Endocrine and metabolic features of familial longevity : the Leiden Longevity Study

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Chapter 7: Reduced serum IGF-1 and familial longevity

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Abstract

Reduced insulin/ IGF-1 signaling has been associated with life span extension in various model organisms. However, the role of insulin/ IGF-1 signaling in human longevity remains controversial. In this study we related serum IGF-1 levels in nonagenarian siblings from the Leiden Longevity Study to the family mortality history score of their parents. We found that a lower parental family mortality history score (less mortality) was associated with lower IGF-1 serum levels in female but not in male nonagenarian siblings. These findings suggest that reduced IGF-1 activity is associated with exceptional familial longevity.

Introduction

The role of the evolutionarily conserved insulin/ insulin-like growth factor (IGF-1) signaling (IIS) pathway in the regulation of lifespan is well documented in worms [1], flies [2], and rodents [3, 4]. Genetic mutations that inhibit IIS activation prolong lifespan in these organisms, particularly in the female sex. The involvement of IIS modulation in human longevity is less clear. In agreement with the findings in model organisms, reduced IIS pathway activity was associated with old age survival in sporadic female octogenarians and different cohorts of nonagenarians [5, 6]. Furthermore, centenarians were shown to be enriched for rare IGF-1R mutations associated with IGF-1 resistance [7]. In contrast to these apparent beneficial effects, lower serum IGF-I levels in humans have been associated with an increased risk of developing cardiovascular disease and diabetes [8].

In order to identify heritable determinants of longevity we set up the Leiden Longevity Study. This study includes nonagenarian siblings, recruited from 421 Caucasian families based on proband siblings that both exhibit exceptional longevity [9] and their offspring [10]. Earlier we reported on the lack of differences in IGF-1 serum levels between middle-aged offspring of familial nonagenarians and controls [11]. In the nonagenarian siblings however, comparative analysis IGF-1 axis parameters is hampered by their extreme age, precluding the use of age-matched controls. Therefore we calculated a family mortality history score describing the mortality of the parents of the nonagenarian siblings [12]. We reasoned that in nonagenarian siblings from parents with a lower family mortality history score (i.e. lower than expected mortality), characteristics associated with longevity are more prominent than in nonagenarian siblings from parents with a higher family mortality history score. In the current study we aim to examine the association between parental family mortality history score of the parents of the nonagenarian siblings and serum parameters related to insulin/IGF-1 signaling in the nonagenarian siblings.

Materials and methods

In the Leiden Longevity Study, 421 families were recruited consisting of long-lived Caucasian siblings together with their offspring and the partners thereof. For the current study, data on IGF-1 and IGFBP3 levels were available for 859 of the 944 nonagenarian participants from the Leiden Longevity Study. The Medical Ethical Committee of the Leiden University Medical Centre approved the study and informed consent was obtained from all subjects. For details on enrollment please see previous publications [10, 11].

All serum measurements were performed with fully automated equipment. For IGF-1 and IGFBP3, the Modular E170 was used, for high sensitivity C-reactive protein (hsCRP) the Cobas

Integra 800 was used, both from Roche, Almere, the Netherlands. The coefficients of variation of these measurements were all below 5 %. ADL, IADL, MMSE and self perceived health was available for 779 participants.

Data on body height were available for 77 participants. Body height was measured using a tape measure when standing upright without shoes. Disability was determined using the activities of daily living scale (ADL) and Instrumental Activities of Daily Living scale (IADL). [13] Global cognitive function was assessed with the Mini Mental State Examination (MMSE). Self perceived health was assessed by one question with five alternatives: 1 = `very good', to 5 = `very poor'. ADL, IADL, MMSE and self perceived health was available for 779 participants.

For each parent we computed the sex and birth cohort cumulative hazards using the life tables of the Dutch population. Note that since both parents are deceased one minus the cumulative hazard equals the martingale residual. The martingale residual is defined as the difference between the event status (0 if alive, 1 if deceased) and the cumulative hazard at the observed age (current age or age at death). The sum of the martingale residuals measures the deviation of survival of the parents with respect to their birth cohort. Therefore negative values mean excess survival and positive values mean excess mortality.

The association between family mortality history score and IGF-1 axis parameters was assessed using a linear mixed model with a random sibship effect to model correlation of sibling data. Distributions of continuous variables were examined for normality and logarithmically transformed when appropriate (high sensitivity C-reactive protein). 17 individuals with serum IGF-1 or IGFBP3 levels beyond 3 standard deviations from the mean were excluded from the analyses: thus, in total 842 individuals were included in the analyses. The Statistical Package for the Social Sciences (SPSS) program for Windows, version 14.0, was used for data analysis. Graphs were drawn using Graph Pad Prism version 5.

Results

The baseline features of the study population are displayed in **table 1**. The median age of the population was 92.9 years and the population included 518 females (61.5%).

Table 1. Baseline characteristics of the study population

	Study population
Number participants (N)	842
Males (N, %)	518 (61.5)
Age (year)	92.9 (91.4 – 94.8)
IGF-1 (nmol/L)	10.0 (7.6 – 12.9)
IGFBP3 (mg/L)	2.9 (2.4 – 3.4)
IGF-1 IGFBP- Ratio	0.10 (0.08 – 0.12)
High sensitivity C-reactive protein (mg/L)	2.8 (1.3 – 5.7)
Disability (points)	
ADLs	18 (15 - 20)
Instrumental ADLs	8 (4 - 11)
Mini Mental State Examination	26 (22 - 28)
Self perceived health	3 (3 - 4)

Unless stated otherwise, all data are given as median values with interquartile range (25% - 75%).

Table 2 shows the association between the family mortality history score and the different IGF-1 axis parameters for males and females separately according to two models. Model 1 was adjusted for age only. As IGF-1 levels are known to be affected by illness, we repeated all analyses after adjustment for various parameters of physical disability in model 2. In both models a lower family mortality history score (lower than expected mortality) was associated with lower IGF-1 levels in females, but not in males (**figure 1**). No significant relation was observed between the family mortality history score and levels of IGFBP3 or the ratio of IGF-1 over IGFBP3, although in females a higher family mortality history score tended to be associated with a higher IGF-1 IGFBP3 molar ratio.

Next we determined the relation between family mortality history score and height for females and males separately. Although far from significant, in figure 2 higher family mortality history tended to be related to increased height in females (p=0.16), but not in males (p=0.95).

Table 2. Association between Family Mortality History Score and IGF-1 axis parameters

	Change per Family History Score Unit	p-value
Model 1: adjusted for age		
Females		
IGF-1 (nmol/L)	0.19 (-0.004 – 0.38)	0.055
IGFBP3 (mg/L)	0.02 (-0.02 – 0.07)	0.25
IGF-1 IGFBP-3 Molar Ratio (*10^4)	9.3 (-3.0 – 21.6)	0.14
Males		
IGF-1 (nmol/L)	0.003 (-0.24 – 0.25)	0.98
IGFBP3 (mg/L)	-0.01 (-0.06 – 0.04)	0.78
IGF-1 IGFBP3 Molar Ratio (*10^4)	4.2 (-12.4 – 20.8)	0.62
Model 2: as model 1 adjusted for ADLs, IADLs, MMSE, SPH and logCRP		
Females		
IGF-1 (nmol/L)	0.26 (0.05 – 0.46)	***0.017***
IGFBP3 (mg/L)	0.04 (-0.01 – 0.08)	0.11
IGF-1 IGFBP3 Molar Ratio (*10^4)	12.0 (-0.6 – 24.6)	0.061
Males		
IGF-1 (nmol/L)	0.05 (-0.21 – 0.32)	0.70
IGFBP-3 (mg/L)	-0.01 (-0.06 – 0.04)	0.74
IGF-1 IGFBP3 Molar Ratio (*10^4)	9.8 (8.0 – 27.6)	0.28

Data are presented as mean change per one unit increase in Family Mortality History Score and 95% confidence intervals. Results were adjusted for sex and age, MMSE, ADLs, instrumental ADLs, High sensitivity C - reactive protein and Self Perceived Health.

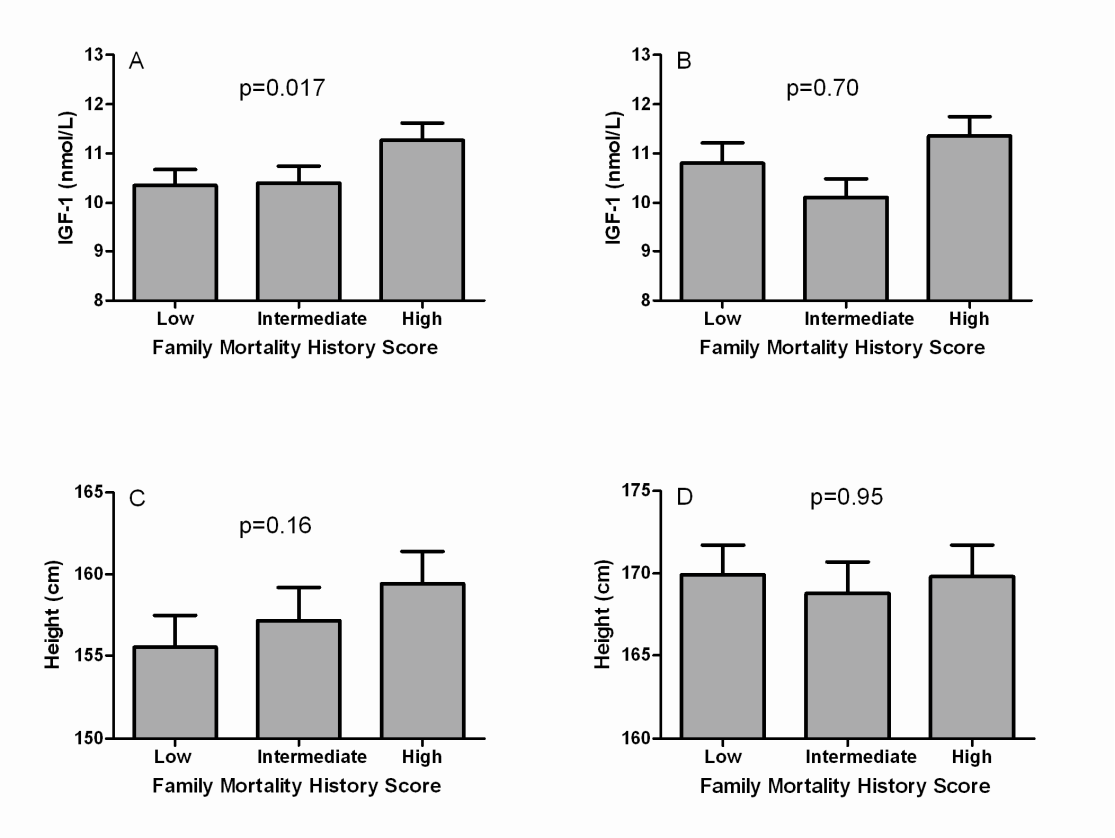

Figure 1. Association between family mortality history score and IGF-1 serum levels, for females (A) and males (B). *Bars represent tertiles of family mortality history scores adjusted for age, ADLs, IADLs, MMSE, self perceived health and log serum high sensitivity C-reactive protein. Association between family mortality history score and height for females (C) and males (D). Bars represent tertiles of family mortality history scores. Results were adjusted for age.*

Discussion

Our findings suggest that lower serum IGF-1 levels are a heritable determinant for exceptional longevity as observed in the Leiden Longevity Study. These results concur with the observed association between reduced IIS activity and longevity in various model organisms as well as in human studies showing life extending effects of reduced IGF-1 signaling [1-4, 6]. In these studies lifespan extending effects were mostly confined to females, in agreement with the results presented here.

Our findings are in contrast with the lack of difference in IGF-1 serum levels previously observed between middle-aged offspring of familial nonagenarians and controls. These contrasting results may be partly due to differences in age. The estimated contribution of genetic factors is modest (20-30%) but was shown to become more important and specific at higher ages [14, 15]. Therefore it is possible that the effects of genetic variation in the IIS pathway only become detectable at

advanced ages. In line, the association between FOXO3A and longevity was for example found to be stronger in centenarians than in nonagenarians [16]. Another possible explanation for these contrasting observations could be differences in imprinting of the IGF-1 gene, reflecting historical differences in maternal nutrition between the two generations [17].

Several weaknesses of our study should be considered. First, anthropometric data were only available for a small subset of the studied population. The non-significant association between family mortality history scores and small stature could therefore well be due to lack of power [6].
In conclusion, we present preliminary evidence that in females but not in males reduced IGF-1 levels are associated with exceptional familial longevity.

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