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# Demographic factors influencing the GH system: Implications for the detection of GH doping in sport

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ABSTRACT

Application of methods for detecting GH doping depend on being able to discriminate between abnormal levels due to doping and normal physiological levels of circulating proteins that change in response to exogenous administration. Constituents of the IGF and collagen systems have been shown to be promising markers of GH abuse. Their ultimate utility, however, depends on identification of the factors that regulate their concentrations in blood. Among these are demographic factors that are known to influence these markers in the general population.

In a large cross-sectional study of the GH-responsive markers in over 1000 elite athletes from 12 countries representing 4 major ethnic groups and 10 sport types, we have shown that there is a significant negative correlation between age and all the IGF and collagen markers we studied, with a rapid decrease in early adolescence. Age was the major contribution to the variability, equivalent to >80% of the attributable variation in IGF-I and the collagen markers. The IGF axis markers were all significantly higher in women, and the collagen markers significantly higher in men, however, the contribution of gender was smaller than that of age, except for IGFBP-3 and ALS. BMI had a minor contribution to variability of the GH-responsive markers. After adjustment for the confounding influences of age, gender and BMI, the effect of ethnicity in elite athletes was trivial except for IGFBP-3 and ALS, which were both lower in Africans and higher in Caucasians. Compared to age and gender, the contribution of sport type was also modest. Our findings on the influence of age, gender, BMI and sport type have also been confirmed in a study of mostly Caucasian elite athletes in the post-competition setting.

In conclusion, age and gender are the major determinants of variability for IGF-I and the collagen markers, whereas ethnicity and sport type have a minor influence. Therefore, a test based on IGF-I and the collagen markers must take age into account for men and women, and ethnicity and sport type are unlikely to be confounders for these markers.



## 1. Introduction

The main approaches to detecting doping with GH, as discussed in detail elsewhere in this issue, are based on measurement of circulating proteins or ratios of proteins that change in response to exogenous administration of GH. These methods depend on the ability to discriminate between abnormal levels due to doping and normal physiological levels of these proteins or ratios of proteins. Therefore, application of these detection methods depends firstly on identifying the main factors that influence circulating levels of these proteins, using extensive normative data from elite athletes.

One approach to detecting GH utilises serum GH-responsive proteins of the insulin-like growth factor (IGF) system and specific collagen peptides, which are markers of bone and connective tissue turnover. Studies in the general population have indicated that these markers are influenced by demographic factors including age, gender and ethnicity, therefore identifying the influence of these factors in elite athletes is critical. In this chapter, the influence of age, gender, BMI, ethnicity and sport type on GH-responsive markers will be reviewed. The influence of demographic factors on GH isoforms is reviewed elsewhere (refer Chapter 6).

We have undertaken a large cross-sectional study of the GH-responsive markers in over 1000 elite athletes [1]. The IGF axis markers IGF-I, IGF binding protein-3 (IGFBP-3) and the acid labile subunit (ALS), and the collagen peptides N-terminal propeptide of type I procollagen (PINP), C-terminal telopeptide of type I collagen (ICTP) and N-terminal propeptide of type III procollagen (PIIINP) were measured in serum samples collected from 699 male and 404 female elite athletes from 12 countries, representing 4 major ethnic groups and 10 major sport types (Table 1). Serum samples were collected on a casual basis, namely at random with regard to the time of day, food intake, exercise and competition,

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**Table 1**
Characteristics of elite athletes in cross-sectional study of GH-responsive markers.

| Ethnic group | Male (n) | | Female (n) |
|---|---|---|---|
| Caucasian | 354 | | 236 |
| Asian | 223 | | 126 |
| African | 82 | | 27 |
| Oceanian and others | 40 | | 15 |
| Characteristic/analyte | Males (n = 699) | Females (n = 404) | [a]P-value |
| Age (yr) | 22.6 ± 5.4 | 21.4 ± 4.4 | <0.0001 |
| Weight (kg) | 75.0 ± 14.6 | 60.3 ± 8.5 | <0.0001 |
| Height (cm) | 178.0 ± 9.2 | 167.1 ± 8.2 | <0.0001 |
| Body mass index (kg/m$^2$) | 23.5 ± 3.3 | 21.6 ± 2.2 | <0.0001 |
| IGF-I (μg/L) | 154.8 ± 45.6 | 161.9 ± 52.4 | 0.020 |
| IGFBP-3 (mg/L) | 3.6 ± 0.6 | 3.8 ± 0.6 | <0.001 |
| ALS (nmol/L) | 283.7 ± 47.9 | 324.7 ± 58.8 | <0.001 |
| PINP (μg/L) | 121.0 ± 90.0 | 85.2 ± 54.9 | <0.001 |
| ICTP (μg/L) | 6.5 ± 3.0 | 5.6 ± 1.6 | <0.001 |
| PIIINP (μg/L) | 5.4 ± 2.3 | 5.1 ± 1.5 | 0.003 |

Values are means ± SD.
Adapted from [1], Copyright 2006, The Endocrine Society.
[a] Significantly different between females and males by *t*-test.

representing the out-of-competition setting. The influence of demographic factors was determined by simple regression and by multivariate analysis. Our findings in elite athletes on the influence of age, gender, BMI and sport type have also been confirmed in another large study of mostly Caucasian elite athletes, using samples collected within 2 h of a major competitive event, representing the post-competition setting [2].

## 2. Age

In our large cross-sectional study, there was a significant negative correlation between age and all the IGF axis and collagen markers (Fig. 1, shown as large cross-sectional elite athlete cohort) [1]. All the markers declined with increasing age, with the relationships best fitted by quadratic (IGF-I, PINP, ICTP and PIIINP) or linear (IGFBP-3 and ALS) functions with the reciprocal of age. The influence of age was considerably higher for IGF-I ($r = -0.41$) than for IGFBP-3 ($r = -0.14$) and ALS ($r = -0.25$). All the collagen markers were strongly correlated with age, with the influence of age greatest for ICTP ($r = -0.58$), followed by PIIINP ($r = -0.45$) and PINP ($r = -0.44$).

In multiple regression analysis, age accounted for the largest proportion of the attributable variation, accounting for 20–52% of total variation, equivalent to >80% of the attributable variation, in IGF-I and the collagen markers. However, for IGFBP-3 and ALS, age exerted only a modest influence in the multiple regression model. This dissociation of the effect of age between IGF-I and its binding proteins IGFBP-3 and ALS has not been previously observed [3], possibly because not all studies in the general population have accounted for demographic confounders such as gender and ethnicity. The stronger relationship between IGF-I and age, as compared to that between IGFBP-3 and age has also been reported in a recent study of Chinese adolescents [4].

The highly significant influence of age on GH-responsive markers in elite athletes was also observed in a study from the United Kingdom of 813 elite athletes in the post-competition setting [2]. The IGF axis markers IGF-I, IGFBP-3 and ALS, and collagen markers C-terminal propeptide of type I procollagen (PICP), ICTP and procollagen type III (PIIIP) all declined with age, and age was also shown to be the major determinant of post-exercise serum levels of these markers in elite athletes. Therefore, IGF axis markers decrease with age in elite athletes, despite the athletes' high level of fitness, similarly to the decrease observed in the general population. The rapid decrease in IGF axis markers following early puberty, particularly for IGF-I, and the continued decline with increasing age in healthy adults has been well described in the general population [3,5–8]. Bone and connective tissue turnover markers also decrease with age following early adolescence in the general population [9–12].

It is well established that the IGF system is activated during puberty in parallel with the growth spurt and developmental maturation. The circulating levels of components of the IGF system increase from relatively low levels before puberty, peaking around late puberty in normal children. Whether this pattern is similar for elite athletes is not known, but is an important issue because of the representation of this age group in various elite sports. Additionally, the changes in collagen peptides in childhood and puberty have not been extensively studied. Our original elite athlete cohort encompassed a wide age range but did not include sufficient young athletes to study changes in the IGF axis and collagen peptides in early adolescence. We extended the study in this age spectrum by collecting serum samples from 56 young elite athletes (32 girls and 24 boys), aged 12–18 years (15.4 ± 1.4 yrs, mean ± SD) who were mostly Caucasian (95%). The athletes participated at the elite level in diving and/or gymnastics ($n = 21$), swimming ($n = 11$) and athletics ($n = 24$).

The influence of age in this younger group is shown in the plots (Fig. 1) with the IGF axis and collagen marker data shown both for the young athletes and for the larger cross-sectional cohort previously reported [1]. In the young elite athletes, the concentrations of the IGF axis markers (IGF-I, IGFBP-3 and ALS) increased in early adolescence to a late pubertal peak, then decreased with age after puberty (Fig. 2). These changes are similar to those described in adolescence in the general population [3,7,13]. The collagen markers PINP, ICTP and PIIINP were all markedly elevated in early adolescence in the elite athletes, in particular for PINP. The decrease with age of the collagen markers in the young elite athletes is consistent with changes in the general population in adolescence, however, in the general population, the reductions during adolescence are preceded by increases in late childhood to pubertal peaks [14–17]. These pubertal peaks were not as apparent in our sample of young elite athletes, possibly due to the limited age range or sample size of our young elite athlete group. However, the possibility that the high levels early in puberty reflect a biological characteristic of children engaging in sport at an elite level cannot be ruled out.

In summary, in elite athletes there is a significant negative correlation between age and all the IGF and collagen markers we studied, similar to that observed in the general population, with a rapid decrease from high levels in early adolescence. Age is the major contribution to the variability of these markers, equivalent to >80% of the attributable variation in IGF-I and the collagen markers.

## 3. Gender

In our large cross-sectional study, there were differences between women and men for all markers in elite athletes. The serum IGF markers were all higher in women, whereas the collagen markers were higher in men (Table 1). For the IGF axis markers, the difference was greater for ALS (14% higher in women, $p < 0.001$) than for IGFBP-3 (6%, $p < 0.001$) and for IGF-I (5%, $p = 0.02$). For the collagen markers, the differences were considerable for PINP (42% higher in men, $p < 0.001$) and ICTP (16%, $p < 0.001$), while PIIINP was only moderately higher (6%, $p = 0.003$). The differences between genders were still significant following correction for differences in age. In our young athletes, we also observed a gender difference, with IGF-I, IGFBP-3 and ALS higher in young girls than in young boys, though significantly higher only for IGFBP-3 (Fig. 2). PINP, ICTP and PIIINP were not significantly different. In multiple regression analysis of our large cross-sectional study, the contribution of gender was smaller compared to that of age, and varied from 0.6% to 12.5%, with the greatest effect on ALS, equivalent to 48% of the attributable variation.

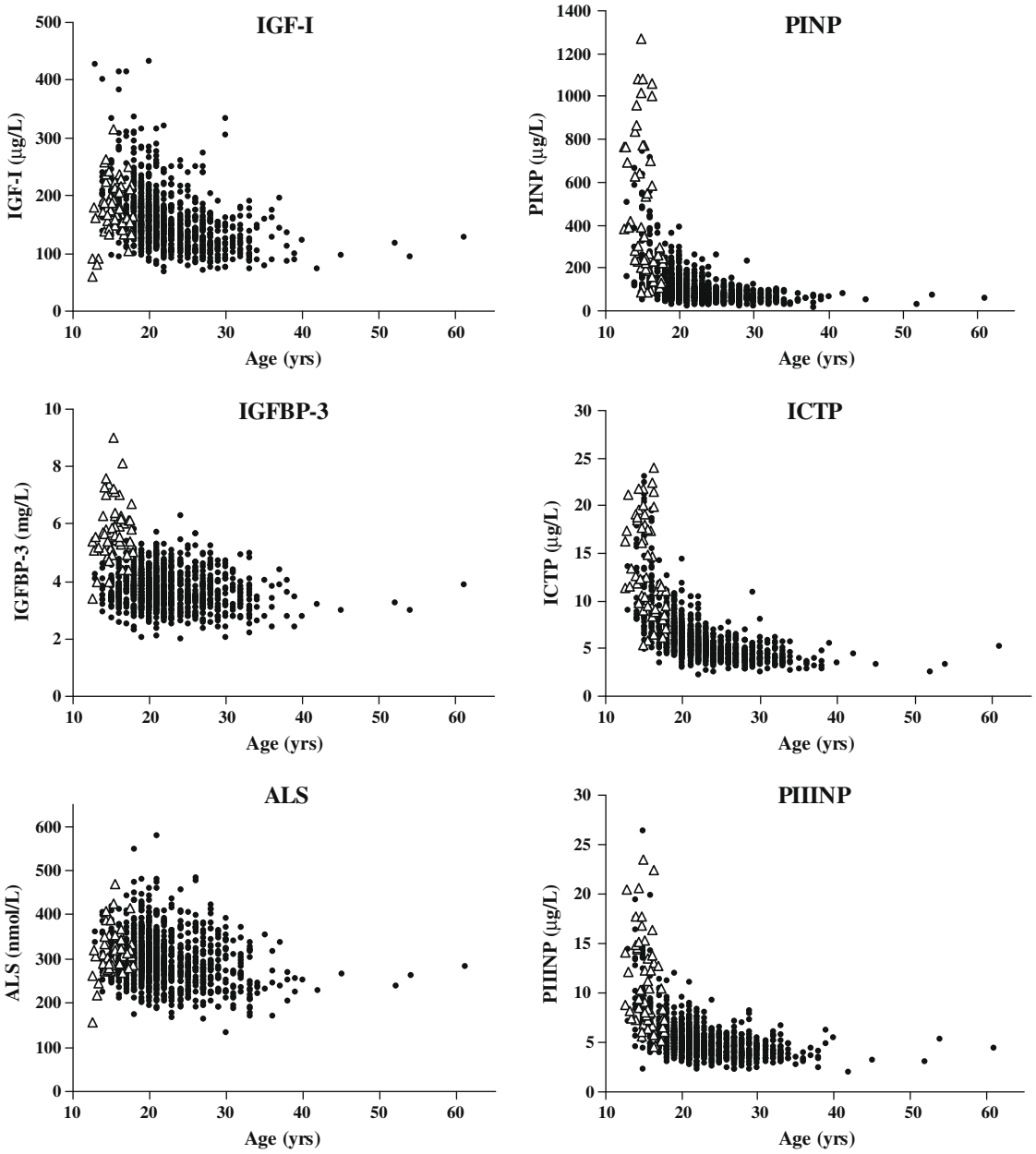


**Fig. 1.** Effect of age on IGF axis and collagen markers in young elite athletes and large cross-sectional elite athlete cohort. The measurements are plotted against age for IGF-I, IGFBP-3 and ALS (left panel), and PINP, ICTP and PIIINP (right panel) for the young elite athletes (Δ) and for the large cross-sectional elite athlete cohort (●), adapted from [1], Copyright 2006, The Endocrine Society.

The differences between genders, namely higher IGF axis markers in women and higher collagen markers in men, were also observed in the largely Caucasian group of elite athletes in the post-competition setting [2]. Inconsistent effects of gender on IGF axis markers have been reported in the general population. In the majority of studies in the general population, no effect of gender on IGF-I has been observed, as reviewed [3], although recent studies have reported lower IGF-I concentrations in women than in men in large multicentre [7] and multiethnic studies [18], and higher IGFBP-3 concentrations in women [18].

## 4. Effect of BMI

The relationships between BMI and the GH-responsive markers in our demographic study were weak in general. There was no correlation between BMI and IGF-I or ALS and IGFBP-3 was positively correlated with BMI, however the correlation was weak ($r = 0.06$, $p = 0.047$). All collagen markers were negatively but weakly correlated with BMI (PINP, $r = -0.16$, $p < 0.001$; ICTP $r = -0.15$, $p < 0.001$; PIIINP $r = -0.16$, $p < 0.001$). In multiple regression analysis, BMI made a small contribution to the total variation of 0.02–3%, equivalent to <12% of the attributable variation of all the markers. The study in elite athletes in the post-competition setting reported no significant effect of BMI on IGF-I, IGFBP-3 or ALS and a small positive influence on BMI for PICP [2].

Therefore, BMI has a minor contribution to variability of the GH-responsive markers in elite athletes. It is possible that associations found in the general population may not be observed in the elite athlete group, because the BMI in elite athletes is within a relatively narrow range. In the general population, both negative and positive associations have been observed between IGF axis

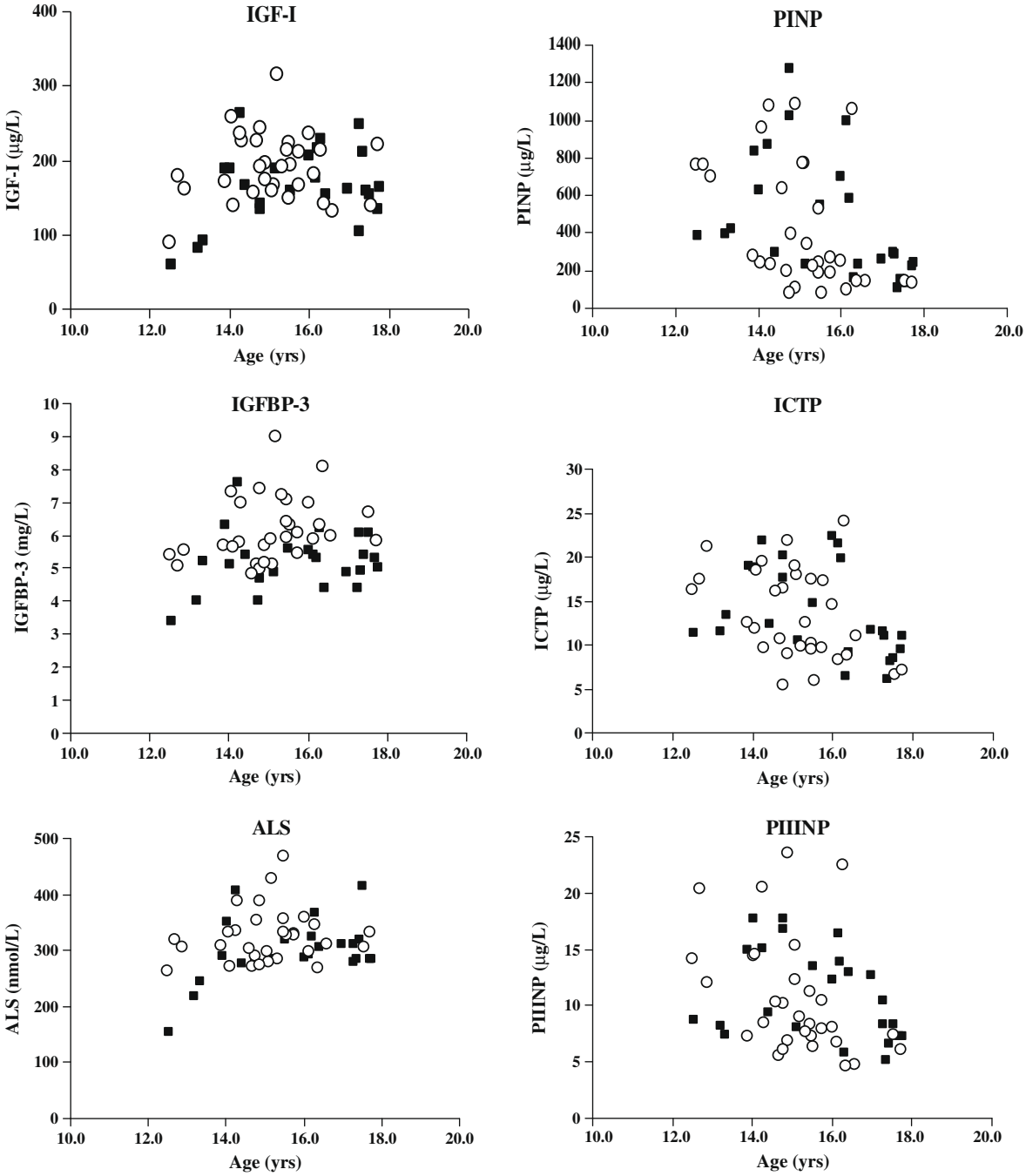


**Fig. 2.** IGF axis and collagen markers in young elite athletes. The measurements are plotted against age for IGF-I, IGFBP-3 and ALS (left panel), and PINP, ICTP and PIIINP (right panel) for the young elite athletes: boys (■) and girls (○).

markers and BMI [3,18], and there is recent evidence for a biphasic relation between IGF-I and BMI [19]. The negative correlations between the bone turnover markers and BMI in this study are consistent with the observation of a negative trend in serum osteocalcin, another marker of bone formation, in a large cohort of Norwegians aged 25–74 years [20].

## 5. Ethnicity

Our study in elite athletes also examined the influence of ethnicity on GH-responsive markers. The study population was drawn from 12 different countries, representing 4 major ethnic groups. Because of significant differences in age, gender and BMI between the ethnic groups, the analysis was adjusted for these variables. For IGF-I, PINP and ICTP, there were no significant differences between ethnic groups following adjustment for age, gender and BMI, whereas for IGFBP-3, ALS and PIIINP, there were significant differences. IGFBP-3 was higher in Caucasians than in Asians and Africans (by 8% and 18%, respectively, $p < 0.001$), and lower in Africans ($p < 0.001$) compared to each of the other groups. ALS was higher in Caucasians than in Asians and Africans (by 5% and 15%, respectively, $p < 0.001$), and lower in Africans ($p < 0.001$) compared to each of the other groups. PIIINP was higher in Asians than in Caucasians by 8.5% ($p < 0.0001$).

In multiple regression analysis, the contribution of ethnicity to the variation in IGF axis and bone turnover markers was small (⩽2% of total variation, equivalent to <6% of the attributable varia-

tion), except for IGFBP-3 and ALS. Ethnicity accounted for 14.7% of total variation for IGFBP-3, and 5.7% for ALS, equivalent to 65% and 22% of the attributable variation, respectively. In one other small comparison of 35 black athletes with matched white athletes, IGFBP-3 was lower in black than in white athletes [2], in agreement with our study. There is evidence in the general population for ethnic differences in IGF axis markers, as reviewed [3], however it is somewhat inconsistent. IGF-I and IGFBP-3 were lower in African Americans than Asians or Caucasians in a study of American men [21], whereas no difference in IGFBP-3 was shown between black and white American women in a small study [22]. In young adults in the UK, IGFBP-3 was higher in Caucasian than in Asian subjects, as observed in our study, but there was no significant difference in IGF-I [23]. In a large multi-ethnic cohort, significant variation with racial/ethnic group was observed for IGFBP-3, but for IGF-I only in women [18]. In the general population, there have been reports of genetic effects on type I collagen markers [24,25] but there is limited evidence for ethnic differences in bone turnover markers [16].

In summary, after adjustment for the confounding influences of age, gender and BMI, our data in elite athletes showed a trivial effect of ethnicity except for IGFBP-3 and ALS, which were both lower in Africans and higher in Caucasians. These differences appear similar to those reported in the general population.

## 6. Sporting type

In our cross-sectional study, we performed analysis of a subset ($n = 995$) of seven sporting categories, namely athletics, combat, endurance, power, power/endurance, racket and team ball sports, excluding from the analysis aesthetic, skill sports and multiple sports where numbers were low or from a single ethnic group. To avoid confounding effects, the data were again adjusted for age, gender, BMI and ethnicity. In general, IGF markers were lower in combat sports and higher in power and power/endurance sports, whereas the collagen markers were higher in combat sports, which could reflect increased bone and connective tissue turnover in response to minor injuries. IGF-I was significantly lower in combat sports than in power or power/endurance sports (by 21% and 19% respectively, $p < 0.005$) and lower in team ball than in power or power/endurance sports (by 22% and 19% respectively, $p < 0.005$). IGFBP-3 and ALS were significantly lower in combat sports than endurance, power or power/endurance sports (by 11–14% for IGFBP-3 and 6–8% for ALS, $p < 0.005$). The collagen markers were all significantly higher ($p < 0.005$) in combat sports than in most of the other sporting groups, by 29–77% for PINP, by 11–40% for ICTP, and by 13–28% for PIIINP.

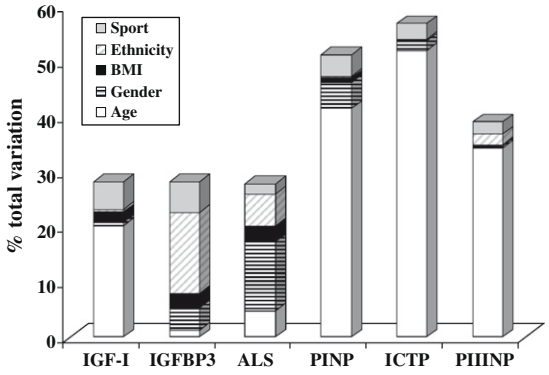


**Fig. 3.** Multiple regression analysis of the effects of demographic factors and sporting type in the cross-sectional study. The contribution of the age, gender, BMI, ethnicity and sport type to the total variation is shown for each marker: IGF-I, IGFBP-3, ALS, PINP, ICTP and PIIINP. Reproduced from [1], Copyright 2006, The Endocrine Society.

In a multiple linear regression model with age, gender, BMI and ethnicity, sporting type accounted for 2–5.5% of the total variation of IGF and collagen markers, equivalent to 5–19% of the attributable variation (Fig. 3). Therefore, compared to age and gender, the contribution of sport type was fairly modest. In the study in the post-competition setting, no major differences were found between sporting categories after correction for age, in elite athletes [2]. The results of both these studies in elite athletes therefore indicate that sporting type need not be considered as a potential confounder in establishing reference ranges for these markers for a GH doping test.

## 7. Summary

In our cross-sectional study of elite athletes from a wide range of ethnic backgrounds, age, gender, BMI, ethnicity and sport type accounted for up to 56% of the total variability of the IGF axis markers IGF-I, IGFBP-3 and ALS, and the collagen markers PINP, ICTP and PIIINP (Fig. 3). Age and gender were the major determinants of variability for IGF-I and the collagen markers. Our findings on the major influence of age and gender, and the negligible influence of sport type, have also been confirmed in a study of mostly Caucasian elite athletes in the post-competition setting [2].

Age, which was negatively correlated with all the markers, exerted the greatest effect for IGF-I and for all the collagen markers in our study, accounting for >80% of the attributable variation. The contribution of gender was smaller, except for IGFBP-3 and ALS. The IGF axis markers were all significantly higher in women, and the collagen markers were significantly higher in men. BMI made a minor overall contribution. The differences between ethnic groups were small apart from IGFBP-3 and ALS, following adjustment for age, gender and BMI. Ethnicity accounted for 15% and 6% total variability for IGFBP-3 and ALS respectively, compared to $\leqslant$2% for the other markers. Sport type exerted a modest influence on variability, with few significant differences following adjustment for age, gender, BMI and ethnicity. We also found by analysing extreme values (outside the 99% reference intervals), that no individuals had extreme values both for IGF-I and for the collagen markers in the same sample, suggesting that in non-abusing athletes, the use of IGF-I and a collagen marker will increase the specificity of the test.

## 8. Conclusions

Age and gender are the major determinants of variability for IGF-I and the collagen markers, whereas ethnicity and sport type have a minor influence. Therefore, a test based on IGF-I and the collagen markers must take age into account for men and women, and ethnicity and sport type are unlikely to be confounders for these markers.

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