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Serum insulin-like growth factor 1 and facial ageing: high levels associate with reduced skin wrinkling in a cross-sectional study

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Conflicts of interest
None declared.

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Summary

Background Insulin-like growth factor (IGF)-1 is a growth factor that can influence fibroblast functioning, with effects including the inhibition of collagenases and the induction of collagen expression.

Objectives To assess whether serum IGF-1, IGF-binding protein (IGFBP)3 and the ratio between IGF-1 and IGFBP3, as a measure of IGF-1 bioavailability, are associated with facial ageing and skin wrinkling.

Methods From a random sample comprising 617 subjects from the Leiden Longevity Study, perceived age and skin wrinkling were assessed from facial photographs, and IGF-1 and IGFBP3 were measured in serum. The associations were assessed using linear regression models, adjusted for chronological age, sex, body mass index, smoking and sun exposure.

Results Across tertiles of the ratio of IGF-1 to IGFBP3, and after adjusting for all potential confounding factors, the mean perceived age decreased from 60·6 years in the lowest tertile to 59·5 years in the highest (P_{trend} = 0·045). Similarly, the mean skin wrinkling grade decreased from 4·8 in the lowest tertile to 4·5 in the highest (P_{trend} = 0·011). Adding skin wrinkling as a covariate in the analysis between IGF-1 and perceived age diminished this association.

Conclusions This study demonstrates that a higher ratio of IGF-1 to IGFBP3 associates with a lower perceived age, via its association with reduced skin wrinkling. Whether high IGF-1 levels actually delay the accumulation of skin wrinkling now needs investigating.

Insulin-like growth factor (IGF)-1 is a hormone regulated by the growth–hormone axis and is predominantly secreted by the liver. In blood, IGF-1 is often bound to IGF-binding protein (IGFBP)3, which extends the half-life of IGF-1 and reduces the capacity of IGF-1 to bind to its receptor. The most important functions of IGF-1 are metabolic and proliferative. The insulin/IGF signalling pathway comprises the metabolic function of IGF-1. In humans, serum IGF-1 levels decrease with increasing age.[1] In addition, low IGF-1 levels associate with numerous clinical endpoints, including an increased risk of cardiovascular disease[2] and an increased risk of mortality.[3,4] These data support the notion that serum IGF-1 is a marker of ageing as well as health.

IGF-1 signalling is also active in the skin, and has been linked to skin ageing. Skin fibroblasts and keratinocytes of the stratum granulosum produce IGF-1, whereas basal keratinocytes express the IGF-1 receptor.[5] In addition, *in vitro* experiments have shown that IGF-1 upregulates the expression of collagen and inhibits the expression of matrix metalloproteinase (MMP)-1, a collagenase that breaks down the collagen matrix in the dermis.[6] The activity of MMP-1 is higher in old skin,[7,8] which might indicate that high serum IGF-1 levels result in a lower activity of this enzyme, and therefore might be associated with biologically younger-looking skin.

Perceived age (how old participants look to others in facial photographs)[9] is a good marker for overall facial ageing and

is highly correlated to several facial features, including skin wrinkling,[10] skin colour homogeneity,[11] lip size[10] and sag.[12] Several intrinsic and extrinsic factors have been described as influencing perceived age. For example, sun exposure, smoking and low body mass index (BMI), as well as high serum glucose levels[13] and high morning serum cortisol levels,[14] associate with an older appearance, whereas a high social class and high education associate with a younger appearance.[15] In addition, some of the differences in perceived age between individuals of a similar age can be explained by genetic factors.[10,16] Whether IGF-1 levels associate with perceived age or aspects of skin ageing at a population level has yet to be investigated. In this study we assessed the association of serum IGF-1 levels with perceived age and skin wrinkling in a random sample comprising 617 middle-aged subjects from the Leiden Longevity Study.

Patients and methods

Study population

The Leiden Longevity Study was designed to identify phenotypic and genetic markers related to human longevity. A more detailed description of the study design and recruitment strategy has been provided elsewhere.[17,18] In short, a total of 421 families were recruited, consisting of long-lived white siblings together with their offspring and the partners of the offspring. Inclusion was performed only when at least two long-lived siblings were still alive and fulfilled the age criteria of 89 years for men and 91 years for women. The siblings were not selected on any health conditions or demographics.[17] As proper controls at high age are lacking, the offspring of these nonagenarian siblings were asked to participate as well, because they have a higher propensity to reach a very old age.[17] The partners of the offspring were included in the study as controls matched for environment and age.

From the middle-aged subjects, a random subpopulation consisting of 670 subjects was enrolled for this cross-sectional study (comprising 335 offspring and 335 partners). Blood sample measurements were missing from 15 subjects, and the wrinkle grading could not be determined in men with a beard ($n = 37$) or with a skin graft ($n = 1$). For this reason, all analyses were conducted in a population of 617 subjects.

Blood measurements

Nonfasting blood samples were drawn and processed within 2 h. Serum samples were stored at −80 °C until the time of analysis. IGF-1 and IGFBP3 levels were measured using a chemiluminescent immunometric assay on a Siemens Immulite 2500 analyser (Siemens Healthcare Medical Diagnostics, Bad Nauheim, Germany). Creatinine levels, as a crude measure of kidney function, were measured with the kinetic alkaline picrate methodology, implemented on an Abbott ci8200 Integrated System (Abbott Laboratories, Libertyville, IL, U.S.A.).

Facial ageing assessment

The method for assessing a person's perceived age, as an overall measure of facial skin ageing, has been described and validated previously.[9,10,19] In short, subjects came to the study centre without any make-up or hairstyling products. From every subject one facial photograph from the front and one at 45 degrees were taken. Photographs, with concealed hair and clothing, were assessed by 60 independent assessors. The mean age assessment of all 60 independent assessments is herein called the perceived age. On average, subjects were perceived to be younger than their chronological ages, in line with previous assessments of age by British age assessors.[9] The inter-rater reliability of the perceived age assessment was determined using Cronbach's alpha and was 0·99. Skin wrinkling was graded on a nine-point scale by a visual assessment of front-on, whole-face photographs using the number and depth of fine and coarse wrinkles as described and validated previously.[19,20] A higher wrinkle grade equated to a higher degree of skin wrinkling.

Other variables

Weight and height, for calculation of BMI, were measured by research nurses at the study centre. Additionally, information on each subject's sun exposure in the past (not outside, often outside and mostly outside) and smoking habits was obtained by questionnaire. BMI was calculated by dividing the subject's weight (in kilograms) by height (in metres) squared. The ratio between IGF-1 and IGFBP3 represents a crude measure of the amount of bioavailable IGF-1 in serum.[21] For calculations, the following molecular masses were used: IGF-1, 7·5 kDa and IGFBP3, 28·5 kDa.

Statistical analyses

The associations between IGF-1, IGFBP3 and their ratio, with perceived age and skin wrinkling, were examined using linear regression models. For the analyses, the subjects were divided into tertiles sized as equally as possible according to their levels of IGF-1, IGFBP3 and the ratio of IGF-1 to IGFBP3. The mean perceived age and wrinkle grading dependent on these tertiles were adjusted for possible confounding factors using linear regression. Chronological age, sex, current smoking and BMI were considered confounding factors. As skin wrinkling is a major component of overall facial skin ageing, we assessed whether or not the association between IGF-1, IGFBP3 and their ratio was independent of skin wrinkling (if so, this might be indicative that other facial skin features are influenced by IGF-1), by including the skin wrinkle grading as a covariate in the analysis between the marker and perceived age. A sensitivity analysis was performed to assess whether the associations were influenced by the prevalence of disease. This was done by including creatinine levels (as a crude measure of kidney function), and type 2 diabetes and hypertension (as both are chronic and the most common diseases in our study) as additional covariates in the model. A second sensitivity analysis was performed with sun exposure (not outside, often

outside, mainly outside in the summer) included as a covariate, as it has a major influence on skin ageing.[22]

All statistical analyses were performed using SPSS v.17 for Windows (SPSS Inc., Chicago, IL, U.S.A.). P-values below 0.05 were considered statistically significant.

Results

Characteristics of the study population

General characteristics of the study population are presented in Table 1. On average, subjects were perceived to be younger than their chronological ages, in line with previous assessments of age by British age assessors.[9] Most of the subjects (60%) said that they were outside in the sun most of the day, while a small group stayed inside most of the day (13%). Compared with participants who mostly stayed inside, participants going out regularly had a higher perceived age and a higher wrinkle grade, but the ratio between IGF-1 and IGFBP3 was not affected (Fig. S1; see Supporting Information). For the covariates used in this study, chronological age, sex, BMI (mainly caused by weight), current smoking and sun exposure were significantly associated with both perceived age and wrinkle grade (Table S1; see Supporting Information).

Association of serum insulin-like growth factor 1 levels with perceived age and skin wrinkling

Subjects were divided into tertiles for IGF-1, IGFBP3 and the ratio of IGF-1 to IGFBP3. Chronological age, perceived age, and skin wrinkle grade were analysed across these tertiles. Analyses were adjusted for sex, BMI and current smoking, and, for perceived age and skin wrinkling, chronological age. Results of these analyses are presented in Table 2. High levels of IGF-1 were associated with a younger chronological age ($P_{trend} < 0{\cdot}001$), a trend towards a lower perceived age ($P_{trend} = 0{\cdot}061$) and a trend towards less skin wrinkling ($P_{trend} = 0{\cdot}082$). High levels of IGFBP3 were associated with a younger chronological age ($P_{trend} = 0{\cdot}001$) and a lower perceived age ($P_{trend} = 0{\cdot}040$), but not with the degree of skin wrinkling ($P_{trend} = 0{\cdot}25$). Finally, for the molar ratio of IGF-1 to IGFBP3, as a measure of free serum IGF-1, the mean chronological age was similar across the three tertiles ($P_{trend} = 0{\cdot}63$), the mean perceived age decreased from 61·1 years in the lowest tertile to 60·0 years in the highest tertile ($P_{trend} = 0{\cdot}032$) and the mean skin wrinkling decreased from 4·94 in the lowest tertile to 4·64 in the highest tertile ($P_{trend} = 0{\cdot}008$). The associations did not materially change (and remained statistically significant) when we additionally adjusted for creatinine levels (as a crude measure of kidney function), type 2 diabetes and hypertension. When adjusting the analysis of perceived age for the grade of skin wrinkling, the association diminished completely ($P_{trend} = 0{\cdot}88$), meaning that the association between the ratio of IGF-1 to IGFBP3 and perceived age was mainly driven by skin wrinkling. These associations were similar for men and women, and for offspring of long-lived families and their partners.

As sun exposure is a major influence on skin wrinkling,[22] we assessed whether the observed association between the ratio of IGF-1 to IGFBP3 and perceived age or skin wrinkling was dependent on sun exposure. Figure 1 shows the mean perceived age (a) and the wrinkle grade (b), dependent on the tertiles of the ratio between IGF-1 and IGFBP3, after adjustment for sun exposure (denoted as not outside, often outside and mostly outside). A high ratio of IGF-1 to IGFBP3 was still significantly associated with a lower perceived age and less skin wrinkling ($P_{trend} = 0{\cdot}045$ and $0{\cdot}011$, respectively). The association between the molar ratio and perceived age was not observed after additional adjustment for the wrinkle grading (results not shown).

Table 1 Characteristics of the study population

	Total (n = 617)
Women, n (%)	332 (53·8)
Chronological age (years)	62·9 ± 6·7
Perceived age (years)	59·6 ± 7·8
Wrinkle grade (points)	4·6 ± 1·3
Body mass index (kg m^{-2})	26·6 ± 4·0
Height (m)	1·72 ± 0·09
Weight (kg)	78·6 ± 13·6
Smoking, n (%)	78 (12·6)
Creatinine (mmol L^{-1})	82·7 ± 13·0
Blood parameters	
IGF-1 (nmol L^{-1})	17·2 ± 4·9
IGFBP3 (mg L^{-1})	4·40 ± 0·9
[a]Molar ratio	0·112 ± 0·03
Sun exposure, n (%)	
Not outside	80 (13·0)
Often outside	169 (27·4)
Mostly outside	368 (59·6)
Disease history, n (%)	
Type 2 diabetes	34 (5·5)
Hypertension	148 (24·0)

All parameters are presented as the mean ± SD unless indicated otherwise. IGF, insulin-like growth factor; IGFBP, IGF-binding protein. [a]IGF-1 / IGFBP3 ratio.

Discussion

In this study, we showed that higher values of the ratio of IGF-1 to IGFBP3, as a measure of bioavailable IGF-1 in serum, were associated with a lower perceived age, mainly through association with a lower degree of skin wrinkling on the face. This can be explained by the high correlation between perceived age and the degree of skin wrinkling, which is an important component of overall facial ageing.[10] Similar results were observed with IGF-1 alone (not taking into account IGFBP3 levels), although the results were just outside statistical significance.

A possible biological explanation for the association between serum IGF-1 levels and skin wrinkling is through skin fibroblastic functioning. The activity of the MMP-1

Table 2 Perceived age and wrinkle grade dependent on tertiles of insulin-like growth factor (IGF)-1, IGF-binding protein (IGFBP)3 and their molar ratio

	Tertiles of parameter			
	Low	Medium	High	P_{trend}
IGF-1				
N	209	203	205	
Range (nmol L^{-1})	3·90–14·9	15·0–18·6	18·7–37·4	
Perceived age (years)	60·2 (59·5–60·9)	59·4 (58·7–60·1)	59·3 (58·6–60·0)	0·061
Wrinkle grade (points)	4·90 (4·72–5·07)	4·84 (4·66–5·03)	4·70 (4·52–4·89)	0·082
IGFBP3				
N	217	198	202	
Range (mg L^{-1})	1·8–4·0	4·1–4·7	4·8–8·1	
Perceived age (years)	60·2 (59·6–60·9)	59·4 (58·7–60·1)	59·2 (58·5–59·9)	0·040
Wrinkle grade (points)	4·70 (4·55–4·84)	4·62 (4·46–4·77)	4·57 (4·42–4·72)	0·25
IGF-1 / IGFBP3 ratio				
N	205	206	206	
Range	0·054–0·100	0·101–0·120	0·121–0·232	
Perceived age (years)	61·1 (60·3–62·0)	61·0 (60·1–61·9)	60·0 (59·1–60·9)	0·032
Wrinkle grade (points)	4·94 (4·76–5·11)	4·84 (4·66–5·02)	4·64 (4·46–4·83)	0·008

Analyses were adjusted for sex, current smoking and body mass index, and, for perceived age and skin wrinkling, chronological age. Data are presented as means with 95% confidence intervals unless otherwise stated.

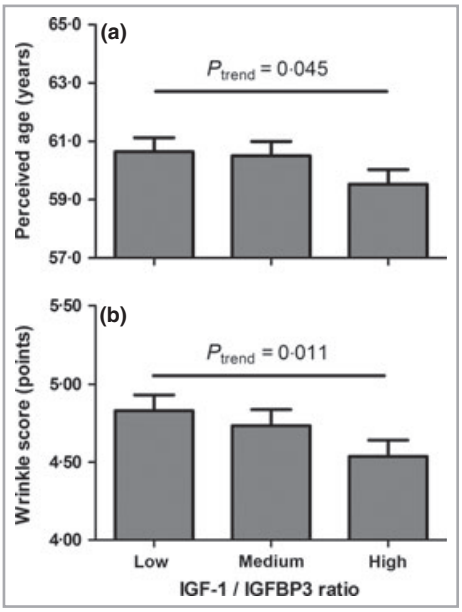

Fig 1. Perceived age and wrinkle grade, dependent on the molar ratio of insulin-like growth factor (IGF)-1 to IGF-binding protein (IGFBP)3, after additional adjustment for sun exposure. The graphs present the adjusted mean perceived age (a) and wrinkle grade (b) over tertiles of the ratio of IGF-1 to IGFBP3. Both analyses were adjusted for chronological age, sex, current smoking, body mass index and sun exposure (categorized as not outside, often outside and mostly outside). (a) Perceived age decreased when the ratio of IGF-1 to IGFBP3 increased. The mean ± SEM perceived age decreased from 60·6 ± 0·5 years in the first tertile to 59·5 ± 0·5 years in the third (P_{trend} = 0·045). (b) Skin wrinkling decreased when the ratio of IGF-1 to IGFBP3 increased. The mean ± SEM wrinkle grade decreased from 4·8 ± 0·1 points in the first tertile to 4·5 ± 0·1 points in the third (P_{trend} = 0·011).

protein is higher in elderly skin. This enzyme breaks down collagen, resulting in a thinner and more disorganized dermal matrix.[7,8] *In vitro* experiments have shown that IGF-1 inhibits the expression of MMP-1 mRNA and protein by fibroblasts, and upregulates the expression of collagen.[6] With increasing age, the serum and skin levels of IGF-1 decrease,[1,7] which might partly explain the age-related upregulation of MMP-1 in skin.[23] Exposure to ultraviolet (UV) radiation also induces expression of MMP-1 in dermal fibroblasts.[24] Interestingly, *in vitro* experiments have shown that adding IGF-1 to cell culture media reduces apoptosis and promotes keratinocyte cellular repair after exposure to UV radiation,[7] indicating that IGF-1 might be protective against UV-induced damage *in vivo*. However, in this study we found that the ratio of IGF-1 to IGFBP3 and its association with skin wrinkling were only marginally weakened by adjustment for sun exposure. Thus, further investigations are required to determine whether higher levels of IGF-1 are associated with less skin wrinkling through their protective effects on UV-induced damage or via other mechanisms.

We also showed that lower levels of IGF-1 are associated with a higher perceived age. Lower levels of IGF-1 have also been associated with a higher mortality rate,[3,4] increased cognitive decline,[25] an increased risk of cardiovascular disease,[2] increased frailty[26] and a weaker grip strength,[27] which associates with higher mortality.[28] In addition, in those over 70 years of age, a higher perceived age has been found to associate with lower cognitive functioning, a lower grip strength and a higher risk of mortality.[19] Thus, the link between perceived age and IGF-1 could be indicative of the role that IGF-1 has in systemic ageing. In support of this, higher levels of IGF-1 are associated with longer telomere

length,[29] which associates with a lower perceived age[19] and lower mortality.[30] However, we have shown previously that the offspring of long-lived families have similar levels of serum IGF-1 compared with age-matched controls,[31] although they do display a more beneficial metabolic profile.[32,33] These results suggest that the effect of IGF-1 on ageing could be more related to cell proliferative capacity than to metabolic functioning. Further work is required to determine whether or not the association between perceived age and IGF-1 via skin wrinkling is indicative of the role that IGF-1 plays in systemic ageing.

This study has a few limitations. As a result of our cross-sectional study design, we cannot infer a causal relationship between IGF-1 and perceived age or skin wrinkling. In addition, it is unclear how reflective the levels of IGF-1 in serum are of those in facial skin, although IGF-1 in facial sebum strongly correlates with IGF-1 levels in serum.[34] The present study also contains two cohorts: the middle-aged subjects from long-lived families and their partners. However, the presented associations were similar in the offspring and partner groups, indicating that they can be treated as one group. The use of nonfasted serum measurements in the current study did not materially affect our study results, as diurnal variation of IGF-1 is small.[35] Finally, the sun-exposure variable was subjective and only an approximation of past sun exposure. Reassuringly, though, we observed a higher perceived age in the participants with a high sun-exposure level, compared with subjects who were mainly inside, indicating that the question did capture, to some degree, past sun-exposure levels.

In conclusion, this study shows that higher levels of IGF-1 (relative to IGFBP3 levels) were associated with a lower perceived age and a lower degree of skin wrinkling, independent of confounding factors, although the association with perceived age was mainly driven by skin wrinkling. More research and replication should now be performed to determine whether IGF-1 is causally linked to perceived age and, if so, through which mechanisms IGF-1 prevents or delays skin ageing.

What's already known about this topic?

- Previous research has indicated that insulin-like growth factor (IGF)-1 might be a marker of ageing, as well as a marker for overall health.
- *In vitro* experiments have shown that IGF-1 can induce collagen expression and inhibit the expression of collagenase.

What does this study add?

- This study showed that high levels of IGF-1 relative to IGF-binding protein 3 were associated with a lower perceived age and a lower degree of skin wrinkling.
- The results suggest that the association with perceived age is mainly driven by skin wrinkling.

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Supporting Information

Additional Supporting Information may be found in the online version of the article:

Fig S1. Comparison of (a) perceived age, (b) wrinkle score and (c) insulin-like growth factor (IGF)-1 to IGF-binding protein (IGFBP)3 ratio between participants mostly staying inside and participants going out regularly.

Table S1. Association of considered confounding factors with perceived age and wrinkle grade.