The role of IGF-1 in obesity, cardiovascular disease, and cancer

Nazanin AsghariHanjani[1], Mohammadreza Vafa*[1,2]

Abstract

Background: Insulin-like growth factor1 (IGF1) is a polypeptide that structurally is similar to human pro-insulin, one of the factors that is altered in obesity and many related diseases, hence a large body of research devoted to evaluate it.

Methods: In this mini-review, we briefly explain the role of IGF1 in different conditions, including obesity, cardiovascular disease, and cancer through the results of review and original articles in both animal and human studies.

Results: The short-term metabolic effect of IGF-1 is insulin-like, and its long-term effect is growth factor-like. IGF1 has different roles in the initiation and progression of different diseases, because in some cases, the anti-apoptotic effect, can help cell survival while in others, it may lead to cancer or increment of adipocytes.

Conclusion: It is highly recommended to consider the different impacts of IGF1 in health and diseases prevention in future studies and interventions.

Keywords: IGF1, Obesity, Cardiovascular disease, Cancer, Apoptosis

Introduction

Globally, obesity is one of the main reasons of preventable and chronic disease. In recent decades, obesity and overweight prevalence have significantly increased. World Health Organization (WHO) reported that the worldwide prevalence of obesity has nearly doubled since 1980. In 2014, epidemiological studies proposed that more than 1.9 billion adults, 18 years and older, were overweight. Obesity is associated with various pathological conditions, such as hypertension, dyslipidemia, insulin resistance (IR) which leads to type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease and cancer that eventually increase mortality and morbidity (1-3). Insu lin-like growth factor1 (IGF1) is one of the factors that is altered in obesity and many related diseases, hence a large body of research devoted to evaluate it. In the following article, we focus on the role of IGF1 and it's downstream signaling in most common chronic disease.

More than forty years ago, two active substances were isolated by Rinderknecht and Humbel from human serum, which were renamed "insulin-like growth factor 1 and 2" (IGF-1 and 2) due to their structural resemblance to pro-insulin. Afterward, it was recognized that IGF-1 plays an important role in the anabolic and mitogenic activity of growth hormone (2, 4).

Growth hormone (GH) and IGF1 have some vital effects on metabolism apart from their role in growth. GH

_____

Corresponding author: Dr Mohammadreza Vafa, vafa.m@iums.ac.ir

1. Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
2. Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

---

↑What is "already known" in this topic:
Recently the effects of IGF1 on aging and chronic diseases attract much attention. IGF1 controls cell growth through anti-apoptotic effects and has some physiological role in the metabolic pathway. IGF1 signaling alteration may lead to pathological conditions.

→What this article adds:
IGF1 has vital effects on metabolism and proliferation. Based on IGF1, different roles in metabolic pathways, the anti-apoptotic effects of IGF1, leads to cell survival while in other cases, it promotes cancer cell growth or adipocytes expansion.

stimulates the production of IGF1 in many tissues and in this way, they together regulate fat, protein, and glucose metabolism (5). GH exerts anti-insulin effect and IGF1 have insulin-like properties (6). IGF-1 and IGF-2, are the main ligand of IGF1 system with three cell-membrane receptors including insulin receptor, IGF-1 receptor (IGF-1R), IGF-2 receptor and 6 IGF-binding proteins, IGFBP-1 to IGFBP-6 that regulate IGF1 availability and activity. IGF-1R is also a tyrosine kinase receptor, which consists of two subunits (α and β). IGF-1 and IGF-2 autophosphorylate their receptor and activate multiple signaling pathways leading to proliferation and apoptosis prevention, including extracellular signal-regulated kinase/ mitogen-activated protein kinase and phosphatidylinositide 3-kinase/ anti-apoptotic serine-threonine kinase pathways (7, 8). The short-term metabolic effect of IGF-1 is insulin-like, and the long-term effect of it is growth factor-like. controlling the cell growth and organ size is mediated via mitotic and anti-apoptotic effects, but it has some physiological role metabolism that is discussed in the following (9).

While calorie restriction is an important dietary intervention, which increases lifespan through downregulating IGF1 pathway, the role of different macronutrients due to overlapping effects of them have been studied as well. Evidence suggests that increased mortality is associated with higher carbohydrate intake, (specifical sugar) as a result of activating insulin cascade (10). Specifically, Glucose enriched diet, decrease the C.elegans lifespan by upregulating IGF1 signaling (11). Protein is the key macronutrient and attracts much attention in the field of calorie restriction, aging and IGF1 pathway within the recent years. There are many studies which compare the effect of calorie or protein restriction on IGF1 signaling and aging. However, recently it has been shown that calorie restriction has a profound effect compared to the protein or amino acid restriction (12). High-fat diet (ketogenic diet) is also able to decrease insulin/IGF1 and exert some beneficial effects on health (13). In more details, chronic high fat diet leads to IF and NAFLD through reduction of the IGF1 receptor or their binding ability (14).

Methods
This is a mini-review which focused on the role of IGF1 in different conditions including obesity, cardiovascular disease, and cancer through discussing the results of review and original articles in both animal and human studies. The following keywords were searched including: IGF1, obesity, cardiovascular disease, cancer, and apoptosis.

Results
IGF1 and obesity
Obesity means developing adipose tissue followed by a combined process including enlargement of older adipocytes, proliferation, and differentiation of new adipocytes. IGF1 has a vital role in the progression of cell cycle and mitogenesis. In this regard, IGF1 may contribute to the development of obesity, which is in contrast to the role of this molecule in an oxidative capacity, as discussed later (15, 16). Obesity, metabolic syndrome, and IF may highly dysregulate IGF1 system, offering to hyperinsulinemia and

increased free IGF-1. Data suggest that in obesity, GH secretion is diminished, but it is not associated with reducing the IGF1 level. Because it is hypothesized that, hyperinsulinemia due to obesity reduce IGF1 binding protein and subsequently increase IGF1 free concentrations (17). However, the effect of obesity on IGF1 concentration is controversial. In some studies, it is reported that human recombinant GH ameliorates metabolic syndrome parameter through increasing total IGF1 level, take into consideration that free IGF1 level increased despite the total IGF1 level (18). High dose of GH induce lipolysis and exert anti-insulin effect, in GH-deficient adults and in subjects with metabolic syndrome a very low dose GH therapy (0.1 mg/day) without affecting the body composition improved insulin sensitivity, which may be the result of increasing free IGF1 bioavailability without the induction of lipolysis (19, 20) . The other study in obese subjects with ectopic fat storage has shown that Sirtuin 4 level- an NAD+ dependent deacetylase- is low in the skeletal muscle and liver, which are associated with the increased cardiovascular risk factor. Interestingly, lower serum Sirt4 levels and higher BMI and waist circumference have been reported in those obese subjects with low peak GH and low IGF-1 levels. Since the GH/IGF1 promote mitochondrial oxidative capacity, its reduced level can decrease the B oxidation, as an example of the maladaptive changes during obesity (21, 22). In the other study, GH treatment for 1 year resulted in VO2 max increment and the reduction of waist circumference and body fat mass (23).

IGF1 and Cardiovascular disease
In 15-years prospective study of 231 cases and 374 matched controls without any sign of ischemic heart disease (IHD) at the baseline of the study, those with baseline IGF-I levels in the lowest quartile had a 2-fold increased risk of IHD (when the major IGF-binding protein, IGFBP-3, was controlled). It is hypothesized that low IGF1 is correlated with, obesity, low physical activity, and IF(24, 25). On the other hand, some clinical and epidemiological studies revealed that IGF1 could protect myocyte and play a role in their survival. Moreover, Mammalian Myocardial Contractility can be augmented by IGF1 through sensitizing the myofilaments to Ca^{2+} without increasing myocyte and inhibit reperfusion-induced apoptosis of cardiac myocytes after myocardial ischemia (26, 27). Arterial intima-media thickness (IMT) has been recognized as a good predictor of the risk of cardiovascular events. In GH deficient adult carotid arterial intima-media thickness increased and after one-year treatment decreased. The author suggests that increasing nitric oxide formation and activity in response to IGF1 is a reason for these changes (23).

IGF1, apoptosis, and cancer
IGF1 is a survival agent and growth factor for a diverse range of normal and malignant cells. IGF-1 plays a key role in the anti-apoptotic and mitogenic pathway in many cell types. Since IGF-1, stimulates progression of the cell cycle from G1 to S phase, has been identified as a cell cycle progression factor. IGF-1 activates phosphatidylinositol-3-kinase (PI-3K)/Akt signaling cascade and mitogen-activated

protein kinase (MAPK). Activated Akt can suppress apoptosis through inhibiting the activation of the interleukin-1β-converting enzyme (28)–like proteases, glycogen synthase kinase 3 (GSK3) and the mammalian target of rapamycin (mTOR) (29-31). Over-activation of PI-3K/Akt triggers NF-κB signaling and accelerates the aging process while impairment of PI-3K/Akt signaling leads to activation of FoxO factors and extending the lifespan (32).

In this regard, A six-year study of 32,826 nurses, indicated that highest levels of IGF-1 are associated with two-and-a-half times greater risk of colorectal cancer (33). Moreover, cell line studies have shown that interleukin-6 (IL-6) promote the proliferation of multiple myeloma (MM) cells and protect them against dexamethasone-induced apoptosis by means of IGF-1 (29). Besides that, IGF1 or IGF1R over activation lead to migration and motility of cancer cell through the extension of lamellipodia in neuroblastoma cell lines (34). Strong evidence suggests that IGF1 is overexpressed in the early stage of breast cancer and is correlated with radio-resistance and tumor recurrence (35). Also increased serum IGF-1 level is associated with a doubling of the prostate cancer risk (36). Interestingly, carbohydrate restriction, even without calorie restriction decreased obesity-associated inflammation and slow tumor growth through IGF1 reduction (37). Generally, different observations revealed that carbohydrate restriction, specifically in ketogenic diet form, increase intracell K^+ in cancer cell through downregulating insulin/IGF1 pathway specially on the tumors that are dependent to glycolysis (38).

Conclusion

IGF1 is a polypeptide that structurally is similar to human pro-insulin. IGF1 signaling plays a major role in controlling aging and lifespan. This factor is altered in obesity and many related diseases, including cardiovascular diseases and cancer. This molecule has a vital effect on metabolism and proliferation. It is hypothesized that its short-term effect is insulin-like, and the long-term effect is growth factor-like. Hence, IGF1 has different roles in the initiation and progression of different diseases, because in some cases the anti-apoptotic effect, can help cell survival, which in other cases it, may lead to cancer or increment of adipocytes. Therefore, it is important to take into account the role of this molecule in specific situations, which has been discussed or analyzed.

Conflict of Interests
The authors declare that they have no competing interests.

References

1. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15(4):6184-223.
2. [Internet] NW-FOp. [cited http://www.wiredhealthresources.net/resource]. 2011.
3. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141-50.
4. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol. 2001;54(5):311.
5. Berryman D, Glad C, List E, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat Rev Endocrinol. 2013;9(6):346-56.
6. Yuen KC, Dunger DB. Impact of treatment with recombinant human GH and IGF-I on visceral adipose tissue and glucose homeostasis in adults. Growth Horm IGF Res. 2006;16:55-61.
7. Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. Eur J Pharmacol. 2004;490(1):127-33.
8. Imsumran A, Adachi Y, Yamamoto H, Li R, Wang Y, Min Y, et al. Insulin-like growth factor-I receptor as a marker for prognosis and a therapeutic target in human esophageal squamous cell carcinoma. Carcinogenesis. 2006;28(5):947-56.
9. Ren J, Samson WK, Sowers JR. Insulin-like Growth Factor I as aÈCardiac Hormone: Physiological and Pathophysiological Implications in Heart Disease. J Mol Cell Cardiol. 1999;31(11):2049-61.
10. Ravichandran M, Grandl G, Ristow M. Dietary Carbohydrates Impair Healthspan and Promote Mortality. Cell Metab. 2017;26(4):585-7.
11. Lee D, Son HG, Jung Y, Lee SJV. The role of dietary carbohydrates in organismal aging. Cell Mol Life Sci. 2017;74(10):1793-803.
12. Simpson SJ, Le Couteur DG, Raubenheimer D, Solon-Biet SM, Cooney GJ, Cogger VC, et al. Dietary protein, aging and nutritional geometry. Ageing Res Rev. 2017;39:78-86.
13. Brown-Borg HM. Disentangling High Fat, Low Carb, and Healthy Aging. Cell Metab. 2017;26(3):458-9.
14. Longato L, Tong M, Wands JR, de la Monte SM. High fat diet induced hepatic steatosis and insulin resistance: role of dysregulated ceramide metabolism. Hepatol Res. 2012;42(4):412.
15. Gregoire FM, Smas CM, Sul HS. Understanding adipocyte differentiation. Physiol Rev. 1998;78(3):783-809.
16. Hausman D, DiGirolamo M, Bartness T, Hausman G, Martin R. The biology of white adipocyte proliferation. Obes Rev. 2001;2(4):239-54.
17. Le Marchand-Brustel Y, Heydrick S, Jullien D, Gautier N, Van Obberghen E. Effect of insulin and insulin-like growth factor-1 on glucose transport and its transporters in soleus muscle of lean and obese mice. Metabolism. 1995;44:18-23.
18. Maccario M, Grottoli S, Procopio M, Oleandri S, Rossetto R, Gauna C, et al. The GH/IGF-I axis in obesity: influence of neuro-endocrine and metabolic factors. Int J Obes (Lond). 2000;24(2):S96-S9.
19. Yuen K, Dunger D. Therapeutic aspects of growth hormone and insulin-like growth factor-I treatment on visceral fat and insulin sensitivity in adults. Diabetes Obes Metab. 2007;9(1):11-22.
20. Hana V, Silha JV, Justova V, Lacinova Z, Stepan JJ, Murphy LJ. The effects of GH replacement in adult GH-deficient patients: changes in body composition without concomitant changes in the adipokines and insulin resistance.Clin Endocrinol (Oxf). 2004;60(4):442-50.
21. Savastano S, Di Somma C, Colao A, Barrea L, Orio F, Finelli C, et al. Preliminary data on the relationship between circulating levels of Sirtuin 4, anthropometric and metabolic parameters in obese subjects according to growth hormone/insulin-like growth factor-1 status. Growth Horm IGF Res. 2015;25(1):28-33.
22. Short KR, Moller N, Bigelow ML, Coenen-Schimke J, Nair KS. Enhancement of muscle mitochondrial function by growth hormone. J Clin Endocrinol Metab. 2008;93(2):597-604.
23. Borson-Chazot Fo, Serusclat A, Kalfallah Y, Ducottet X, Sassolas Gv, Bernard S, et al. Decrease in carotid intima-media thickness after one year growth hormone (GH) treatment in adults with GH deficiency. J Clin Endocrinol Metab.1999;84(4):1329-33.
24. Juul A, Scheike T, Davidsen M, Gyllenborg J, Jørgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease. Circulation. 2002;106(8):939-44.
25. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2004;89(1):114-20.
26. Cittadini A, Ishiguro Y, Strömer H, Spindler M, Moses AC, Clark R, et al. Insulin-like growth factor-1 but not growth hormone augments mammalian myocardial contractility by sensitizing the myofilament to Ca2+ through a wortmannin-sensitive pathway. Circ Res. 1998;83(1):50-9.

27. Buerke M, Murohara T, Skurk C, Nuss C, Tomaselli K, Lefer AM. Cardioprotective effect of insulin-like growth factor I in myocardial ischemia followed by reperfusion. Proc Natl Acad Sci U.S.A. 1995;92(17):8031-5.

28. Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review. World J. Gastroenterol. 2017;23(9):1697.

29. Mitsiades CS, Mitsiades N, Poulaki V, Schlossman R, Akiyama M, Chauhan D, et al. Activation of NF-[kappa] B and upregulation of intracellular anti-apoptotic proteins via the IGF-1/Akt signaling in human multiple myeloma cells: therapeutic implications. Oncogene. 2002;21(37):5673.

30. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med. 2003;54(1):131-52.

31. Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyva Y, Kline WO, et al. The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. Mol Cell. 2004;14(3):395-403.

32. Kim DH, Kim JY, Yu BP, Chung HY. The activation of NF-κB through Akt-induced FOXO1 phosphorylation during aging and its modulation by calorie restriction. Biogerontology. 2008;9(1):33-47.

33. Vanamala J, Reddivari L, Radhakrishnan S, Tarver C. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. BMC cancer. 2010;10(1):238.

34. Guvakova MA. Insulin-like growth factors control cell migration in health and disease. Int J Biochem Cell Biol. 2007;39(5):890-909.

35. Surmacz E. Function of the IGF-I receptor in breast cancer. J Mammary Gland Biol Neoplasia. 2000;5(1):95-105.

36. Wolk A, Mantzoros CS, Andersson S-O, Bergström R, Signorello LB, Lagiou P, et al. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. J. Natl. Cancer Inst. 1998;90(12):911-5.

37. Allott EH, Macias E, Sanders S, Knudsen BS, Thomas GV, Hursting SD, et al. Impact of carbohydrate restriction in the context of obesity on prostate tumor growth in the Hi-Myc transgenic mouse model. Prostate Cancer Prostatic Dis. 2017;20(2):165.

38. Fine EJ, Feinman RD. Insulin, carbohydrate restriction, metabolic syndrome and cancer. Expert Rev Endocrinol Metab. 2015;10(1):15-24.