Obesity Facts
The European Journal of Obesity

Review Article

Obesity Facts 2008;1:176–182
DOI: 10.1159/000145930

Published online: August 14, 2008

Fat Tissue and Long Life

Matthias Blüher

Department of Medicine, University of Leipzig, Germany

Key Words
Longevity · Adipose tissue · Insulin signaling · FIRKO · Animal models · SIRT1 · dFOXO

Summary
Studies over the last several years have revealed important roles of the body fat content, caloric intake and nutrition, insulin/IGF-1 signaling systems, and pathways involved in oxidative stress and control of protein acetylation on life span. Although the discovery of longevity genes supports the concept that life span is genetically determined, adipose tissue seems to be a pivotal organ in the aging process and in the determination of life span. Leanness and caloric restriction have been shown to increase longevity in organisms ranging from yeast to mammals. Increased longevity in mice with a fat-specific disruption of the insulin receptor gene (FIRKO) suggests that reduced adiposity, even in the presence of normal or increased food intake, leads to an extended life span. Reduced fat mass has an impact on longevity in a number of other model organisms. In *Drosophila*, a specific reduction in the fat body through overexpression of forkhead type transcription factor (dFOXO) extends life span. Sirtuin 1 (SIRT1), the mammalian ortholog of the life-extending yeast gene silent information regulator 2 (SIR2), was proposed to be involved in the molecular mechanisms linking life span to adipose tissue. Moreover, in the control of human aging and longevity, one of the striking physiological characteristics identified in centenarians is their greatly increased insulin sensitivity even compared with younger individuals. On the other hand, overweight and obesity seem to be associated with decreased life span in humans. In addition, it was recently shown that modifiable risk factors during the later years of life, including smoking, obesity, and hypertension, are associated not only with lower life expectancy, but also with poor health and function during older age. There is growing evidence that the effect of reduced adipose tissue mass on life span could be due to the prevention of obesity-related metabolic disorders including type 2 diabetes and atherosclerosis.

Introduction

The traditional view of adipose tissue as a passive energy reservoir has changed. Adipose tissue is a complex, highly active metabolic and endocrine organ [1]. With obesity as an increasingly important public health threat, a major development in the understanding of adipose tissue biology has come with observations in different biological spheres. Such observations include growing evidence for an important role of adipose tissue in longevity. Both too much and too little fat are associated with increased mortality in humans [2]. The role of adipose tissue, as well as caloric restriction and energy metabolism in the aging process seems to be especially well conserved throughout evolution [3]. There are many theories of aging and parameters that influence life span, including genetic instability, telomerase activity, and oxidative stress [4]. Associated with the aging process is a progressive loss of physiological functions, both within individual cells and within the whole organism that increases the vulnerability to age-related health complications. Systematic screening for longevity genes and the identification of several mutations that increase life span in diverse organisms including the yeast *Saccharomyces cerevisiae*, the nematode *Caenorhabditis elegans*, and the fruit fly *Drosophila melanogaster* support the concept that life span is genetically determined [5]. In diverse organisms and in all mammalian species studied so far, caloric restriction is the most potent environmental variable and has been shown to extend life span [6]. The effect of restricted feeding on life span has been studied in rodents for over 60 years [7], but it has been difficult to separate the beneficial effect of caloric restriction from that of reduced adipose tissue mass and leanness [6, 7]. If reduced adipose tissue mass leads to increased life span, one could speculate that ablation of white adipose tissue extends longevity. The consequences of transgenic lipoatrophy have been studied in several mouse models. However, most mouse models of lipoatrophy die shortly after birth or have at least a shortened life span [8–10]. These lipoatrophy

KARGER

Fax +49 761 4 52 07 14
E-mail Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/ofa

Prof. Dr. med. Matthias Blüher
Department of Medicine
University of Leipzig
Philip-Rosenthal-Straße 27, 04103 Leipzig, Germany
Tel. +49 341 97-15984, Fax -22439
bluma@medizin.uni-leipzig.de

models suggest that, despite the beneficial effects of reduced adipose tissue mass on extended life span, adipose tissue is required for a normal longevity most likely because of its role in maintaining whole body glucose homeostasis, lipid metabolism, and insulin sensitivity.

The molecular mechanisms of how adipose tissue might be linked to longevity are not completely understood. Decreased triglyceride storage in adipose tissue and small fat cell size are related to increased life span and could be caused by caloric restriction. Caloric restriction produces a variety of biological effects, including retardation of growth and development as well as a decrease in fertility [11]. However, the primary factor in the life-extending effect of caloric restriction seems to be a reduction in adipose tissue [5]. Accumulation of adipose tissue is associated with an age-related decrease in insulin sensitivity, which subsequently leads to the development of obesity, diabetes, hypertension, and atherosclerosis. In humans, these diseases strongly affect morbidity and mortality, especially among the elderly [12]. Caloric restriction and reduced body fat mass blunt sexual maturation and fertility, which allows long-term survival through energy sparing and reverses age-related reduced insulin sensitivity [5, 13]. In addition, increased fat mass could contribute to the development of insulin resistance in the aging process through alterations in adipose-derived hormone production and increased free fatty acid release as a result of lipolysis in adipose tissue.

Studies over the past several years have revealed a central role of the insulin/IGF-1 pathway in modulating fat mass and controlling aging and longevity in diverse organisms from invertebrates to humans. Insulin and IGF-1 signaling play an important role in the control of development and metabolism, including down-regulation of antioxidant enzymes, and reduced accumulation of fat and glycogen. Therefore, decreased activity of insulin/IGF-1 signaling pathways could extend longevity by simulating caloric restriction.

Decreased Insulin/IGF-1 Signaling as Potential Link between Leanness and Longevity

Aging and longevity may be controlled by a genetic-hormonal system that may have originated from an early common ancestor [14]. One of the evolutionary best conserved pathways that has been implicated in aging is growth hormone (GH)/IGF-1 and insulin signaling [3]. Lower species have been the source of most of our current knowledge on the role of insulin/IGF-1 signaling in modulating life span. Although yeasts do not have an insulin signaling pathway, they appear to have precursors of such pathways that function in a glucose/nutrient signaling cascade. Screening for long-lived mutants in the yeast *S. cerevisiae* identified that mutations in genes coding for precursors of such signaling molecules can extend life span of non-dividing cells up to three-fold [15].

Moreover, longevity genes have been identified in the insulin/IGF-1 receptor signaling system in nematodes and fruit flies. While disruption of the insulin/IGF-1 receptor in nematodes and flies increases life span significantly, mammals with genetic or acquired defects in the insulin signaling pathway are at risk of age-related diseases and increased mortality [3, 14]. This paradox could be explained by the acquisition of more complicated metabolic pathways in mammalians over evolution. Mammals have distinct and functionally different insulin and IGF-1 receptors on the surface of most cells, whereas lower species have a common insulin/IGF-1 receptor signaling mainly through the nervous system. Striking evidence suggests that decreased IGF-1 levels and signaling during early development may predominantly modulate longevity in many species [16]. In the mouse, several spontaneous or experimentally induced mutations that interfere with GH biosynthesis, GH actions, or sensitivity to IGF-1 lead to extended longevity [17]. Increases in the average life span in these mutants range from approximately 20–70% depending on the nature of the endocrine defect, gender, diet, and/or genetic background. Extended longevity of hypopituitary and GH-resistant mice appears to be due to multiple mechanisms including reduced insulin levels, enhanced insulin sensitivity, alterations in carbohydrate and lipid metabolism, reduced generation of reactive oxygen species, enhanced resistance to stress, reduced oxidative damage, and delayed onset of age-related diseases [17, 18]. There is considerable evidence to suggest that the genetic and endocrine mechanisms that influence ageing and longevity in mice with alterations of the GH/IGF-1 system may play a similar role in other mammalian species, including humans [17].

Insulin/IGF-1 Signaling in Invertebrate Animal Models

Over the past few years, several studies have provided evidence for the involvement of the insulin/IGF-1 signaling pathway in the control and regulation of ageing and longevity in different genetically modified animal models.

Caenorhabditis elegans

A powerful genetic model in the search for life span-controlling genes is the worm *C. elegans* because of its small size, relatively short life span, rapid reproduction rate, and well characterized genetics [4]. The insulin signaling pathway consists of molecules encoded by the genes daf-2 (the insulin/IGF-1 receptor homologue) [19, 20], ins-7 (1 out of at least 37 insulin-like ligands), age-1 (similar to mammalian p110 catalytic subunit of PI 3-kinase) [21], akt-2 (homologue of Akt/PKB), daf-16 (homologue of the forkhead family of transcription factors) [22], and daf-18 (PTEN homologue) [reviewed in 3, 4]. Mutations of these genes led to extended life span by 50% or more, and therefore revealed the importance of the insulin/IGF-1 signal transduction as a central regulator of longevity in *C. elegans* [19, 20].

Drosophila melanogaster

The major advance of genetics in ageing research has been made through the selection of long-lived *D. melanogaster* lines. Fruit fly lines, which have been selected for extended longevity, are characterized by resistance to heat and desiccation, enhanced storage of lipid and glycogen, increased efficiency in the utilization of nutrients, and a greater metabolic capacity. Thus, the long-lived *Drosophila* lines share many of the phenotypic characteristics described in yeast and *C. elegans* with extended life span [3, 4]. Mutations in genes homologous to the mammalian insulin/IGF-1 receptor signaling pathway can increase life expectancy in *D. melanogaster* [23–25]. It was shown that mutation in the insulin receptor substrate homologue 'chico' can extend life span in fruit flies [23]. Moreover, a mutation of the *Drosophila* insulin-like receptor (InR) gene, which is homologous to mammalian insulin and IGF-1 receptors, significantly extends longevity in the flies [25]. Taken together, these findings suggest that in *D. melanogaster* modification in the insulin-like signaling cascade play a significant role in the control of life span and ageing.

Moreover, it was recently shown that activation of dFOXO in the *Drosophila* adult fat body, the fly equivalent of the mammalian liver and white adipose tissue, increased life span and reduced fecundity of female flies by 20–50%. No effect of dFOXO overexpression was reported in male flies [26]. Expression of dFOXO, the homologue of mammalian FOXO, during early larval development causes inhibition of larval growth, alterations in feeding behavior, and may lead to adults that are reduced in size due to a decreased cell size and cell number. These dFOXO-mediated alterations are similar to the effects of starvation in yeast and worms, suggesting a role for dFOXO in the response to nutritional changes. Taken together, these findings suggest that in *D. melanogaster* both reduction in adipose tissue mass and modification in the insulin-like signaling cascade play a significant role in the control of life span and aging.

Long-Lived Mice with Alterations in Hormonal Signaling

The importance of IGF-1 and insulin signaling in the control of aging in mammals was deducted from results obtained in long-lived mutant mice. At least 2 genes have been identified ($Pit1^{dw}$, $Prop1^{df}$) in which naturally occurring loss-of-function mutations lead to dwarfism (Pit-1: Snell Dwarf mouse; Prop-1: Ames Dwarf mouse) with reduced levels of IGF-1 and insulin [27, 28]. These mice are deficient in serum GH, thyroid-stimulating hormone, and prolactin, as well as IGF-1 which is normally secreted by the liver upon stimulation with GH and mediates most of its activity. The prolonged longevity in of Ames and Snell dwarf mice is most likely due to GH deficiency, because comparable extension of life span was described in mice that cannot release GH in response to GH-releasing hormone due to a GH receptor/GH-binding protein knock-out (GHR-KO) [29]. Moreover, there is additional evidence that decreased activity of the insulin/IGF-1 pathway plays a key role in the longevity of the Pit-1 mutant Snell dwarf mouse [30]. Ames dwarf, Snell dwarf, and GHR-KO mice share many phenotypic and physiological characteristics, some of which may represent mechanisms of extended longevity.

Although IGF-1 knockout mice are not viable [31], a moderate decrease in IGF-1 receptor levels [32] has been shown to extend longevity in mice. The loss of a single copy of the Igf1r gene was shown to be sufficient to increase life span by 33% in females and 16% in males, accompanied by only a minimal reduction in growth [32]. In contrast to the naturally occurring long-lived Ames and Snell Dwarf mice, Igf1r heterozygous mice have no alteration in the age of sexual maturation and fertility. Serum IGF-1 concentrations are higher in Igf1r heterozygous mice compared to controls. Males tend to have higher fed glucose levels and impaired glucose tolerance, whereas the longer-lived females are more insulin sensitive and have lower fed plasma glucose concentrations [32]. Interestingly, Igf1r heterozygous mice are more resistant to oxidative stress, suggesting that increased life span of these mice could at least in part be due to resistance to oxidative stress [32]. Moreover, mice with a heterozygous IGF-1R knockout specifically in the central nervous system, which are genetically modified to be hyposensitive for IGF-1 in the brain, have an increased life span and a significant decrease in mortality [11]. We recently generated mice with an adipose tissue-specific ablation of the IGF-1 receptor [33]. Conditional IGF-1R inactivation resulted in increased adipose tissue mass with a predominantly increased lipid accumulation in epigonadal fat pads. IGF-1 receptor signaling in adipocytes does not appear to be crucial for the development and differentiation of adipose tissue in vivo [33]. Preliminary data suggest that longevity is not affected by adipose tissue reduction of IGF-1 signaling, further suggesting that reduced adipose tissue mass is more important for increased life span than defective IGF-1 signaling in adipose tissue.

Extended Longevity and Adipose-Specific Insulin Resistance

Calorically restricted (CR) models have reduced fat mass and improved whole body insulin sensitivity, which is associated with extended longevity. Mice with fat-specific disruption of the insulin receptor gene (FIRKO) have the same phenotype with a 50% reduced adipose tissue mass, improved whole body insulin sensitivity, and extended longevity [34, 35]. The main difference between CR and FIRKO mice is that FIRKO mice display adipose tissue-specific insulin resistance. In contrast, CR models have, supposedly, improved insulin sensitivity in adipose tissue. It is therefore very likely that extended life span in FIRKO mice is not due to blunted IFG/insulin sig-

Table 1. Comparison of phenotypic characteristics of a mouse model for extended longevity, the fat-specific insulin receptor knockout (FIRKO) mice with healthy human centenarians, and calorie restricted animals [modified from 4]

Parameter	FIRKO mice (vs. controls)	Centenarians (vs. younger subjects)	Caloric restriction
Body mass index	↓	↓	↓
Body fat content	↓	↓	↓
Waist circumference	NA	↓	NA
Insulin sensitivity	↑	↑	↑
Fasting plasma insulin	↓	↓	↓
Plasma LDL cholesterol	NA	↓	→
Plasma HDL cholesterol	NA	↑	NA
Plasma FFA	→	↓	↓ (→)
Plasma leptin	↑	↑ (→)	↓

NA = Not applicable; LDL = low density lipoprotein; HDL = high density lipoprotein; FFA = free fatty acids.

naling in adipose tissue but to beneficial effects, such as improved whole body insulin sensitivity, derived from reduced fat mass.

In brief, FIRKO mice are born with the expected frequency, survive well after weaning, are fertile, and do not develop diabetes [34]. Growth curves were normal in male and female FIRKO mice from birth to 4 weeks of age, however, by 8 weeks of age, FIRKO mice had gained less weight than controls. Fasted and fed glucose concentrations are indistinguishable between FIRKO and control mice, whereas FIRKO mice have significantly lower fasted insulin concentrations compared to controls (table 1). FIRKO mice are protected against insulin resistance and impaired glucose tolerance [34]. This phenotype leads to an extended longevity, and demonstrates that reduced fat mass, even in the presence of normal or increased food intake, can extend life span [35]. Since reduced adiposity tends to result in lower insulin levels and protection from diabetes, the FIRKO mouse mimics important effects of calorie restriction without actual caloric restriction [3]. To determine the mechanisms by which a lack of insulin signaling in adipose tissue might lead to increased longevity, we performed physiological and gene expression studies in FIRKO and control mice at different time points of the ageing process [36]. We confirmed that FIRKO mice have increased metabolic activity and increased expression of genes and proteins involved in the mitochondrial oxidative metabolism in adipose tissue [36]. FIRKO mice also have lower expression of genes involved in oxidative stress, which together with their decreased fat mass and higher energy expenditure may support their increase in life span. These results reveal the close molecular relationship between aging and energy metabolism, and confirm a central role of adipose tissue in longevity. We identified maintenance of mitochondrial activity and metabolic rates in adipose tissue as important contributors to longevity [36]. This concept is further supported by recent data in nematodes, demonstrating that glucose restriction promotes mitochondrial metabolism, causing increased reactive oxygen species formation and subsequently leading to an extension of life span [37].

Recently, Taguchi et al. [38] found an up to 18% extended life span in mice with a reduction of insulin receptor substrate-2 (Irs2) signaling both at the whole body level, but also if Irs2 was reduced just in the brain. In agreement with FIRKO and CR models, whole body Irs2+/– mice have improved whole body insulin sensitivity [38]. Surprisingly, brain-specific Irs2 knockout mice display increased life span, despite an overweight, hyperinsulinemic, and glucose-intolerant phenotype. Compared with control mice, brain-specific Irs2 knockout mice were more active and displayed greater glucose oxidation. Thus, less Irs2 signaling in aging brains can promote healthy metabolism, attenuate meal-induced oxidative stress, and extend the life span of overweight and insulin-resistant mice [38].

Genetic Alterations in Adipose Tissue and Longevity

Little is known about the effect of other adipose tissue-specific genetic alterations on longevity. Thus, no studies have been performed on the insulin receptor substrates, PI3 kinase, or Akt with regard to life span [3]. Adiponectin, a physiologically active polypeptide secreted by adipocytes, shows insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties in rodents and humans. Transgenic expression of human adiponectin was shown to inhibit the excessive fat accumulation, and reduce the morbidity and mortality in mice fed a high-calorie diet [39]. This model suggests that high circulating adiponectin levels might prevent premature death due to adverse effects of hypercaloric nutrition.

The glucose transporter 4 (GLUT4) is the major insulin-sensitive glucose transporter in white adipose tissue. It has been demonstrated that functional GLUT4 protein is essential for sustained growth, normal cellular glucose and fat metabolism, and longevity. Whole body GLUT4$^{-/-}$ mice are characterized by growth retardation and decreased longevity associated with cardiac hypertrophy markedly reduced white adipose tissue mass accompanied by normoglycemia and a normal response to glucose load [40]. However, selective inactivation of the GLUT4 gene in adipose tissue had no effect on growth, body weight, and fat mass in vivo, but these mice exhibit impaired insulin action in muscle and liver leading to glucose intolerance and insulin resistance [41]. The effect of adipose-specific GLUT4 knockout on longevity has not been investigated.

SIRT1 was shown to be involved in the molecular mechanisms linking life span to adipose tissue [42]. Overexpression of SIRT1 in 3T3-L1 cells, a cell model of white adipocytes, reduces adipogenesis and triglyceride accumulation in the lipid droplets of adipocytes by repressing peroxisome proliferator-

activated receptor-γ (PPARγ) transactivation [5]. In vivo, fasting and caloric restriction induce the recruitment of SIRT1 to PPARγ-response elements (PPREs) and promote lipolysis by inhibiting PPARγ-mediated fatty acid trapping. In addition, SIRT1 modulates the effects of PGC-1alpha repression of glycolytic genes in response to fasting and pyruvate [42]. However, this model does not account for how SIRT1 mediates increased insulin sensitivity under long-term caloric restriction if it represses PPARγ. The insulin-sensitizing effect of SIRT1 is, on the other hand, more likely linked to enhanced mitochondrial activity and energy expenditure as recently demonstrated [43, 44]. In Sirt1+/– mice, release of fatty acids from white adipocytes upon fasting is reduced, supporting SIRT1-mediated PPAR inactivation as part of the molecular pathway connecting caloric restriction to life extension in mammals [42]. Consistent with the $Sirt1^{+/-}$ mouse model, however, is the fact that the human Pro12Ala PPARγ variant with reduced function is also associated with increased longevity [45]. Moreover, it was recently shown that SIRT1 reduces p53-mediated apoptosis, and that SIRT1 represses the activity of forkhead transcription factor FOXO3a and other mammalian forkhead factors. Therefore, it was speculated that down-regulation of the damage-responsive p53 and FOXO3a may lead to reduced cancer incidence and favor a long life span under caloric restriction [3]. Finally, SIRT1 may link caloric restriction with forkhead-mediated metabolic changes including gluconeogenesis, insulin action, lipid usage, and ketogenesis [5]. Thus, caloric restriction could extend life span by promoting the long-term survival of irreplaceable cells [3].

Exceptional Human Longevity

Prospective data on genetic, behavioral, and environmental determinants of exceptional longevity in humans are limited. In particular, the modifying factors of exceptional longevity and their functional role are largely unknown. The average life span for humans in many developed countries is now more than 80 years, whereas only 200 years ago the average life span was about 24 years due to high infant mortality, poor hygiene, and the inability to treat infectious diseases [reviewed in 3]. In contrast, maximum life span has not changed dramatically, and seems to be stable at about 120 years [46]. Thus, although the number of centenarians has increased, maximum human life span has not. The phenotype of exceptional longevity including centenarians may improve our understanding of genetic, biologic, evolutionary, and social aspects of human longevity. One of the prominent characteristics of a centenarian is increased insulin sensitivity even compared with younger individuals [47, 48]. Healthy centenarians have in addition to more favorable anthropometric characteristics including lower body fat content and increased insulin-mediated glucose uptake (table 1), an increased plasma IGF-1/IGFBP-3 ratio compared with aged but younger subjects. Moreover, data from more than 450 healthy volunteers with an age range from 28 to 110 years revealed a significantly improved insulin sensitivity in 90- to 100-year-old individuals, even after adjusting for body mass index [48]. Although there might be selection biases of a protected population or common longevity-favoring genetic or environmental factors in these studies, these data demonstrate that low body fat mass, insulin sensitivity, and a non-atherogenic lipid profile may be associated with human longevity. A recent analysis of a prospective cohort study of 2,357 healthy men within the Physicians' Health Study revealed that modifiable healthy behaviors during early elderly years, including smoking abstinence, weight management, blood pressure control, and regular exercise, are associated with enhanced life span [49]. Taken together, aging is associated with the progressive development of insulin resistance affecting insulin-mediated physiologic processes including glucose uptake in peripheral tissues, inhibition of lipolysis, and hepatic control of glucose production [5].

Increased Mortality in Obesity

The association between body mass index and mortality is U-shaped, i.e. an increased mortality rate is observed at very low and high body weights [2]. Increased mortality in obesity is most likely due to obesity-associated co-morbidities including type 2 diabetes und coronary artery disease [50]. Thus, projections from the World Health Organization predict for the first time a decline in the mean life expectancy as a consequence of obesity-associated co-morbidities such as atherosclerosis, diabetes, and cancer in 2020. Therefore, there are good reasons to believe that weight loss in overweight and obese subjects should lead to reduced mortality [50]. However, recent studies support the paradox in obesity research that weight loss causes increased mortality compared with maintenance of the same weight [52–55]. Moreover, epidemiological studies, including recent ones that use conservative analytic approaches such as distinguishing between apparently intentional weight loss and unintentional weight loss, adjusting for potential confounders and excluding apparently unhealthy subjects, indicate that apparently intentional weight loss appears to neither increase nor decrease mortality rate [reviewed in 2]. On the contrary, short-term studies indicate that intentional weight loss among obese persons significantly improves health variables that are often precursors or markers of chronic diseases including heart diseases and type 2 diabetes [2]. In addition, several controlled clinical trials suggest that intentional weight loss may reduce mortality rate [56, 57]. It was recently demonstrated that bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality [57]. Furthermore, long-term total mortality, particularly deaths from diabetes, heart disease, and cancer, was significantly reduced after gastric bypass surgery [58]. What is the missing link between the still unsolved controversy between increased mortality after weight

loss and the evidence for decreased mortality after intentional weight loss from interventional studies? The key explanation could be that there is an important difference whether one reduces body fat mass or loses body (fat-free) mass. Selective loss of fat mass was shown to be associated with reduced mortality, whereas weight loss as such leads to increased mortality [59]. This suggests that loss of fat-free mass is deleterious and responsible for the excess mortality following weight loss. Unfortunately for practical considerations and therapeutic consequences, weight changes in the population are associated with proportional changes both in fat mass and fat-free mass, independent of obesity, previous weight changes, attempts to lose weight, and physical activity [60].

Conclusion

Across different organisms, reduction in adipose tissue mass either caused by caloric restriction, naturally occurring mutations in insulin/IGF-1 signaling pathway, or genetic modification in animal models, increases life span. Studies of worms and fruit flies have revealed hundreds of genes and proteins that, when mutated, extend life span. Extended life span in flies with overexpressed dFOXO in adult fat body and in mice with fat-specific disruption of the insulin receptor gene (FIRKO mice) demonstrate the important role of reduced adiposity, and suggest a special role for the insulin signaling pathway in adipose tissue in the longevity process. In humans, preserved insulin sensitivity and low fat mass or reduction in body fat mass are associated with lower mortality and beneficial effects on well-being.

To Lose or not to Lose Weight?

There is no doubt that weight loss in co-morbid obesity has beneficial effects on diabetes, other cardiovascular risk factors, cardiovascular symptoms, sleep apnea, joint pain, and health-related quality of life. A recommendation to healthy overweight or obese individuals to lose weight must be based on weighing the short-term benefits of weight loss against the possible risk of an increased mortality in the long term.

References

1 Kershaw EE, Flier JS: Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548–2556.
2 Yang D, Fontaine KR, Wang C, Allison DB: Weight loss causes increased mortality: cons. Obes Rev 2003;4:9–16.
3 Katic M, Kahn CR: The role of insulin and IGF-1 signaling in longevity. Cell Mol Life Sci 2005;62:320–343.
4 Klöting N, Blüher M: Extended longevity and insulin signaling in adipose tissue. Exp Gerontol 2005;40:878–83.
5 Picard F, Guarente L: Molecular links between aging and adipose tissue. Int J Obes Relat Metable Disord 2005;29:S36–S39.
6 Weindruch R, Walford L: The Retardation of Aging and Diseases by Dietary Restriction. CC Thomas, Springfield, IL, 1998.
7 Koubova J, Guarente L: How does calorie restriction work? Genes Dev 2003;17:313–321.
8 Ross SR, Graves RA, Spiegelman BM: Targeted expression of a toxin gene to adipose tissue: transgenic mice resistant to obesity. Genes Dev 1193;7:1318–1324.
9 Moitra J, Mason MM, Olive M, Krylov D, Gavrilova O, Marcus-Samuels B, Feigenbaum L, Lee E, Aoyama T, Eckhaus M, Reitman ML, Vinson C: Life without fat: a transgenic mouse. Genes Dev 1998;12:3168–3181.
10 Shimomura I, Hammer RE, Richardson JA, Ikemoto S, Bashmakov Y, Goldstein JL, Brown MS: Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes Dev 1198;12:3182–3194.
11 Holzenberger M, Kappeler L, De Magalhaes Filho C: IGF-1 signaling and aging. Exp Gerontol 2004;39:1761–1764.
12 Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607.
13 Mora S, Pessin JE: An adipocentric view of signaling and intracellular trafficking. Diabetes Metable Res Rev 2002;18:345–356.
14 Rincon M, Rudin E, Barzilai N: The insulin/IGF-1 signaling in mammals and its relevance to human longevity. Exp Gerontol 2005;40:873–877.
15 Fabrizio P, Pozza F, Pletcher SD, Gendron CM, Longo VD: Regulation of longevity and stress resistance by Sch9 in yeast. Science 2001;292:288–290.
16 Rincon M, Muzumdar R, Atzmon G, Barzilai N: The paradox of the insulin/IGF-1 signaling pathway in longevity. Mech Ageing Dev 2004;125:397–403.
17 Bartke A: Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology 2005;146:3718–23.
18 Sun LY, Al-Regaiey K, Masternak MM, Wang J, Bartke A: Local expression of GH and IGF-1 in the hippocampus of GH-deficient long-lived mice. Neurobiol Aging 2005;26:929–937.
19 Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R: A C. elegans mutant that lives twice as long as wild type. Nature 1993;366:461–464.
20 Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G: daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. Science 1997;277:942–946.
21 Johnson TE: Increased life-span of age-1 mutants in Caenorhabditis elegans and lower Gompertz rate of aging. Science 1990;249:908–912.
22 Lin K, Dorman JB, Rodan A, Kenyon C: daf-16: an HNF-3/forkhead family member that can function to double the life-span of Caenorhabditis elegans. Science 1997;278:1319–1322.
23 Clancy DJ, Gems D, Harshman LG, Oldham S, Stocker H, Hafen E, Leevers SJ, Partridge L: Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. Science 2001;292:104–106.
24 Sun J, Tower J: FLP recombinase-mediated induction of Cu/Zn-superoxide dismutase transgene expression can extend the life span of adult Drosophila melanogaster flies. Mol Cell Biol 1999;19:216–228.
25 Tatar M, Kopelman A, Epstein D, Tu MP, Yin CM, Garofalo RS: A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. Science 2001;292:107–110.
26 Giannakou ME, Goss M, Junger MA, Hafen E, Leevers SJ, Partridge L: Long-lived Drosophila with overexpressed dFOXO in adult fat body. Science 2004;305:361.
27 Li S, Crenshaw EB 3rd, Rawson EJ, Simmons DM, Swanson LW, Rosenfeld MG: Dwarf locus mutants lacking three pituitary cell types result from mutations in the POU-domain gene pit-1. Nature 1990;347:528–533.
28 Sornson MW, Wu W, Dasen JS, Flynn SE, Norman DJ, O'Connell SM, Gukovsky I, Carrière C, Ryan AK, Miller AP, Zuo L, Gleiberman AS, Andersen B, Beamer WG, Rosenfeld MG: Pituitary lineage determination by the Prophet of Pit-1 homeodomain factor defective in Ames dwarfism. Nature 1996;384:327–333.
29 Coschigano KT, Clemmons D, Bellush LL, Kopchick JJ: Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. Endocrinology 2000;141:2608–2613.
30 Hsieh CC, DeFord JH, Flurkey K, Harrison DE, Papaconstantinou J: Effects of the Pit1 mutation on the insulin signaling pathway: implications on the longevity of the long-lived Snell dwarf mouse. Mech Ageing Dev 2002;123:1245–1255.
31 Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A: Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF (Igf1r). Cell 1993;75:59–72.
32 Holzenberger M, Dupont J, Ducos B, Leneuve P, Geloen A, Even PC, Cervera P, Le Bouc Y: IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature 2003;421:182–187.

33 Klöting N, Koch L, Wunderlich T, Kern M, Ruschke K, Krone W, Brüning JC, Blüher M: Autocrine IGF-1 action in adipocytes controls systemic IGF-1 concentrations and growth. Diabetes 2008 (Epub ahead of print).
34 Blüher M, Michael MD, Peroni OD, Ueki K, Carter N, Kahn BB, Kahn CR: Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Dev Cell 2002;3:25–38.
35 Blüher M, Kahn BB, Kahn CR: Extended longevity in mice lacking the insulin receptor in adipose tissue. Science 2003;299:572–574.
36 Katic M, Kennedy AR, Leykin I, Norris A, McGettrick A, Gesta S, Russell SJ, Bluher M, Maratos-Flier E, Kahn CR: Mitochondrial gene expression and increased oxidative metabolism: role in increased lifespan of fat-specific insulin receptor knock-out mice. Aging Cell 2007;6:827–839.
37 Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M: Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 2007;6:280–293.
38 Taguchi A, Wartschow LM, White MF: Brain IRS2 signaling coordinates life span and nutrient homeostasis. Science 2007;317:369–372.
39 Otabe S, Yuan X, Fukutani T, Wada N, Hashinaga T, Nakayama H, Hirota N, Kojima M, Yamada K: Overexpression of human adiponectin in transgenic mice results in suppression of fat accumulation and prevention of premature death by high-calorie diet. Am J Physiol Endocrinol Metab 2007;293: E210–218.
40 Katz EB, Stenbit AE, Hatton K, DePinho R, Charron MJ: Cardiac and adipose tissue abnormalities but not diabetes in mice deficient in GLUT4. Nature 1995;377:151–155.
41 Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, Minnemann T, Shulman GI, Kahn BB: Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 2001;409:729–733.
42 Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, Leid M, McBurney MW, Guarente L: Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature 2004;429:771–776.
42 Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P: Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. Nature 2005;434:113–118.
43 Heikkinen S, Auwerx J, Argmann CA: PPARgamma in human and mouse physiology. Biochim Biophys Acta 2007;1771:999–1013.
44 Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J: Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127: 1109–1122.
45 Barbieri M, Bonafe M, Rizzo MR, Ragno E, Olivieri F, Marchegiani F, Franceschi C, Paolisso G: Gender specific association of genetic variation in peroxisome proliferator-activated receptor (PPAR) gamma-2 with longevity. Exp Gerontol 2004;39: 1095–100.
46 Fries JF: Aging, natural death, and the compression of morbidity. N Engl J Med 1980;303:130–135.
47 Paolisso G, Ammendola S, Del Buono A, Gambardella A, Riondino M, Tagliamonte MR, Rizzo MR, Carella C, Varricchio M: Serum levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action, and cognitive function. J Clin Endocrinol Metab 1997;82:2204–2209.
48 Paolisso G, Barbieri M, Bonafe M, Franceschi C: Metabolic age modelling: the lesson from centenarians. Eur J Clin Invest 200;30:888–894.
49 Yates LB, Djoussé L, Kurth T, Buring JE, Gaziano JM: Exceptional longevity in men: modifiable factors associated with survival and function to age 90 years. Arch Intern Med 2008;168:284–290.
50 Drenick EJ, Bale GS, Seltzer F, Johnson DG: Excessive mortality and causes of death in morbidly obese men. JAMA 1980;243:443–445.
51 Sørensen TI: Weight loss causes increased mortality: pros. Obes Rev 2003;4:3–7.
52 Mikkelsen KL, Heitmann BL, Keiding N, Sørensen TIA: Independent effects of stable and changing body weight on total mortality. Epidemiology 1999; 10:671–678.
53 Wannamethee SG, Shaper AG, Walker M: Weight change, weight fluctuation, and mortality. Arch Int Med 2002;162:2575–2580.
54 Yaari S, Goldbourt U: Voluntary and involuntary weight loss. associations with long term mortality in 9,228 middle-aged and elderly men. Am J Epid 1998;148:546–555.
55 Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B: Mortality associated with body fat, fat free mass and body mass index among 60-year-old Swedish men – a 22 year follow-up. Int J Obes 2000;24:33–37.
56 Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, Niaz MA: Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one-year follow-up. BMJ 1992;304:1015–1019.
57 Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM; Swedish Obese Subjects Study: Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357: 741–752.
58 Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC: Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–761.
59 Allison DB, Zannolli R, Faith MS, Heo M, Pietrobelli A, VanItallie TB, Pi-Sunyer FX, Heymsfield SB: Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. Int J Obes 1999;23:603–611.
60 Heitmann BL, Garby L: Composition (lean and fat tissue) of weight changes in adult Danes. Am J Clin Nutr 2002;75:840–847.