, tedavi ve izlemde bazen yanlış yönlenmeye neden olabilmektedir. Biz bu amaçla sağlıklı yetişkin Türk toplum örnekleminde IGF-I ve IGFBP-3 düzeylerini inceledik. **Gereç ve Yöntemler:** Sekiz yüz otuz üç olgu (512 kadın, 321 erkek) çalışmaya alındı. Serum IGF-I ve IGFBP-3 seviyeleri tüm olgularda bir immünoradyometrik tetkikle ölçüldü. Çalışma populasyonu yaş grupları (18-20, 21-23, 24-25, 26-30, 31-40, 41-50, >50 yaş) ve cinsiyet gruplarına (<30 yaş populasyon kadın ve erkekler olarak ayrılırken >30 yaş grubunda birlikte) ayrıldı ve sonuçlar üretici firmanın referans bir toplumu temsil eden referans değerleri ile karşılaştırıldı. **Bulgular:** Serum IGF-I değerleri ≤30 yaştaki bütün kadın yaş gruplarında referans seviyelerinden istatistiksel olarak anlamlı düzeyde daha yüksekti ($p< 0.05$). Erkeklerde sadece 26-30 yaş arası grupta IGF-I seviyeleri istatistiksel olarak anlamlı düzeyde daha yüksekti ($p< 0.05$). Otuz yaş üstündeki cinsiyet yönünden birlikte ele alınan gruplarda IGF-I seviyeleri referans seviyelerinden istatistiksel olarak daha yüksekti ($p< 0.05$). Serum IGFBP-3 seviyeleri 24-25 yaş arası grupta her iki cinsiyette, 18-20 yaş arası grupta ise erkeklerde referans değerlerinden daha düşüktü ($p< 0.05$). Serum IGFBP-3 seviyeleri 26-30 yaş arası grupta erkeklerde ve >30 yaş üstünde cinsiyet yönünden birleşik gruplarda istatistiksel açıdan anlamlı derecede daha yüksekti ($p< 0.05$). **Sonuç:** Çalışma populasyonumuzdaki serum IGF-I konsantrasyonları ticari kitin referans değerlerinden genelde daha yüksekti. GH'la ilişkili bozukluklarla ilgilenen merkezlerin tanı ve izlemde olası hatalardan kaçınabilmek amacıyla kendi populasyonlarının normal IGF-I ve IGFBP-3 değerlerini belirlemeleri yararlı olabilecektir.

Anahtar Kelimeler: İnsan insülini benzer büyüme faktörü-I; insan IGFBP-3 proteini; Türkiye; nüfus; cinsiyet

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Insulin-like growth factor-I (IGF-I) is a 70 amino-acid single chain polypeptide with a molecular weight of 7.65 kDa and it is structurally homologous to insulin.[1] IGF-I is produced by a number of tissues in the body, most prominently in the liver. It has effects on protein, carbohydrate metabolism, and on cell proliferation, differentiation and apoptosis.[2] IGF-I levels increase gradually during childhood, show a peak during puberty, and then start to decrease through adulthood.[3,4] They decrease in states of growth hormone (GH) deficiency and increase in GH excess, and thus constitute a useful marker in monitoring GH replacement therapy and following the response to treatment in patients with acromegaly.[1,3]

The IGF system acts via a specific cell membrane receptor, insulin-like growth factor-I receptor (IGF-IR), which has tyrosine kinase activity. IGF binding proteins (IGFBP-1 to -6) support the interaction between IGFs and IGF-IR[2]. IGFBPs inhibit the actions of IGFs via blocking the binding of IGFs to IGF-IR, or they enhance the action of IGFs by increasing their availability to the target tissues.[5] IGFBP-3 is a 264 amino-acid peptide with a molecular weight of 29 kDa, and it is a member of the IGFBP group.[6] The synthesis of IGFBP-3, like IGF-I, is under the control of GH. Serum IGFBP-3 levels rise gradually during childhood, show a peak at puberty and decrease during adult life.[7] However the levels of IGFBP-3 are less age-dependent than IGF-I levels.[7] IGF-I and IGFBP-3 levels have also been shown to be affected by factors like nutrition and liver disease.[1,3,8] In addition, IGF-I levels may be different in different ethnic groups.[9] Due to delicate nature of these proteins, many centers have difficulties in interpreting their IGF-I and IGFBP-3 level results during the assessment of GH disorders.

In this study, we aimed to establish our own IGF-I and IGFBP-3 limits. For this purpose, we examined the levels of IGF-I and IGFBP-3 in a healthy, adult population living in Ankara and compared our data with the manufacturer's age and sex specific normal values which had been obtained from a reference population.

MATERIAL AND METHODS

STUDY DESIGN

This study was performed in four different urban areas of Ankara, where a total of 300 429 inhabitants from every district of Turkey have been living. As a representative of 300 429 inhabitants, 4 393 subjects were randomly visited, and 833 meeting the inclusion criteria were included in the study. The inclusion criteria were: (i) age ≥18 years, (ii) normal physical examination, (iii) random venous plasma glucose <140 mg/dl or fasting venous plasma glucose <100 mg/dl, (iv) blood pressure <140/90 mmHg and no history of antihypertensive treatment, (v) body mass index < 27 kg/m^2. The exclusion criteria were as follows: (i) history of diabetes mellitus, hypertension, renal or liver diseases, coronary heart disease, cardiac failure, acromegaly, GH insufficiency or presence of any malignancy, (ii) any medications for chronic illnesses, (iii) use of glucocorticoids within one month prior to the study and antibiotics within a week prior to the study, (iv) physical exercise more than four hours per week.

The study population was divided into age groups [18-20, 21-23, 24-25, 26-30, 31-40, 41-50, >50 years of age (yr)] and gender groups (females and males separately in the population≤ 30 yr, combined in groups> 30 yr) according to the references defined by the kit manufacturer, and the results were interpreted accordingly. As the reference values were not given gender-specific over 40 yr, and both separate and combined data were provided for population between 31-40 yr, we have not separated our IGF-I and IGFB-3 levels according to gender in subjects older than 30 years of age.

This study was approved by the local ethics committee of Gazi University Medical Faculty. Informed consent was obtained from all participants.

SAMPLE COLLECTION, IGF-I AND IGFBP-3 MEASUREMENTS

Venous blood samples were drawn from an antecubital vein between 08.00 and 10.00 a.m., in the fasting state and transported to the endocrinology laboratory of our medical center immediately.

They were centrifuged at 3 000 rpm for 15 minutes and serum samples were stored at -80°C until the analysis of IGF-I and IGFBP-3.

Serum IGF-I concentrations were measured by a specific immunoradiometric assay (IRMA) using a commercially available kit (DSL-2800, Diagnostic System Laboratories Inc., Webster, TX, Lot No 08083). The results were analyzed by Iodine-125 labelled Berthold LB 2111 gamma counter at a standart interval of 8.35-919 ng/ml.

Serum IGFBP-3 levels were measured using a specific IRMA kit (DSL-6600, Diagnostic System Laboratories Inc., Webster, TX, Lot No 08083). All samples were diluted with 1:50 with IGFBP-3 sample diluent prior to assay (10 ml serum + 490 ml IGFBP-3 sample diluent). The results were analyzed by Iodine-125 labeled Berthold LB 2111 gamma counter at a standart interval of 2-125 ng/ml. The results were multiplied by fifty (diluent factor).

STATISTICAL ANALYSIS

SPSS software package (version 15.0 for Windows) was used for statistical analyses. The results of serum IGF-I and IGFBP-3 were given as mean ± standart deviation (SD). The 95% confidence interval and absolute range (the lower and upper limits of IGF-I and IGFBP-3 levels) of values were determined for each group. One-sample t test was used to compare the mean values of the study population with the reference "kit" values. Statistical significance was assumed at the level of $p< 0.05$.

RESULTS

Of the total 833 participants, 512 were females and 321 were males. The number of participants in each group is presented in Tables 1 and 2.

Serum IGF-I levels of the study population and reference values are presented in Table 1. The mean IGF-I levels in all age groups ≤ 30 yr in females were significantly higher than the reference mean values ($p<0.05$). The absolute ranges of IGF-I were wider and the upper limits of absolute ranges were higher than the reference group in each age group ≤ 30 yr in females. In males, although the mean IGF-I levels in all age groups ≤ 30 yr were higher than the reference mean values, a statistically significant difference was obtained only in the 26-30 yr age group ($p< 0.05$). The absolute ranges for each age group in males ≤ 30 yr were wider, and the upper limits were higher than the reference values. In age groups >30 yr, which were gender-combined,

TABLE 1: The comparison of the serum IGF-I levels of the study groups and the reference values.

		Study			Reference		
Age groups	n	Mean ± SD	95% CI	Absolute range	Mean ± SD	Absolute range	p
Females							
18-20 yr	97	529.7 ± 247.9	479.8-579.7	174.9-925.5	367.9 ± 106.1	193.0-575.0	<0.05
21-23 yr	63	420.1 ± 242.2	359.0-481.1	101.0-905.7	288.9 ± 109.8	110.0-521.0	<0.05
24-25 yr	47	347.7 ± 157.7	301.4-394.1	133.3-641.0	274.9 ± 93.1	129.0-480.0	<0.05
26-30 yr	77	326.1 ± 135.6	295.3-356.8	135.5-619.1	253.5 ± 106.6	96.0-502.0	<0.05
Males							
18-20 yr	46	578.6 ± 215.2	514.7-642.6	221.8-965.7	489.0 ± 206.7	197.0-956.0	NS
21-23 yr	26	464.2 ± 169.9	395.6-532.9	158.1-826.8	420.1 ± 114.7	215.0-628.0	NS
24-25 yr	33	388.8 ± 198.2	318.5-459.1	174.4-902.4	320.7 ± 106.3	169.0-591.0	NS
26-30 yr	35	347.8 ± 159.6	292.9-402.6	175.4-700.5	236.7 ± 81.2	119.0-476.0	<0.05
Combined							
31-40 yr	172	282.0 ± 127.4	262.8-301.2	126.2-509.1	214.0 ± 88.3	100.0-494.0	<0.05
41-50 yr	123	253.6 ± 176.2	222.2-285.1	89.1-522.0	180.4 ± 48.3	101.0-303.0	<0.05
>50 yr	114	217.2 ± 165.6	186.4-247.9	57.6-447.7	153.7 ± 49.3	78.0-258.0	<0.05

All IGF-I concentrations were given as ng/ml. NS: not significant; SD: standart deviation; CI: confidence interval; IGF-I: Insulin like growth factor-I; yr: years.

TABLE 2: The comparison of the serum IGFBP-3 levels of the study groups and the reference values.

		Study			Reference		
Age groups	n	Mean±SD	95% CI	Absolute range	Mean±SD	Absolute range	p
Females							
18-20 yr	97	4531 ± 1084	4313-4750	2883-6407	4430 ± 1530	2310-7480	NS
21-23 yr	63	4239 ± 1162	3944-4534	2207-6263	4668 ± 1446	2760-7350	NS
24-25 yr	47	4064 ± 1080	3746-4381	1775-5691	4567 ± 1319	2920-7000	<0.05
26-30 yr	77	4185 ± 1190	3914-4455	2307-6125	4220 ± 1191	2050-7600	NS
Males							
18-20 yr	46	4514 ± 1126	4179-4848	2501-6307	4932 ± 1218	2680-7290	<0.05
21-23 yr	26	4436 ± 1213	3946-4926	2554-6875	4645 ± 1020	2930-7380	NS
24-25 yr	33	3771 ± 827	3478-4065	2446-5239	4253 ± 907	2250-5480	<0.05
26-30 yr	35	4169 ± 1016	3820-4518	2049-5733	3642 ± 957	2330-6680	<0.05
Combined							
31-40 yr	172	4199 ± 1088	4035-4363	2349-5911	3493 ± 900	1730-7260	<0.05
41-50 yr	123	4254 ± 883	4096-4411	2660-5670	3152 ± 497	2080-4310	<0.05
>50 yr	114	3869 ± 1224	3642-4096	1847-5903	2966 ± 439	2020-3990	<0.05

All IGFBP-3 concentrations were given as ng/ml. NS: not significant; SD: standart deviation; CI: confidence interval; IGF-I: Insulin like growth factor-I; yr: years

the mean values of IGF-I were significantly higher than the references ($p< 0.05$). The absolute ranges and the upper limits of IGF-I were higher as well.

Serum IGFBP-3 levels of the study population and reference values are presented in Table 2. The mean IGFBP-3 levels of females were significantly lower in the 24-25 yr group ($p< 0.05$). The mean values of IGFBP-3 were lower than the reference mean values in 18-20 yr and 24-25 yr groups and significantly higher in the 26-30 yr group of males ($p< 0.05$ for all groups). In the population> 30 yr of age, mean IGFBP-3 levels were significantly higher than the reference values ($p< 0.05$).

DISCUSSION

In clinical practice, GH excess and deficiency are the most important situations in which IGF-I and IGFBP-3 measurements are used as diagnostic and follow-up markers. However, many factors affect the serum IGF-I and IGFBP-3 levels. Abnormally low levels of IGF-I, according to age and sex, are helpful in the diagnosis of GH deficiency syndromes both in children (i.e. Laron dwarfism)[10] and in adults (i.e. panhypopituitarism),[11] although a normal IGF-I value does not exclude GH deficiency in some adult patients.[12] IGFBP-3 levels also decline in parallel to IGF-I levels in these situations.[13] IGF-I and IGFBP-3 levels can also be used for monitoring the effectiveness of GH replacement therapy in GH deficient patients.[14,15] Abnormally elevated IGF-I and IGFBP-3 levels in acromegaly are used as a diagnostic tool and in monitoring the efficacy of surgical or medical treatment. Serum IGF-I levels may be affected by multiple factors, and this presents an important problem in diagnosis and follow-up of these patients. We frequently obtain high IGF-I levels in patients with nonfunctional pituitary tumors. We also find high serum IGF-I concentrations in symptom-free acromegalic patients with well suppressed GH response to oral glucose load after surgical or during medical treatment. Therefore, our observations motivated us for the present study.

IGF-1 and IGFBP-3 levels may vary among different populations. This variability may arise from genetic and/or nutritional factors in healthy subjects. In the study of Cruickshank et al., IGF-I concentrations were higher in African-Caribbeans with a normal glucose tolerance status when compared to Europeans and Pakistani people.[9] Pakistanis with normal glucose tolerance had the lowest IGF-I concentrations, and IGF-I was independently and negatively related to Pakistani ethnicity.[9] To the best of our knowledge, this is the first popula-

tion-based study that compares its own population's IGF-I and IGFBP-3 normal values with the reference values of a different population that is presented by the manufacturer.

The IGF-I levels of our population were higher than the manufacturer's values in every age group in women and over 25 years in men. We hope that this finding will resolve the dilemma in the diagnosis and treatment of the Turkish patients with GH disorders. This discrepancy between our results and the reference values may arise from genetic or nutritional differences of our study population, however further studies should be performed in order to understand the underlying causative factors.

In conclusion, serum IGF-I concentrations of our study population are generally higher than the reference values of the commercial kit that represents a different population's normals. IGFBP-3 levels also have some differences from reference values, but they are not as definitive as IGF-I levels. The use of these new normal limits may be helpful for our population in managing diagnostic and follow-up problems that we face in Turkish patients with GH disorders. Centers dealing with GH disorders might benefit from defining their own population's normal values for IGF-I and IGFBP-3 to overcome possible diagnostic and follow-up pitfalls.

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