Growing Old: A meta-analysis of IGF-1 expression throughout human life

Frontiers in Aging

IGF-1 is integral to the process of aging and human health throughout life. Many investigations have looked at IGF-1 expression within age ranges of interest and it is understood that this expression is reduced throughout life. However, there does not exist a detailed understanding of when these changes occur. To the audience of this journal, it is imperative that the published literature be analyzed to concrete our understanding of baseline IGF-1 expression and increase the precision of IGF-1 levels at each age in order to promote research that can focus more closely on phenomena of aging at these critical junctures.

This research aims to answer questions about the level of IGF-1 expression throughout human life and to deepen our understanding of specific timepoints relevant to stages of aging.

Our findings indicate that the level of total IGF-1 reduction from sexual maturity to extreme age is 30% higher than previously described. Within age groups, IGF-1 shows significant fluctuation at X years (this work will be done after class).

This manuscript is not in consideration by any other journals and all authors have approved of its submission.

Growing Old: A meta-analysis of IGF-1 expression throughout the human lifespan

Taylor McKibben, Tonia Schwartz1\*, Alan Wilson,2

1Schwartz Lab of Eco-evolutionary Genomics, Auburn University, Department of Biological Sciences, Auburn, Alabama, United States of America

2Wilson Lab, Auburn University, School of Fisheries, Aquaculture & Aquatic Studies, Auburn, Alabama, United States of America

**\* Correspondence:**Taylor McKibben  
twm0009@auburn.edu

Keywords: Insulin-Like Growth Factor1, Metabolomics2, Systematic Literature Review3, Aging4, IIS/TOR5.

Abstract

Insulin-like Growth Factor 1(IGF-1) is a prominent signaling hormone in the Insulin and Insulin-like pathway. This pathway regulates many metabolic processes, prominently the glycolytic and gluconeogenic pathways; effectively, the production of energy storage molecules. These processes interact with every cell in the body and IGF-1 additionally acts to signal for cell proliferation and to inhibit apoptosis. This protein is known to be upregulated during puberty and to decrease expression with age; conditions such as dwarfism, gigantism, and cancer can all be caused by regulatory issues of IGF-1 production. Due to this impact, it should be a factor considered in all studies related to aging, but it lacks a detailed baseline of expression across the human lifespan. The goal of this meta-analysis is to synthesize studies of longitudinal IGF-1 expression and create a timeline of its expression. Our results showed a significant effect size (Log Risk Ratio, lnR = -0.10) equaling an 80% reduction in IGF-1 from age 20-110, a 30% higher loss than previously described.

# Introduction

IGF-1 is a hormone similar in structure to insulin. It is one member of a family of IGF proteins formed through gene duplication1. It can bind to the insulin receptor (IR) as well as IGF receptors, all with varying degrees of binding affinity. It most strongly binds to its own receptor, IGF1R, and preferentially activates that signaling pathway2. Produced primarily in the liver, this hormone is circulated throughout the bloodstream and can quickly react to the uptake of nutrients like carbohydrates and proteins3. It is also expressed at a lower level within cells and tissues, distributed in both a paracrine and endocrine fashion4. IGF-1 primarily binds IGF1R, the IGF-1 receptor. This signaling activates the MTOR and MAPK pathways, causing cell proliferation, DNA synthesis, and anti-apoptotic behavior5.

The expression of IGF-1 changes throughout life and is regulated by the production of growth hormone and IGF1BP, a binding protein that sequesters IGF-16. The pubertal growth period shows the highest levels of IGF-1 expression, stabilizing around 20 years old before tapering off throughout life7. At age 20 there is a marked drop in expression, falling to approximately 1000 ng/ul. By age 70 IGF-1 concentration has lowered to 500 ng/ul8. Some data have suggested that there may be a stage of dysregulation during old age correlated with increased risk of health problems and mortality9. With the regulation of cellular growth and apoptosis, IGF-1 is linked to the development of many types of cancer10. The risk of cancer increases over the human lifespan with the accumulation of cells showing aberrant growth behavior11. Thus, establishing the base levels of expression at detailed timepoints will allow for more focused investigation into risk factors for this disease and improve diagnostic power when assessing patients.

The goal of this meta-analysis is to combine studies of different age groups and produce a more accurate timeline of IGF-1 expression, assessed by the best fit of data by age range. The basis of this timeline will require an accurate description of baseline expression at each stage of life. To do so, the authors performed a systematic literature search, a meta-analysis of IGF-1 expression at different age ranges, and a time-series analysis of the resulting effect sizes binned by best fit of age groups and IGF-1 levels.

# Materials and methods

## Systematic literature search

This literature search was conducted within PRISMA guidelines12 (figure 1). The literature searched contains both white literature from Web of Science and PubMed as well as grey literature from ProQuest. These databases contain research from both scientific inquiry and biomedical standpoints. Search or MeSH terms used contain [“IGF-1” AND “Age” AND “human”] within the title along with variants of the same terms. Exclusionary terms were [NOT “IGFBP” OR “IGFR”] within the title along with variations of the same terms. IGF-1 associated proteins were not considered as they are irrelevant to serum and mRNA measurements of IGF-1. Searches were regularly conducted from February 2023 through April 15th, 2023.

A diagram of records

Description automatically generated with low confidence

Fig 1.) PRISMA flow chart describing systematic literature search. Final number of studies with applicable data (n = 16)

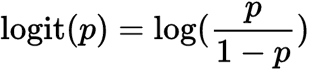
## Data collection and filtering

To qualify for inclusion, data must be presented in a control/treatment fashion that includes changes in IGF in response to age. Experimental data was also acceptable in addition to observational studies. No data from diseased or artificially induced expression samples were included. MetaDigitise13 was used to collect data from graphs. When available, data was sourced from tables and supplementary files. Error measures such as standard error and 95% confidence interval were converted to standard deviation. Ages were extracted as individual years when not already binned as mean ages. Measurements of IGF-1 were not converted as the effect size, log odds response ratio (LRR), compares relative change. Any available factors such as sex, weight, and level of fitness were recorded. The control group was set as the youngest age group within any data set.

## Statistical methods

### Effect size calculation

Effect sizes calculated using the log Response Ratio. The LRR can be calculated both using raw data and data previously reported under a different effect size such as Hedge’s g, granting the ability to use all available data. The LRR is calculated as the correlation of measurements between two variables. The use of a natural log transformation also serves to normalize the distribution of data to minimize the effects of variability in distribution within small data sets.



Rstudio (022.7.2.576) and the metafor14 package were used to calculate the effect sizes. A weighted random-effects model was used to test our effect sizes as the true correlation is unknown. Heterogeneity was assessed through I2 and H2 values produced by via random mixed-effects analysis.

### Sensitivity and bias testing

Tests of bias were calculated to test for issues within the data set. Publication bias was tested using the leave1out model to test the level of influence from individual data sets on the final effect, supplemented by a trim and fill analysis as a non-parametric test of data bias sensitivity, and Egger’s regression to test for overall effect size sensitivity to data heterogeneity. Fail safe analysis was done to account for the “File-drawer problem”, a test for the number of null-effect studies needed to fail the alternative hypothesis.

## Time-series analysis

This section does not fall under the scope of the meta-analysis class. This is an ultimate goal of the paper but will not be started until after the class.

# Results

## Systematic literature search

The search results returned 1649 papers (WoS = 1295, PubMed = 259, Proquest = 95). After removing duplicates, 1205 papers remained. Our inclusion criteria required: Open access or access through the Auburn University library, not a review, included human measurements, had data combining IGF-1 and aging, contained a non-diseased control, and were longitudinal. After filtering, 111 papers remained. Papers were then examined for extractable data, leaving 16 studies9,15–28.

## Effect size calculations

A weighted mixed-effects model showed a LRR of -0.097 (p = 0.02) relationship of IGF-1 decreasing with age (Figure 2). This LRR shows a 73% reduction in IGF-1 levels from maturity to senescence. The data contained significant heterogeneity in data, but not sampling (T2 = 0.0174, I2 = 79.83%).

A picture containing text, screenshot, parallel, line

Description automatically generated

Fig. 2.) Forest plot of weighted mixed-effects Log Response Ratio effect sizes. Final effect size is -0.10 on a log scale. This indicates a negative correlation between IGF-1 concentrations as age progresses; this represents a 78% reduction in IGF-1 from maturity to senescence.

## Bias testing

The tests for publication bias showed non-significant bias (T2 = 0.026, p = 0.35). Egger’s regression showed no bias in the dataset due to heterogeneity in individual effect sizes (Figure 3). The fail-safe analysis showed only 232 papers needed to significantly change the interpretation, possibly suggesting that additional data needs to be collected.

A picture containing diagram, text, line, plot

Description automatically generated

Fig 3.) Funnel plot of heterogeneity between studies by standard error and mean difference. Data outside of the white space indicates studies that are significantly different from the overall dataset.

## Time-series analysis

The time-series analysis will not be performed during this class but will be included in the final submission.

# Discussion

## Baseline IGF-1 concentrations across age ranges

IGF-1 has major effects on health and longevity29. While this effect has been studied within many age ranges, there is no available data that compares studies to create a detailed timeline of IGF-1 expression across human lifespan. This data is necessary for the field as high-resolution timelines will allow for detailed research into concurrent comorbidities, more effective IGF-1 therapy, and inquiry into molecular mechanisms of aging and IGF-1 expression’s downstream consequences30–33.

To validate the established expectation of reduction in IGF-1 over time, we conducted a meta-analysis of studies looking at human concentrations of IGF-1 across lifespan. Within studies, the control group was set as the youngest age range reported, setting the direction of examination as changes in IGF-1 as age increases. With an LRR effect size of -0.10, we see an 80% reduction in IGF-1 levels from sexual maturity to extreme age. This indicates that the current understanding of IGF-1 expression is correct and that the reduction from sexual maturity to death is significant. This baseline of reduction also serves as a control value when building our timeline and fitting models.

This data set had significant heterogeneity and would benefit from additional data. Many data were protected health research with restricted access; this included several national databanks with detailed longitudinal data and large populations. In future studies, we will analyze various mechanisms associated with IGF-1 with an impact on aging and health.

## Time series analysis

###To be done after the conclusion of this class.

# Conflict of Interest

Authors disclosed no conflicts of interest

# Author Contributions

Taylor McKibben: Literature Review, Data Work, Statistical Analysis, Manuscript preparation

# Acknowledgments

Thank you to Patricia Hartmann of Auburn University for her aid in organizing and reviewing our systematic literature search.

# Supplementary Material

Supplementary provided by the publisher under the same DOI as the publication.

# Data Availability Statement

Data and code are accessible in github: [https://github.com/TWMckibben-Biology/MetaAnalysis]. All materials are stored permanently in Zenodo, to be submitted prior to submission for publication. [DOI link for Zotero]

# References

1. Katic, M. & Kahn, C. The role of insulin and IGF-1 signaling in longevity. *CELLULAR AND MOLECULAR LIFE SCIENCES* **62**, 320–343 (2005).

2. Timmer, L., Hoogaars, W. & Jaspers, R. The Role of IGF-1 Signaling in Skeletal Muscle Atrophy. in *MUSCLE ATROPHY* (ed. Xiao, J.) vol. 1088 109–137 (2018).

3. Arai, Y., Kojima, T., Takayama, M. & Hirose, N. The metabolic syndrome, IGF-1, and insulin action. *Mol Cell Endocrinol* **299**, 124–128 (2009).

4. Johnson, S. Nutrient Sensing, Signaling and Ageing: The Role of IGF-1 and mTOR in Ageing and Age-Related Disease. in *BIOCHEMISTRY AND CELL BIOLOGY OF AGEING, PT I: BIOMEDICAL SCIENCE* (eds. Harris, J. & Korolchuk, V.) vol. 90 49–97 (2018).

5. Iams, W. T. & Lovly, C. M. Molecular Pathways: Clinical Applications and Future Direction of Insulin-like Growth Factor-1 Receptor Pathway Blockade. *Clinical Cancer Research* **21**, 4270–4277 (2015).

6. Frystyk, J. Aging Somatotropic Axis: Mechanisms and Implications of Insulin-Like Growth Factor–Related Binding Protein Adaptation. *Endocrinology and Metabolism Clinics of North America* **34**, 865–876 (2005).

7. Yakar, S. & Adamo, M. L. Insulin-Like Growth Factor 1 Physiology. *Endocrinology and Metabolism Clinics of North America* **41**, 231–247 (2012).

8. Frystyk, J. Free insulin-like growth factors -- measurements and relationships to growth hormone secretion and glucose homeostasis. *Growth Horm. IGF Res.* **14**, 337–375 (2004).

9. Buford, T. *et al.* Composition and richness of the serum microbiome differ by age and link to systemic inflammation. *GEROSCIENCE* **40**, 257–268 (2018).

10. Mari, D. Role of the IGF/insulin system in longevity. *Minerva Endocrinol* **36**, 181–185 (2011).

11. Biro, F., Huang, B., Wasserman, H., Gordon, C. & Pinney, S. Pubertal Growth, IGF-1, and Windows of Susceptibility: Puberty and Future Breast Cancer Risk. *JOURNAL OF ADOLESCENT HEALTH* **68**, 517–522 (2021).

12. Page, M. J. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* n71 (2021) doi:10.1136/bmj.n71.

13. Reproducible, flexible and high-throughput data extraction from primary literature: The metaDigitise R package.

14. Viechtbauer, W. Conducting Meta-Analyses in *R* with the **metafor** Package. *J. Stat. Soft.* **36**, (2010).

15. Ashpole, N. M., Sanders, J. E., Hodges, E. L., Yan, H. & Sonntag, W. E. GROWTH HORMONE, INSULIN-LIKE GROWTH FACTOR-1 AND THE AGING BRAIN. *Exp Gerontol* **68**, 76–81 (2015).

16. Elis, S. *et al.* Elevated serum levels of IGF-1 are sufficient to establish normal body size and skeletal properties even in the absence of tissue IGF-1. *J Bone Miner Res* **25**, 1257–1266 (2010).

17. Franco, L. *et al.* Assessment of age-related changes in heritability and IGF-1 gene effect on circulating IGF-1 levels. *AGE* **36**, 1443–1452 (2014).

18. Greer, K. A., Hughes, L. M. & Masternak, M. M. Connecting serum IGF-1, body size, and age in the domestic dog. *Age (Dordr)* **33**, 475–483 (2011).

19. Yuan, J.-D., Chen, Z.-Y., Huang, X., Gao, X.-C. & Zhang, Q.-Y. Establishment of three cell lines from Chinese giant salamander and their sensitivities to the wild-type and recombinant ranavirus. *Veterinary Research* **46**, 58 (2015).

20. Bucci, L. *et al.* Circulating levels of adipokines and IGF-1 are associated with skeletal muscle strength of young and old healthy subjects. *BIOGERONTOLOGY* **14**, 261–272 (2013).

21. Gielen, E. *et al.* Endocrine determinants of incident sarcopenia in middle-aged and elderly European men. *JOURNAL OF CACHEXIA SARCOPENIA AND MUSCLE* **6**, 242–252 (2015).

22. Hassan-Smith, Z. K. *et al.* Gender-Specific Differences in Skeletal Muscle 11β-HSD1 Expression Across Healthy Aging. *J Clin Endocrinol Metab* **100**, 2673–2681 (2015).

23. Lassale, C., Batty, G., Steptoe, A. & Zaninotto, P. Insulin-like Growth Factor 1 in relation to future hearing impairment: findings from the English Longitudinal Study of Ageing. *SCIENTIFIC REPORTS* **7**, (2017).

24. Roelfsema, F. & Veldhuis, J. Growth Hormone Dynamics in Healthy Adults Are Related to Age and Sex and Strongly Dependent on Body Mass Index. *NEUROENDOCRINOLOGY* **103**, 335–344 (2016).

25. Sonawane, N., Kale, V., Erande, S. & Chaudhary, J. Effect of GenF20 Plus on serum IGF-1 levels in healthy adults: a randomized controlled study. *OPEN ACCESS JOURNAL OF CLINICAL TRIALS* **7**, 35–42 (2015).

26. Strazhesko, I. *et al.* Growth Hormone, Insulin-Like Growth Factor-1, Insulin Resistance, and Leukocyte Telomere Length as Determinants of Arterial Aging in Subjects Free of Cardiovascular Diseases. *FRONTIERS IN GENETICS* **8**, (2017).

27. Vatsalya, V., Issa, J., Hommer, D. & Ramchandani, V. Pharmacodynamic Effects of Intravenous Alcohol on Hepatic and Gonadal Hormones: Influence of Age and Sex. *ALCOHOLISM-CLINICAL AND EXPERIMENTAL RESEARCH* **36**, 207–213 (2012).

28. Willems, S. *et al.* Association of the IGF1 gene with fasting insulin levels. *EUROPEAN JOURNAL OF HUMAN GENETICS* **24**, 1337–1343 (2016).

29. Vitale, G., Pellegrino, G., Vollery, M. & Hofland, L. J. ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians’ Perspective. *Front Endocrinol (Lausanne)* **10**, 27 (2019).

30. Zhang, W. & Milman, S. Looking at IGF-1 through the hourglass. *AGING-US* **14**, 6379–6380 (2022).

31. Tritos, N. & Klibanski, A. Effects of Growth Hormone on Bone. in *GROWTH HORMONE IN HEALTH AND DISEASE* (ed. Casanueva, F.) vol. 138 193–211 (2016).

32. Shimokawa, I. Hormonal Influence and Modulation in Aging. in *NUTRITION, EXERCISE AND EPIGENETICS: AGEING INTERVENTIONS* (ed. Yu, B.) vol. 2 69–83 (2015).

33. Schumacher, B. Transcription-blocking DNA damage in aging: a mechanism for hormesis. *BIOESSAYS* **31**, 1347–1356 (2009).