

Review Article

Adiponectin and Healthy Aging in Centenarians

Yasumichi Arai, Nobuyoshi Hirose

Division of Geriatric Medicine, Department of Internal Medicine, Keio University School of Medicine

Abstract

As the aging population expands rapidly worldwide, it has become increasingly important to identify factors that offer means to promote healthy aging. It is well documented that advancing age is associated with increased body fat and blunted insulin action. Centenarians, who are the best model of successful aging, are a unique exception to this phenomenon. Increasing evidence has documented the preservation of insulin sensitivity and glucose homeostasis along with the very low prevalence of metabolic syndrome, diabetes, and cardiovascular disease among centenarians. We demonstrated that centenarians have a high serum concentration of adiponectin, which was associated with a favorable metabolic phenotype, including higher levels of HDL-C and lipoprotein lipase, and lower levels of hemoglobin A1c, C-reactive protein, and E-selectin concentrations. These observations suggested that high adiponectin concentration may be potentially important for maintaining health and function and could be a target for Anti-Aging Medicine.

KEY WORDS: Healthy Aging, Centenarians, adiponectin, metabolic syndrome**Introduction**

One of the most striking features of modern society is the steady increase in life expectancy, accompanied by the rapid growth of the “oldest old” population, defined as those 85 years or older^{1,2}. In Japan, where female life expectancy at birth reached 86 years in 2007, the number of the oldest old surpassed 3.6 million, or about 2.8% of the total population in 2009, a 322% increase since 1990. Because the oldest old are vulnerable to age-related multiple chronic conditions and disabilities, a major concern is that extension of life will be accompanied by increasing levels of disease and disability, which demand considerable personal and social care costs. It has therefore become increasingly important to identify lifestyle factors as well as pharmacological intervention which offer means to alleviate age-related chronic conditions and promote healthy aging. Centenarians are the best model for healthy aging in humans, and increasing evidence has documented a very low prevalence of age-related chronic conditions including metabolic syndrome, type 2 diabetes (T2DM), and atherosclerosis among centenarians^{1,2}. Elaboration of the mechanistic pathways that enable centenarians to maintain metabolic homeostasis would greatly benefit our understanding of improved healthy aging. In this review, we focus on possible roles of adiponectin, an insulin-sensitizing adipokine, on regulating longevity in humans.

Clinical Phenotypes of Centenarians

For more than a decade, centenarians have been studied to identify healthy aging phenotypes and describe how to achieve them³. Several key pathways for health maintenance and longevity have been postulated thus far (**Fig. 1**). In contrast to our early expectations, accumulating evidence has disclosed that most centenarians are survivors of age-related multipathology, rather than disease-free individuals. In late 1980s, Francesch *et al.* first demonstrated the clinical phenotype of centenarians as age-related inflammatory activation or remodeling, so-called inflammaging⁴. They found that inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) are upregulated in peripheral blood monocytes obtained from centenarians. Subsequent study demonstrated hypercoagulability in centenarians, which is characterized by higher levels of plasminogen activator inhibitor-1 (PAI-1)⁵. The findings of accumulating cardiometabolic risk factors in centenarians are in contrast to our prediction and are regarded as the “centenarians’ paradox”. The underlying mechanisms of this phenomenon remain unknown, but one possible explanation is that inflammaging and hypercoagulability may reflect an adaptive process by which centenarians counteract age-related multiple chronic conditions and reduced organ capacity to maintain homeostasis until the very end of the maximum life span.

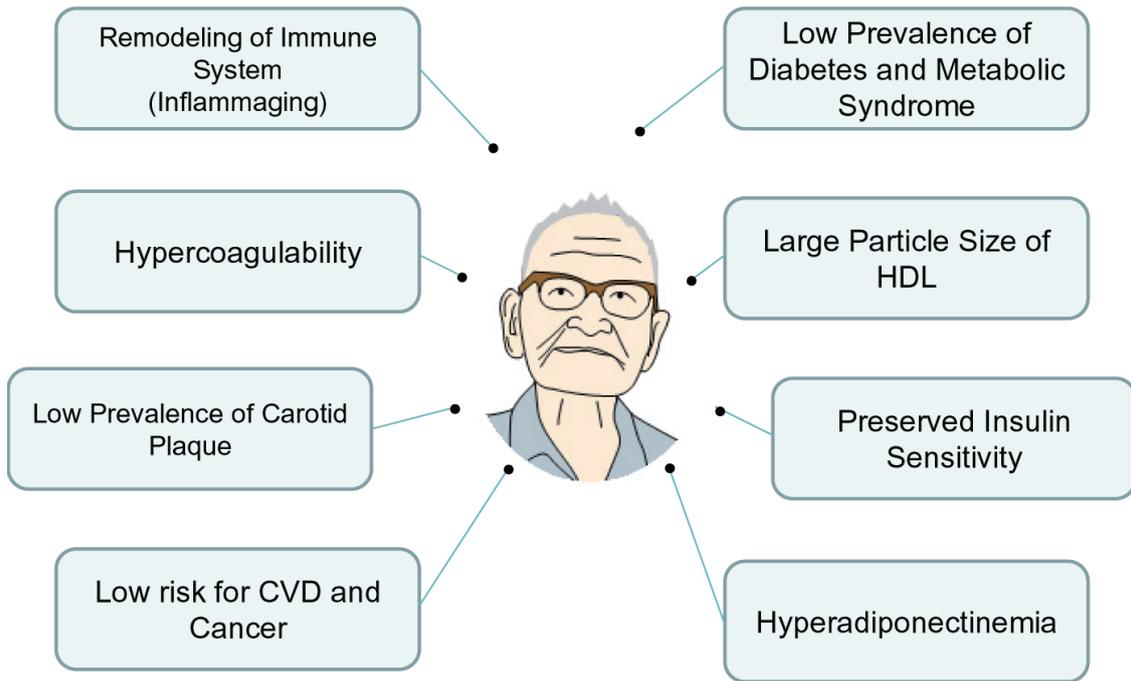


Fig. 1. Clinical phenotypes of centenarians

In late 1990s, a series of studies demonstrated that preservation of insulin action and low prevalence of metabolic syndrome and T2DM are distinctive among centenarians. Paolisso *et al.* used a euglycemic glucose clamp technique to demonstrate that glucose tolerance and insulin sensitivity were better preserved in healthy centenarians than in elderly individuals aged >75 years⁶⁾. Cross-sectional studies have also demonstrated reproducibly that the prevalence of T2DM, which is closely associated with age-related insulin resistance, was very low among centenarians. According to a nationwide survey of the prevalence of circulatory diseases in Japanese adults in 2000 (Ministry of Health, Labour and Welfare), the prevalence of T2DM was 2.6%, 6.3%, 11.6%, 15.3%, and 14.7% among individuals in their 30s, 40s, 50s, 60s, and those age ≥ 70 years, respectively; however, in the Tokyo centenarians study, only 6.0% of centenarians had T2DM⁷⁾. The Finnish Centenarians Study revealed a 10% prevalence of T2DM in Finnish centenarians, which was lower than the prevalence of T2DM in 65- to 85-year-old Finnish individuals. Previously, the Italian Multicenter Study on Centenarians had reported that 4.9% of 602 centenarians had T2DM, and the New England Centenarian Study had reported that 4% of 424 centenarians had T2DM, results which were each lower versus the respective aged, but younger populations. Collectively, these epidemiological findings suggest that centenarians could have protective factors which counteract age-related inflammatory activation and hypercoagulability to maintain insulin sensitivity and energy homeostasis.

Adiponectin Levels in Centenarians

Recent epidemics of obesity have given prominence to adipose tissue as an active endocrine organ that regulates energy homeostasis by secreting a large number of bioactive substances including leptin, TNF- α , IL-6, PAI-1, and adiponectin, which are termed collectively adipokines. Dysregulation of adipokines is now recognized as a common basis for insulin resistance, hyperglycemia, dyslipidemia, hypertension, and obesity-associated metabolic syndrome. Among various adipokines identified, the physiological role of adiponectin (also known as ADIPOQ, apM1, and ACRP30) is unique and important. Adiponectin has been shown to exert anti-diabetic, anti-atherogenic, and anti-inflammatory effects in rodents and humans⁸⁾. In cross-sectional studies, plasma adiponectin concentrations were significantly lower in obese individuals⁹⁾ and in those having diabetes, metabolic syndrome, and CVD¹⁰⁾ and were associated inversely with body adiposity and insulin resistance. Based on these findings, we hypothesized that adiponectin is the protective factor of centenarians, allowing centenarians to maintain their metabolic and vascular homeostasis and thus achieve healthy longevity. We therefore measured plasma adiponectin levels in centenarians and reported that centenarians had higher plasma adiponectin than body mass index (BMI)-matched younger adults¹¹⁾. In addition, the high plasma adiponectin levels in centenarians were associated with a favorable metabolic phenotype, including higher HDL-C and lower hemoglobin A1c, C-reactive protein (CRP), and E-selectin concentrations (**Fig. 2**). Hyperadiponectinemia in centenarians was also reported by Bik *et al.*¹²⁾; they found an inverse correlation with adiponectin in a homeostasis model assessment for insulin resistance (HOMA-IR), which is a reliable marker of insulin resistance.

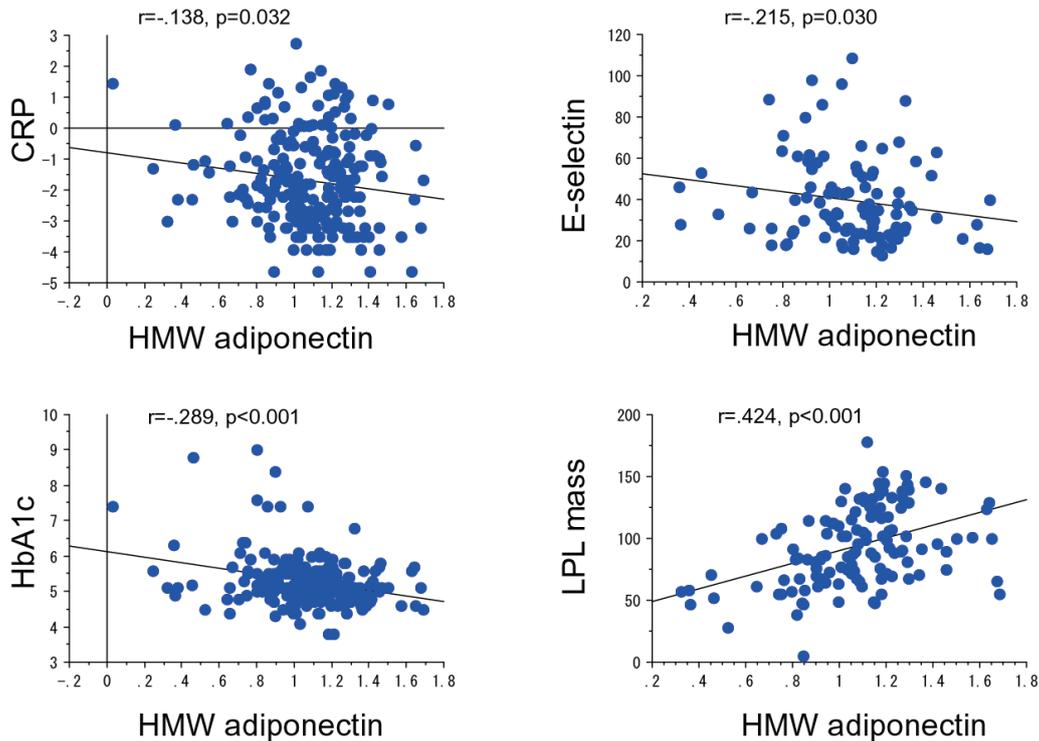


Fig. 2. Association between adiponectin and biomarkers of inflammation and endothelial function

Recently, a possible association between adiponectin and extended lifespan has been indicated in several animal models. Mice with fat-specific disruption of the insulin receptor gene (FIRKO) have been reported to have reduced adiposity, lower fasting insulin levels, and extended life spans, as well as elevated serum adiponectin levels¹³⁾. Transgenic (Tg) mice expressing human adiponectin exhibited lesser fat accumulation and a smaller adipocyte size in both visceral and subcutaneous adipose tissue, with lower levels of fasting glucose, insulin, and leptin versus wild-type mice¹⁴⁾. Transgenic expression of adiponectin also reduced morbidity and mortality associated with attenuated oxidative DNA damage in mice fed a high fat diet. These findings have led to the notion of preserved insulin sensitivity and hyperadiponectinemia as the universal pathway to longevity in mammals including humans.

Adiponectin Gene Variation and Longevity

Several SNPs at the adiponectin locus are reportedly associated with the risk of T2DM in the Japanese population. To examine the possible association between this locus and longevity, 10 polymorphisms at the adiponectin locus, including 8 SNPs described by Hara *et al.*¹⁵⁾, were genotyped in 233 DNA samples from centenarians (188 female, 45 male) and 151 DNA samples from healthy volunteers (90 female, 61 male; mean age 37.7 ± 11.5 y/o, range 20–65 y/o) by direct sequencing¹¹⁾. These polymorphisms showed no significant difference between centenarians and controls. We further studied associations between each genotype and plasma adiponectin concentration in 66 female centenarians and observed a trend

similar to those in previous reports, which showed a gradual but insignificant increase in adiponectin concentration with a T allele of SNP 276. No other significant association was found. In contrast, Aztmon *et al.* found that two common variants of the adiponectin gene (*ADIPOQ*) were associated with higher adiponectin levels and longevity¹⁶⁾. The discrepancies between the two studies are unexplained. Recently, a genome-wide association study (GWAS) found that plasma adiponectin level was strongly associated with a CDH13 promoter SNP on chromosome 16 in a Korean population¹⁷⁾. An international, collaborative GWAS on centenarians has been launched and will focus precisely on the genetic link between adiponectin and longevity.

Adipose Tissue Function and Healthy Aging

In circumstances of excess adiposity, especially visceral adiposity, many adipokines are dysregulated, *e.g.*, overproduction of TNF- α , IL-6, PAI-1, resistin and leptin; whereas, adiponectin is down-regulated, which leads to systemic inflammation and insulin resistance, and eventually, cardiovascular complications. In contrast, loss of adipose tissue as in a variety of lipodystrophies and lipoatrophy can also cause adipokine dysregulation and insulin resistance. Aging is associated with fat redistribution characterized by loss of peripheral subcutaneous fat, as well as accumulation of central fat. Interestingly, recent experimental evidence has demonstrated that cellular aging (senescence) of adipose tissue also stimulates an inflammatory cascade and causes insulin resistance¹⁸⁾. These findings suggest that older people are

susceptible to adipokine dysregulation from either visceral obesity or lipoatrophy of subcutaneous fat, and the burden of dysregulated adipokines could be more significant in the elderly population. To investigate this notion, we examined a series of adipokines, including leptin, adiponectin, and TNF- α , and investigated the associations between adipokine dysregulations and all-cause mortality among a cohort of 252 centenarians ¹⁹. We found that the lowest tertile of leptin and the highest tertile of TNF- α , respectively, was associated significantly with higher all-cause mortality in centenarians. Additionally, cumulative dysregulation of multiple adipokines, including leptin, adiponectin, and TNF- α , constitutes a strong marker of poor prognosis among centenarians independent of conventional risk factors such as low serum albumin, interleukin-6, and HDL-C concentration. In contrast to obesity-related conditions, adipokine dysregulation of centenarians was associated uniquely with very low levels of leptin and low BMI, suggesting that age-related fat loss or lipoatrophy constitutes a dominant part of adipose tissue dysfunction in centenarians. These findings are somehow in accordance with the protective roles of fat mass against morbidity and mortality in geriatric patients and in maintenance hemodialysis. Although further studies are needed to address adipocyte size, aging metabolism, and age-related pathology, maintenance of adipose tissue mass and function may be indispensable for survival under energy deprived states such as cachexia, wasting syndrome, and age-related chronic inflammation.

Conclusion

Accumulating evidence suggests that insulin sensitivity and hyperadiponectinemia are key phenotypes of centenarians; however, the mechanisms of the link between adiponectin and healthy aging remain unknown. While epidemiological and experimental evidence supports the anti-diabetic effect of adiponectin, evidence on the association between adiponectin and cardiovascular risk is conflicting, and several studies have reported that high levels of circulating adiponectin are associated with higher mortality in chronic heart failure patients ²⁰. Further study is needed to elaborate the cardioprotective effects of adiponectin. Preservation of musculoskeletal function and prevention of physical disability are also necessary to maintain health and independence throughout a very long life. Recently, adiponectin was demonstrated to enhance musculoskeletal function through activation of AMPK and SIRT1 ²¹, suggesting that this molecule may have promising effects on prevention of sarcopenia, a common component of frailty associated with aging. Although further studies are needed to clarify the mechanistic pathways, upregulation of adiponectin or enhancement of adiponectin signaling is a potentially promising target for Anti-Aging Medicine.

Acknowledgments

This work was supported in part by grants from the Japanese Ministry of Health, Labour and Welfare for the Scientific Research Project for Longevity (a multidisciplinary approach to centenarians and international comparison, and “Research on healthy aging: Semi-supercentenarians and long-lived sibling study”, Principal investigator, Nobuyoshi Hirose); the Keio Health Consulting Center; and the Foundation for Total Health Promotion.

Conflict of interest statement:

The authors declare no financial or other conflicts of interest in the writing of this paper.

References

- 1) Barzilai N, Atzmon G, Schechter C, et al: Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA*. 2003; 290:2030-2040
- 2) Homma S, Hirose N, Ishida H, Ishii T, Araki G: Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. *Stroke*. 2001; 32(4):830-5
- 3) Perls T, Terry D. Understanding the determinants of exceptional longevity. *Ann Intern Med*. 2003; 139:445-9
- 4) Franceschi C, Monti D, Sansoni P, Cossarizza A: The immunology of exceptional individuals: the lesson of centenarians. *Immunol Today*. 1995; 16(1):12-16
- 5) Mari D, Mannucci PM, Coppola R, et al: Hypercoagulability in centenarians: The paradox of successful aging. *Blood*. 1995; 85:3144-3149
- 6) Paolisso G, Gambardella A, Ammendola S, et al: Glucose tolerance and insulin action in healthy centenarians. *Am J Physiol Endocrinol Metab*. 2006; 270:E890-E894
- 7) Takayama M, Hirose N, Arai Y, et al: Morbidity of Tokyo-Area Centenarians and its Relationship to Functional Status. *J Gerontol. A. Biol. Sci. Med. Sci*. 2007; 62:774-782
- 8) Hotta K, Funahashi T, Arita Y, et al: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler. Thromb. Vasc. Biol*. 2000; 20:1595-1599
- 9) Arita Y, Kihara S, Ouchi N, et al: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; 257:79-83
- 10) Aso Y, Yamamoto R, Wakabayashi S, et al: Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. *Diabetes*. 2006; 55:1954-1960
- 11) Arai Y, Nakazawa S, Kojima T, et al: High adiponectin concentration and its role for longevity in female centenarians. *Geriatr. Gerontol. Int*. 2006; 6:32-39
- 12) Bik W, Baranowska-Bik A, Wolinska-Witort E, et al: The relationship between adiponectin levels and metabolic status in centenarian, early elderly, young and obese women. *Neuro. Endocrinol. Lett*. 2006; 27:493-500
- 13) Bluher M, Kahn BB, Kahn CR: Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science*. 2003; 299:572-574
- 14) Hara K, Boutin P, Mori Y, et al: Genetic variation in the gene encoding adiponectin is associated with an increase risk of type 2 diabetes in the Japanese population. *Diabetes* 2002; 51:536-540
- 15) Atzmon G, Pollin T, Crandall J, et al: Adiponectin levels and genotype: A potential regulator of life span in humans. *J. Gerontol. A. Biol. Sci. Med. Sci*. 2008; 63A:447-453
- 16) Jee SH, Sull JW, Lee JE, et al: Adiponectin concentrations: A genome-wide association study. *Am J Hum Genet*. 2010; 87(4):545-52
- 17) Minamino T, Orimo M, Shimizu I, et al: A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nat Med*. 2009; 15:1082-1087
- 18) Arai Y, Takayama M, Gondo Y, et al: Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age. *J Gerontol A Biol Sci Med Sci*. 2008; 63:1209-1218
- 19) Menon V, Li Wang X, Greene T, et al: Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17:2599-2606
- 20) Kistorp C, Faber J, Galatius S, et al: Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation*. 2005 Sep 20; 112(12):1756-62
- 21) Iwabu M, Yamauchi T, Okada-Iwabu M, et al: Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. *Nature*. 2010; 464:1313-9