JKKI
SCIENTIA EST BASIC VITAE

Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage: https://journal.uii.ac.id/JKKI

Growth hormone administration and exercise combination increase serum IGF-1 levels in perimenopausal wistar rats

Ni Luh Kadek Alit Arsani[1], Luh Putu Ratna Sundari*[2]

[1]Faculty of Medicine, Universitas Pendidikan Ganesha, Bali, Indonesia
[2]Department of Physiology, Faculty of Medicine, Universitas Udayana, Bali, Indonesia

Original Article

ABSTRACT

ARTICLE INFO

Keywords:
Growth hormone,
exercise,
swimming,
IGF-1,
perimenopausal Wistar rats

***Corresponding author:**
luhputu_ratnafk@unud.ac.id

DOI: 10.20885/JKKI.Vol14.Iss1.art9

History:
Received: November 1, 2021
Accepted: March 14, 2023
Online: April 5, 2023

Background: Growth hormone (GH), Insulin-like growth factor 1 (IGF-1), and exercise play a crucial role in female reproductive function. At the perimenopausal age, there is a decrease in GH, estrogen, and testosterone levels. In previous studies, the impact of physical activity on serum IGF-1 levels in geriatric was inconsistent and needed further investigation.
Objective: The purpose of this study was to look into the effect of GH and exercise on serum IGF-1 levels in perimenopausal Wistar rats.
Methods: It is an experimental study with a randomized posttest-only control group design using 24 perimenopausal Wistar rats aged 14 months as the sample. The control rats (C) were given 0.1 ml of distilled water subcutaneously every day for 30 days. Treatment group 1 (T1) rats swam for 30 minutes at a time five times per week. Meanwhile, rats of T2 were given 0.016 IU/0.1ml GH daily injection subcutaneously only for 30 days and T3 were given combination both of GH injection in same dose and swam for 30 minutes at a time 5 times a week for 30 days Data analysis used One-Way ANOVA.
Results: The finding revealed that the mean serum IGF-1 levels in the T3 (588.50 84.04 ng/mL) were significantly higher than the control (242.03 ± 46.08 ng/mL), T1 (334.23 ± 75.90 ng/mL) and T2 (428.69 ± 95.10 ng/mL).
Conclusion: Our study shows that GH administration and exercise combination increases levels of IGF-1 serum higher than only administrated GH or exercise.

Latar Belakang: *Hormon pertumbuhan (GH), insulin-like growth factor 1 (IGF-1) dan olahraga memiliki peran penting dalam fungsi reproduksi wanita. Pada tahap sebelum terjadi keluhan penuaan, terjadi penurunan kadar GH, dan hormon-hormon seks seperti estrogen dan testosteron. Pada riset terdahulu, pengaruh olahraga pada kadar IGF-1 serum pada lansia menunjukkan hasil bervariasi yang memerlukan riset lebih lanjut.*
Tujuan: *Penelitian ini bertujuan untuk mengetahui pengaruh kombinasi GH dan latihan terhadap kadar IGF-1 serum tikus wistar perimenopause.*
Metode: *Studi ini merupakan uji eksperimental dengan rancangan randomized posttest only control group menggunakan 24 ekor tikus wistar perimenopause umur 14 bulan sebagai sampel. Tikus kontrol (C) disuntik secara subkutan dengan akuabides 0,l ml/hari selama 30 hari. Tikus kelompok intervensi 1 (T1) diberi perlakuan berenang secara bersamaan selama 30 menit, 5 kali/minggu selama 30 hari. Sementara itu, tikus T2 disuntik dengan GH 0,016 IU/0,1 ml subkutan saja, sedangkan tikus T3 diberi kombinasi injeksi GH dengan dosis yang sama dan aktivitas berenang 30 menit, 5 kali/minggu selama 30 hari. Data dianalisis dengan uji One-Way ANOVA*
Hasil: *Hasil penelitian menunjukkan bahwa rerata kadar IGF-1 serum pada kelompok T3 (588,50 ± 84,04 ng/mL) secara bermakna lebih tinggi dibandingkan dengan kelompok kontrol (242,03 ± 46,08 ng/mL), T1 (334,23 ± 75,90 ng/mL) dan T2 (428,69 ± 95,10 ng/mL).*
Kesimpulan: *Dari studi ini dapat disimpulkan kombinasi injeksi GH dan aktivitas berenang meningkatkan level IGF-1 serum lebih tinggi daripada pemberian GH saja maupun latihan saja.*

INTRODUCTION

At the perimenopausal age, there is a decrease in GH, estrogen, and testosterone levels. GH production is cut in half every seven years from the age of eighteen to twenty-five. Therefore, an increase in age leads to a reduction in the amplitude of GH impulse. At the transition stage of the aging process, age thirty-five to forty-five years, hormone levels decrease by 25%. Meanwhile, at a later stage of the age of forty-five years and above or clinical stage, the hormone levels steadily decrease, which includes Dehydroepiandrosterone (DHEA), melatonin, growth hormone, testosterone, estrogen, and thyroid hormone. Every three years, there is a decrease in bone density which leads to a decline in muscle mass by one kilogram resulting in the inability to burn calories. These cause an increase in body fat and weight, which eventually trigger chronic illness.[1]

Growth hormone, a vital modulator of female reproduction, works both directly through its receptors and indirectly through the stimulation of insulin-like growth factor-1 (IGF-1).[2] Previous studies reported that GH is a survival factor for primary ovarian follicles that regulates granulosa cell differentiation and inhibits follicular apoptosis and atresia.[3] Furthermore, GH is reported to modulate follicle-stimulating hormone's (FSH) work on granulosa cells by increasing local synthesis of IGF-1. This IGF-1 increases the working effect of gonadotropin at the level of granulosa cells and theca cells' IGF-1 synergism with FSH. Luteinizing hormone (LH) stimulates estrogen and progesterone production by granulosa cells, thereby functioning as a follicular survival factor.[4] In addition to using chemical drugs, physical exercise has been regarded and supported by the community as the crucial and inseparable factor that contributes to maintaining good physical and psychological health. However, the problem is whether the exercise is correct and sufficient to maintain the body’s health.

The goal of exercise in health maintenance is to do enough physical activity that is beneficial to health but not too much that causes stress on the body and mind.[5] Physical activity is a powerful stimulator of GH secretion. However, the exact mechanism of the types of exercise that improve GH secretion still needs to be clarified further.[6] Hypothalamus hormones and neurotransmitters regulate the GH secretion, especially the circulating IGF-1 as the primary mediator downstream for GH activity. It is a strong reason why studies explore the connection between IGF-1 and GH with physical exercise.[6]

Several studies on the advantages of physical exercise on plasma IGF-1 levels showed inconsistent results. A study reports an increase in IGF-1 levels due to physical exercise but another showed no change in IGF-1 levels.[7-10] The effect of exercise on IGF-1 production is affected by supplementation of energy as well as the intensity, type, and duration. However, this required further investigation.[11]

The population of women approaching the age of menopause and its health problems posed a challenge for the world of health. If the rapid decline in follicle numbers during pre-menopause does not occur, the proposed mathematical model estimates that the ovaries will remain functional until the age of seventy-one years.[12] Therefore, studies need to be carried out on factors that maintain or improve ovarian function before the ovarian follicle expires at menopause. Judging from some advantages of physical exercise on GH and IGF-1 levels and GH and IGF-1 as important modulators for female reproduction, studies will investigate the GH administration and physical in increasing serum IGF-1 levels. In addition, a combination of GH administration and physical exercise is proposed to have more benefits than GH or exercise alone.

METHODS

Research design

It was an experimental study with a randomized post-test-only control group design using 24 perimenopausal Wistar rats aged 14 months as a sample. This study was in the Biomedical Integrated Laboratory of the Faculty of Medicine, Udayana University. Furthermore, it has been reviewed by the Health Research Ethics Commission of the Faculty of Medicine, Udayana University/RSUP Sanglah No. 285 / UN.14.2/KEP/2016

Subject

Fourteen months-old rats with similar calculations with women entering the menopause period were chosen. The inclusion criteria are body weight between 180–200 grams and healthy condition. Using Federer Formula for sample calculation, minimally 24 rats with six rats in each group. The sample amount is added up to 8 rats per group to prevent sample shortages due to dropout.

Laboratory treatment

Before the study, researchers observed the number of times rats swam. It turned out that rats could swim for 40 minutes until exhausted. In this research, rats were given swimming exercises for 30 minutes (3/4 x 40 minute=30 minutes) with frequency, intensity, time, and type (FITT) principles.14 Growth Hormone (GH) in this research used Genotropin® and contains recombinant somatropin 16 IU per 1 ml.

The dose adjustment to rat from human dose was 0.018x0.9 IU/day=0.016 IU/day. Growth hormone daily at 1.6 IU/0.1 ml, was diluted with 9.9 ml aquabidest to get a 0.016 IU/0.1 ml dose. . The control rats (C) were given 0.1 ml of distilled water subcutaneously every day for 30 days. Treatment group 1 (T1) rats swam for 30 minutes at a time five times per week. Meanwhile, rats of T2 were given 0.016 IU/0.1ml GH daily injection subcutaneously only for 30 days and T3 were given combination both of GH injection in same dose and swam for 30 minutes at a time 5 times a week for 30 days. After intervention for 30 days, blood was drawn in the periorbita area of rats about 1 ml per day. Then, serum IGF-1 concentration in ng/mL was tested with the ELISA technique (Enzym-Linked Immunosorbent Assay) in double replication using Rat IGF-1 Elisa Kit from Elabscience.

Data analysis

The data were explored for normality using the Shapiro-Wilk test, homogeneity by the Levene test, and comparison test was analyzed by the One-Way ANOVA test. We also checked for post hoc analysis by LSD (least significant difference) on significance ($p<0.05$).

RESULTS

Serum IGF-1 levels in various treatments and control

The results showed normal distribution and homogeneity. The results of the significance analysis with the One Way Anova test are presented in Table 1 below. Table 1 showed that the average serum IGF-1 levels in the four groups after treatment were differed significantly ($p<0.05$). The Least Significant Difference-test (LSD) results are shown in Table 2.

Table 1. Mean difference of serum IGF-1 levels between groups

Treatment	n	IGF-1 level (ng/mL)	SD	p-value
Control (C)	6	242.03	46.08	0.000
Exercise (T1)	6	334.23	75.90	
GH (T2)	6	428.69	95.10	
GH and exercise (T3)	6	588.50	84.04	

p significance: p<0.05, SD: Standard Deviation

Table 2. Comparison of serum IGF-1 levels after treatment between groups

Treatment	Mean difference (ng/mL)	p-value
C and T1	92.20	0.052
C and T2	186.67	0.000*
C and T3	364.48	0.000*
T1 and T2	94.46	0.047*
T1 and T3	254.27	0.000*
T2 and T3	159.81	0.002*

p* significance: p<0.05, C: Aquabidest only, T1: Exercise Only, T2: GH only, T3: GH and exercise

Table 2 showed that the comparison of C and T1 was not significantly different, but the other group was. It showed that group exercise only did not get a significant result when compared with group GH only or combination exercise and GH. It means higher serum IGF-1 levels in combination with GH and exercise reinforces the theory that exercise stimulates GH production physiologically and enhances GH action through increased circulating IGF-1 secretion.[15]

DISCUSSION

The results showed that the GH group rats' serum IGF-1 levels were significantly higher than the control group (Table 1). It is in line with Kraemer et al. that the administration of GH may increase IGF-1 serum levels of old female mice to reach the level of IGF-1 at a young age.[16]

Various tissue-specific stimulatory factors can increase the production of IGF-1 in a specific tissue. As described, gonadotropin and sex hormone stimulate the production of IGF-1 in reproduction organs, such as the testis, ovarium, and uterus in humans.[17]

Growth hormone works physiologically both directly and indirectly through its receptors, stimulating the formation of IGF-1, a vital mediator of GH activity, produced in the liver and peripheral tissues. Analysis and interpretation of IGF-1 levels is a beneficial and essential diagnostic tool for follow-up in growth hormone deficiency (GHD) and GH-related disorders. Growth hormone administration generally aims to address clinical complaints with appropriate GH doses and within safe limits.[2]

The results of this study showed that the average serum IGF-1 levels in the exercise group were greater than in the control group, but the difference was not statistically significant (Table 2. However, results from previous studies on the effects of physical exercise on IGF-1 levels are not consistent on whether physical exercise increases IGF-1 levels. Serum IGF-1 levels elevated during resistive and endurance exercise.[18] Moreover, a report shows that physical exercise increases serum IGF-1 levels in transgenic mice with initially low serum IGF-1 levels.[19] Similarly, the study by Cetinkaya et al. in mice given aerobic exercise, also reported an increase in serum IGF-1 levels.[20] This is consistent with the study in older rats given continuous resistance training that reported an increase in IGF-1 levels.[21]

Insulin-like Growth Factor-1 secretion due to physical exercise appears to be more correlated to the duration of the given physical exercise and the session of a single activity.[22] Acute physical exercise causes a temporary increase in serum IGF1 levels for the first 10 minutes before returning to baseline. Stein et al. also stated that the results from the different studies on the effects of physical exercise on IGF-1 levels seem to depend on the type and intensity of physical exercise.[23] Furthermore, it has been reported that continuous mild physical exercise raises serum IGF-1 levels while strength training lowers them.[11,24]

The physical exercise provided in this study is high-intensity training sub maximal type according to the FITT principle, such as 75% from maximum swam ability. This study used maximum swam duration from the mice based on preliminary research (40 minutes). It resulted in no significant increase in serum IGF-1 levels between the two groups (C and T1) due to the relatively short duration of physical exercise (30 days). Several studies found that IGF-1 levels are related to exercise length and intensity.[23,25]

Aside from physical activity, serum IGF-1 levels are influenced by nutrition, age, chronic disease, insulin, and growth hormone.[26] Physical exercise affects IGF-1 levels through mechanisms that are still incompletely understood.[15] It became a limitation of this study because there are numerous variables to investigate in order to determine the effect of physical exercise on IGF-1 secretions.

This study showed that the mean serum IGF-1 levels in the group of rats with a combination of GH injection and swimming (T3) were significantly higher compared to the mean serum IGF-1 levels of the control group (C), T1, and T2.

Physical activity is also a powerful physiological stimulant for GH secretion.[16] After 15 minutes, aerobic exercise stimulates GH secretion, with the peak level occurring after or near the end of the exercise. Furthermore, the GH response to exercise is affected by the intensity and duration of aerobic training, fitness level, sex, and age.[27,28] Following the study about the effect of aerobic exercise may increase GH levels in a group of middle-aged women and geriatrics. Exercise stimulates GH secretion less in older people than in younger people. Meanwhile, GH secretion in postmenopausal women is 5.7-7.3 times lower than in premenopausal women.[28]

The neuroendocrine mechanism in the induction of GH by exercise is still obscure. It is because this naturally involves a complex mechanism, probably due to the input on the hypothalamus. This mechanism could involve the release of Growth hormone-releasing hormone (GHRH) and/or somatostatin withdrawal, as well as the natural release of a Growth hormone releasing peptide (GHRP)-like ligand (such as ghrelin), or some combination of these mechanisms.[16]

In addition, Exercise-induced GH secretion appeared to involve multiple neuroregulatory responses in the GH axis and varied in peripheral feedback signals. A number chemical messenger were played a role, but the typical pathway appeared to involve stimulation of GHRH secretion and/or inhibition of somatostatin release. Furthermore, sympathetic activity may be a crucial mediator of GH response to acute exercise via activation of central α2-adrenergic neurons. One study has reported that increased levels of adrenaline and noradrenaline plasma concentrations lead to an elevated GH concentration due to exercise.[27]

CONCLUSION

This study concluded that serum IGF-1 levels are increased by GH administration and the combination of GH and exercise. Therefore, it will overcome the problems caused by a decline in GH and IGF-1 levels in old age.

Furthermore, higher serum IGF-1 levels obtained from the combination of GH administration and exercise compared to the levels from the use of GH and exercise alone reinforced the theory that exercise was a physiologic stimulus of GH secretion and increased its activity by increasing the secretion of IGF-1 in circulation.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ACKNOWLEDGEMENT

The authors express gratitude to Ketut Tunas, Department of Public Health, Faculty of Health Sciences and Technology, Dhyana Pura University, Bali, Indonesia. Furthermore, thanks to I Gede Wiranata, Pharmacology Department, Faculty of Medicine Universitas Udayana, Indonesia for sharing their pearls of wisdom during the course of this study.

REFERENCES

1. Jones CM, Boelaert K. The Endocrinology of Ageing: A Mini-Review. Gerontology. 2015;61:291–300.
2. Martirossian A, Silverstein J. Diagnosis and management of growth hormone deficiency in adults. Consultant. 2022;62(6):e20–7.
3. Dalcik H, Dalcik C. Insulin-Like Growth Factor I (IGF-I); cytoprotective effects, idea of replacement therapy in the healthy elderly subjects. Medical Research Archives. 2020;8(6).
4. Li J, Chen Q, Wang J, Huang G, Ye H. Does growth hormone supplementation improve oocyte competence and IVF outcomes in patients with poor embryonic development? A randomized controlled trial. BMC Pregnancy Childbirth. 2020;20:310.
5. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. Sports Medicine. 2014;44(1):81–121.
6. Birzniece V. Exercise and the growth hormone–insulin-like growth factor axis. Current Opinion Endocrine Metabolic Research. 2019;9(5):1–7.
7. de Alcantara Borba D, da Silva Alves E, Rosa JPP, Facundo LA, Costa CMA, Silva AC, et al. Can IGF-1 Serum Levels Really be Changed by Acute Physical Exercise? A Systematic Review and Meta-Analysis. Journal of Physical Activity and Health. 2020; 17: 575–84.
8. Chia-Liang T, Chun-Hao W, Chien-Yu P, Fu-Chen C. The effects of long-term resistance exercise on the relationship between neurocognitive performance and GH, IGF-1, and homocysteine levels in the elderly. Frontiers in Behavioural Neuroscience. 2015;9(23):1–12.
9. Devin JL, Bolam KA, Jenkins DG, Skinner TL. The influence of exercise on the insulin-like growth factor axis in oncology: physiological basis, current and future perspectives. Cancer Epidemiology, Biomarkers & Prevention. 2016;25(2):239–49.
10. Jiang Q, Lou K, Hou L, Lu Y, Sun L, Tan SC, et al. The effect of resistance training on serum insulin-like growth factor 1(IGF-1): A systematic review and meta-analysis. Complementary Therapies in Medicine. 2020;50:102360.
11. Kim T, Chang JS, Kim H, Lee KH, Kong ID. Intense Walking Exercise Affects Serum IGF-1

and IGFBP3. Journal of Lifestyle Medicine. 2015;5(1):21–5.
12. Wu J, Liu Y, Song Y, Wang L, Ai J, Li K. Aging conundrum: A perspective for ovarian aging. Frontiers in Endocrinology (Lausanne). 2022;13:1664–2392.
13. Hofstetter J, Suckow MA, Hickman D. The Laboratory Rat Morphophysiology. Second edi. Suckow MA, Weisbroth SH, Franklin CL, editors. London: Elsevier Inc.; 2006.
14. Adhikari S, Tretriluxana J, Dev R, Eglitis E, Nistha S, Kerfeld CP. FITT-CORRECT: Updated dynamic and evidence-based principle of exercise prescription. Journal of Novel Physiotherapy and Rehabilitation. 2021;5:005–9.
15. Sundari LPR, Arsani NLKA. Regular Physical Exercise Increase of Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) Activity in Elderly Improve the Aging Process and Quality of Life: A Mini Review. Biomedical and Pharmacology Journal. 2022;15(2).
16. Kraemer WJ, Ratamess NA, Hymer WC, Nindl BC, Fragala MS. Growth Hormone(s), Testosterone, Insulin-Like Growth Factors, and Cortisol: Roles and Integration for Cellular Development and Growth With Exercise. Frontiers in Endocrinology (Lausanne). 2020;11(33).
17. Ipsa E, Cruzat VF, Kagize JN, Yovich JL, Keane KN. Growth Hormone and Insulin-Like Growth Factor Action in Reproductive Tissues. Frontiers in Endocrinology. 2019;10(777).
18. Giovanni V, Giuseppe P, Maria V, Leo JH. ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective. Frontiers in Endocrinology (Lausanne). 2019;10.
19. Al-Samerria S, Radovick S. The Role of Insulin-like Growth Factor-1 (IGF-1) in the Control of Neuroendocrine Regulation of Growth. Cells. 2021;10(10):2664.
20. Cetinkaya C, Sisman AR, Kiray M, Camsari UM, Gencoglu C, Baykara B, et al. Positive effects of aerobic exercise on learning and memory functioning, which correlate with hippocampal IGF-1 increase in adolescent rats. Neuroscience Letters. 2013;549:177–81.
21. Cenyi W, Jiling L, Yuanyuan R, Jielun H, Baoming J, Guodong W, et al. A Preclinical Systematic Review of the Effects of Chronic Exercise on Autophagy-Related Proteins in Aging Skeletal Muscle. Frontiers in Physiology. 2022;13.
22. Naderi A, Shaabani F, Esmaeili A, Salman Z, Borella E, Degens H. Effects of low and moderate acute resistance exercise on executive function in community-living older adults. Sport, Exercise, and Performance Psychology . 2019;8(1):106–22.
23. Stein AM, Silva TMV, Coelho FGM. Physical exercise, IGF-1 and cognition A systematic review of experimental studies in the elderly. Dementia e Neuropsychologia. 2018;12(2):114–22.
24. Arnarson A, Gudny-Geirsdottir O, Ramel A, Jonsson PV, Thorsdottir I. Insulin-Like Growth Factor-1 and Resistance Exercise in Community Dwelling Old Adults. Journal of Nutrition Health and Aging. 2015;19(8):856–60.
25. Norling AM, Gerstenecker AT, Buford TW, Khan B, Oparil S, Lazar RM. The role of exercise in the reversal of IGF-1 deficiencies in microvascular rarefaction and hypertension. GeroScience. 2020;42(1):141–58.
26. Gulick CN, Peddie MC, Jowett T, Hackney AC, Rehrer NJ. Exercise, Dietary Protein, and Combined Effect on IGF-1. International Journal of Science and Research Methodology. 2020;16(3):61–77.
27. Danese E, Tarperi C, Luca SG, Guzzo A, Sanchis-Gomar F, Festa L, et al. Sympatho-adrenergic activation by endurance exercise: Effect on metanephrines spillover and its role in predicting athlete's performance. Oncotarget. 2018;9:15650–7.
28. Gusatovic J, Gramkow MH, Hasselbalch SG, Frederiksen KS. Effects of aerobic exercise on event-related potentials related to cognitive performance: a systematic review. PeerJ. 2022;10:13604.