Ageing and Longevity Are Related to Growth Hormone/Insulin-Like Growth Factor-1 Secretion

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Ageing · Parameters · Longevity · Insulin-like growth factor-1 · Testosterone · Lean body mass

Abstract
Background: It is known that the growth process is related to an individual’s life-span, but the role of growth hormone (GH) secretion in human ageing remains unknown. Objectives: This study has focussed on the influence of GH on ageing parameters and on its relationship with human longevity. Methods: To deal with the first issue, we compared ageing parameters of young (up to 39) and old (over 70) individuals having similar insulin-like growth factor-1 (IGF-1) blood levels. For the second one, the decline in IGF-1 levels was studied comparing its behaviour in the first half with that in the second half of adult life. The latter represents the period of life in which mortality progressively increases. Two hundred and five healthy individuals were chosen as subjects, well distributed by gender and age (between 19 and 93 years). Results: Old males with IGF-1 levels similar to young ones do not show the age-dependent decrease in serum testosterone and lean body mass, nor the increase in fat body mass. Other hormone-metabolic and nutritional parameters do not reveal any change compared with the results of all individuals. In females, the results do not allow to assume any IGF-1 influence. The behaviour of the linear regression in the second half of adult life of males, which becomes flat because old men having low IGF-1 blood levels die earlier, is consistent with these results. This effect, which is supported by predictive analysis, is not observed in females, i.e. the IGF-1 level declines in the second half of the women’s adult life are only a little flatter than in the first half. Finally, extrapolating the regressions obtained in the first half of adulthood, the age at which the curve crosses the x-axis is 110 years for males and 132 for females. Conclusion: The presented study of IGF-1 levels suggests that the GH secretion in adulthood plays a determinant role not only for some regressive manifestations, but also for life potential.

Introduction
Human adulthood begins once the biological optimum has been reached, after the completion of the growth and differentiation process [1]. The next step is a continuous organic regression until death. Therefore, if ageing is the process of structural and functional regression, the process of growth and differentiation would constitute the opposite. The relationship between life potential and growing time is well known not only for mammals. For example, molluscs or plants live as long as they grow [2].
Moreover, with an increasing growth period, there is also an increase in life-span, as observed in salmon after castration [3].

The blood levels of insulin-like growth factor-1 (IGF-1), which – as is well known – reflect the growth hormone (GH) secretion, behave similarly to the biological development of the human organism: rising up to a maximum and then declining continuously as adult age advances [4–7]. Moreover, a deficiency in GH or IGF-1 seems to be related to a reduced life expectancy [8, 9], and the experimental administration of GH/IGF-1 increases the life-span [10]. This relationship between one’s biological state and GH/IGF-1 secretion has justified its administration in the elderly [11–13].

In this study, we investigated the role of IGF-1 as a determinant of the ageing process. On the basis of data collected from a healthy adult population, we first aimed to detect the influence of IGF-1 on parameters which are normally age dependent. Secondly, we investigated whether IGF-1 levels were related to longevity.

**Material and Methods**

**Material**

Laboratory and nutritional data were collected from a well-defined healthy population of 204 persons aged between 19 and 92 years, homogeneously distributed by age and gender (more details on this population in ref. [14]).

**Analytical Procedures**

(1) Parameters of a sample of individuals aged between 19 and 39 years grouped by gender were first compared with those of persons over 70. Then, each sample was split into three homogeneous subgroups according to the different range of IGF-1 levels. The same was done in the group with the old subjects. The parameters of the young third showing the lowest IGF-1 levels were compared with those of the old third having the highest IGF-1 blood concentrations. Figure 1 represents this procedure pointing out the three different IGF-1 ranges of each sample.

(2) After obtaining the age-dependent curve of IGF-1 levels as y = e(a-bx) for males and females separately, these two population samples were split into two similar parts according to age, considering that the cut-off point of 56 years for males and 55 for females was close to the inflexion point of the original curve. Linear regressions have then been calculated and the corresponding statistical significance confirmed. The mathematical function obtained for the youngest half was then used to predict the age-dependent individual evolution of the measured IGF-1 concentration.

**Laboratory and Nutritional Methods**

IGF-1 serum determinations were performed by RIA using the commercially available kit Incstar after extraction through columns of octadecasyl-silica. The cross-reaction of the IGF-1 antibody with IGF-2, GH, TGF and PGF was <1%; the coefficient of variation (CV) of the interassay was 10.3%. Total testosterone serum concentration was also obtained by RIA (CV 12.3%). This was also true for the other determinations whose methodology was mainly based on standardised techniques for commercial kits. Finally, we measured the serum concentration of the amino-terminal peptide of procollagen type III (PIIIP) (RIA-gnost Behringwerke, Marburg, Germany), which in the adulthood behaves as a marker of arterial wall ageing (see ‘Discussion’). Among other well-known anthropometric measurements, we mainly used the lean body mass (LBM) according to Forbes and Bruining [15], expressed per metre of body height. The fat body mass (FBM) was estimated according to Durnin and Womersley [16] on the basis of the mean skinfold thickness over the triceps and scapula. The individuals’ ages were obtained from their birth date to the exact moment of the determination time.

**Statistic and Demographic Background**

The above-mentioned methodological procedures were chosen after a previous data analysis. Multiple and partial correlations, as well as discriminatory studies using stepwise multiple regression were done. The statistical analysis was performed with the help of the programmes Statgraphics® Version 5.0 and S-Plus® 2000 (Springer). The normal distribution of the results was confirmed by means of the Kolmogorov-Smirnov test; the data were expressed as the mean with the standard deviation (SD). The homogeneity between independent samples was estimated using the t test or Mann-Whitney U test. All regressions shown here are statistically significant, setting the significance at p < 0.05. The difference between regression slopes was calculated according to Armitage and Berry [17]. We extrapolated mortality data which could be basically applied to the Spanish population from mortality tables [18] containing data for the last 15 years. The rate of mortality was given as percent of the total number of deaths for all ages.

![Fig. 1. Scheme of the procedure used to study the influence of IGF-1 secretion on biological parameters. Young (19–39 years) and old (70–90 years) individuals grouped in similar size samples (pie charts) were split into thirds each showing a different range of IGF-1 blood concentration (nmol/l) from high (white slice) to low (dark). Parameters from the third of young individuals having IGF-1 levels within the lowest range (here represented for males) of 18–27 nmol/l (dark slice of left pie chart) were compared with those of the third of old subjects with the highest levels (20–25 nmol/l, white slice, on the right). Therefore, both groups have similar IGF-1 levels in spite of a great age difference.](image-url)
**Fig. 2.** a Age-dependent parameters which normally show a decreasing behaviour. Results of old individuals (70–92 years old) expressed as percent of the value of the young group (19–39 years old). First column (white = male; white-pointed = female) in reference to the total samples; second column (grey = male; dark = female) when comparing old individuals with the highest IGF-1 blood concentrations with the young subjects having the lowest levels. Statistical significance of the difference between the group with the young and the group with the old subjects: * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001, NS = not significant. b The same as in a, but for parameters which show an age-dependent rising behaviour.
Results

Compared with young adults, males over 70 clearly show different values for 9 of the 10 investigated parameters. Nevertheless, as shown in figure 2, these differences with respect to testosterone, LBM, and FBM practically disappear when the IGF-1 levels are similar, indicating that this parameter rather than age is a determinant. No influence has been observed for the other parameters with the exception of apolipoprotein B (apo B) where the loss of age-dependent differences seems to be due to higher apo B concentrations in young individuals with low IGF-1 levels. In contrast to males, the results in females are not conclusive. Old females having higher IGF-1 levels do not show a parameter influence like males. Here, the differences between young and old in testosterone levels and LBM disappear; but this is related to changes in the young group itself, as figure 2 for females shows.

In males, the decline in IGF-1 levels with advancing age is exponential (r = 0.53, r² = 28%, p < 0.0001), showing a progressively lower slope from around age 55 onwards. The linear regression obtained for IGF-1 levels of individuals in their first half of adult life shows a slope clearly higher than in the case of the second half (fig. 3). These regressions are statistically significantly different. In females, the exponential behaviour of the curve is also clear (r = 0.7, r² = 70%, p < 0.0001), but the slope change is not so drastic, as the linearized regression of both components shows. Furthermore, the regression obtained for the young population crosses the x-axis at the age of 110 years in males, whereas it does so 12 years later in females (fig. 3).

Figure 4 represents the longitudinal extrapolation – back to the age of 20 – of the IGF-1 levels in males of the last three decades of life. Applying the regression formula of the first half of adulthood, as mentioned in the methodology, there is an increase in mean values with the age of measurement. 33.3% of 56- to 69-year-old individuals, but only 8.3% of over 80-year olds, should have had IGF-1 levels below 35 nmol/l when they were young.

Comparing the highest with the lowest blood values measured in males, the age-dependent decline shows dif-
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Fig. 5. Comparison between the measured highest \( r = -0.91, r^2 = 83.5 \% \) and lowest IGF-1 levels at several ages with the predicted values in males. Stars = Predicted values for the highest concentration measured in youth at several ages; dark squares = predicted values for the lowest concentration measured in youth.

Discussion

The comparison between the gender of the decline in IGF-1 levels in the whole age range of the studied population between the gender indicates that, as already reported in ref. [19], women show a higher slope than men (fig. 3). In fact, there are two types of regressions with age: one corresponding to the first half of adulthood and one to the second half. The latter is clearly flat in males but not in females. Our results show that IGF-1 levels in old females are slightly higher than expected when considering the slope of decline during the first half of adult life. Furthermore, a dependence of the ageing parameters LBM, FBM and testosterone on IGF-1 levels is not observed in females either, in contrast to males. The older these individuals are, the lesser is the decline. The age-dependent IGF-1 level curve becomes flat, obviously because old males having low IGF-1 levels die earlier. For this reason, the evolution of the measured lowest blood concentrations of IGF-1 do not cross a limit. IGF-1 levels influence the result of the mentioned biomarkers in such a manner that age seems to lose its determinant character. In this context, it has to be stressed that LBM, FBM and testosterone levels are related to GH secretion [6, 20]. This agrees with reports which claim that GH/IGF-1 protects against ageing manifestations [8, 21–23]. In any case, especially in males, the decline in GH/IGF-1 secretion seems to represent the first step within the regression by ageing.
It is known that cross-sectional studies have to take into account that mortality may affect the result, when investigating the age dependence of a specific parameter. For instance, total cholesterol levels increase as age advances, but from around the sixties onwards, a decline begins due to the fact that persons with higher values die earlier. The opposite behaviour is observed in those parameters which decrease with ageing. In both cases, one assumes that the regression curve has been artificially modified by mortality. For this reason, we would like to stress that, since it is very difficult to perform a longitudinal study for the whole adult human life, only that age range in which mortality does not become important can be used to estimate the age dependence of cross-sectionally obtained results. This involves the age range from youth up to mid-adult age. Understandably, the regression curve should be statistically significant to allow a valid extrapolation. We used this method to predict IGF-1 values at later ages. The comparison with corresponding measured levels shows a consistence in males when considering high concentrations, but not in the case of low levels. As mentioned above, the lowest IGF-1 levels measured in old males are clearly over those predicted, obviously because they are selected by mortality.

The differences between males and females could indicate that the latter are less dependent on IGF-1 levels to survive because the decline in the second part of adult life has a slope which is only a little flatter than that of the first half. Nevertheless, the decline measured in the young half is a little slower in females than in males. In fact, the extrapolated curve crosses the x-axis (no GH/IGF-1 secretion should exists at this point) at the age of around 110 for males and 132 for females. This crossing point could indicate the maximal life potential expected in the studied sample, which is not far from that reported by other authors [24, 25], where – compared with males – the year difference in longevity of females is a little over of that known from demographic studies [26–29].

A clear influence of IGF-1 levels on ageing parameters has not been detected in females in contrast to males. This may be due to a less important role of IGF-1 in females’ survival, as discussed above. But on the basis of the results in males, there are parameters whose behaviour is IGF-1-independent, as apo B and glucose levels. On the contrary, these parameters, as total cholesterol and LDL (not shown), could be related to increasing insulin resistance, which in some manner is age dependent [30, 31]. Regarding triiodothyronine levels, it is known that they decrease with age [32–34], but so slightly that, when comparing two age groups as done in our work, the differences do not reach statistical significance, without showing any relationship with IGF-1 levels. The results remain unaltered when comparing old with young subjects having similar IGF-1 levels. With respect to the total caloric and protein intake, the results might be somehow related to IGF-1 levels in males in contrast to females, but we were not able to demonstrate this. Many factors are probably involved here.

There are no data on the role of GH/IGF-1 secretion in collagen III deposition in adulthood, but in the growth period [35]. On the other hand, blood levels of PIIP are a good marker to detect the effect of GH/IGF-1 treatments [36, 37]. As our results do not show any relationship of IGF-1 levels with those of PIIP, we believe that in both males and females, the increase in PIIP as adult age advances is independent of GH secretion. On the contrary, it seems that increasing PIIP levels during adulthood are related to a parallel enhancement of the insulin secretion [38].

Concluding, the presented study of IGF-1 levels points out that the GH secretion in adulthood may play a role as a determinant of some regressive manifestations and of life potential and thus seems to be related to longevity. The results in females, which indicate a lower dependence on GH than those in males in the ageing process, could explain why women live longer.

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References
