



HHS Public Access

Author manuscript

Gerontology. Author manuscript; available in PMC 2017 April 28.

Published in final edited form as:

Gerontology. 2016 ; 62(6): 611–617. doi:10.1159/000445800.

Obesity and aging in humans and nonhuman primates

Kelli L. Vaughan^{1,2} and Julie A. Mattison¹

¹Translational Gerontology Branch, National Institute on Aging, Intramural Research Program, Poolesville, MD

²SoBran, Inc., Burtonsville, MD 20866, USA

Abstract

The prevalence of obesity in this country is increasing exponentially, across gender, age and ethnic group. Obesity and a long-term hypercaloric diet result in what appears to be accelerated aging; often leading to a multi-systemic deterioration known as the metabolic syndrome. Due to their physiological similarity to humans, comparable rates of spontaneous obesity and diabetes mellitus, nonhuman primates provide a useful translational model for the human condition. They allow for in vivo study of disease progression, interaction of comorbidities, and novel interventions. However, defining obesity in aged humans and nonhuman primates is difficult as the physiological changes that occur with aging are not accounted for using our current systems (BMI – body mass index, and BCS – body condition score). Nonetheless, nonhuman primate studies have greatly contributed to our understanding of obesity and metabolic dysfunction and should continue to play a large role in translational research. Here, methods for defining obesity and metabolic syndrome in humans and nonhuman primates are described along with the prevalence and effects of these conditions.

Keywords

obesity; diabetes; animal model; aging; monkeys; macaques

Obesity is quickly replacing smoking as the leading cause of death for adults in developed countries, contributing to nearly 20% of all deaths in the U.S. [1]. Moreover, obesity is associated with many comorbidities, including cardiovascular disease (CVD), type II diabetes mellitus (T2DM), and cancer, thereby presenting a higher risk of all-cause mortality [2, 3]. As such, the economic and healthcare burden of obesity is immense and growing exponentially.

In an attempt to describe the extent of the obesity problem in our country, Ladabaum et al. [4] carried out several cross-sectional surveys. Through their work they determined that, since 1990, the prevalence of abdominal obesity has increased across age groups, with annual increases being more pronounced in the youngest group and abdominal obesity prevalence increasing with age [4]. Similar results were found with regard to average

increases in waist circumference [4]. Since 1990, average body mass index (BMI) and waist circumference have increased by 0.37% per year among men and women of all ages and ethnic groups across the country [4]. In both obese persons and persons of normal weight, waist circumference is an independent predictor of morbidity and mortality [5, 6].

The health consequences of increased visceral adiposity caused by a long-term, chronic, hypercaloric diet is a multi-systemic deterioration resulting in an increased risk for developing metabolic syndrome (MetS) [7]. MetS is diagnosed when 3 or more of the following characteristics are identified, 1) enlarged waist circumference, 2) elevated triglycerides, 3) decreased high density lipoprotein cholesterol (HDL-c), 4) elevated blood pressure, and 5) increased fasting glucose [8]. And, each 11 cm increase in waste circumference is associated with an 80% increase in the risk of developing MetS over the following 5 years [7]. Likewise, as we age, the chance of developing metabolic disorders rises [4]. This statistic, along with the increasing obesity rates seen in the aging population, creates the potential for exponentially higher rates of visceral adiposity, insulin resistance, impaired glucose tolerance, overt T2DM, hypertension, dyslipidemia, and/or cardiovascular complications among the elderly population. In fact, recently published analyses of the NHANES cross-sectional study data, conducted between 2011-2012, revealed that the prevalence of T2DM among a nationally representative sample of U.S. adults was highest in citizens aged 65 and over (33%) compared to younger cohorts (aged 45-64 = 17.5%; aged < 45 = 5.0%)[9]. For this reason, it is progressively becoming more important to find adequate research models of obesity and aging in order to, 1) better define how these conditions interact, 2) examine long-term consequences, and 3) study possible interventions.

Nonhuman primates (NHPs) and companion animals have obesity rates comparable to humans, ranging from 22% to 40% of the U.S. population [10]. Though obesity can be induced in animal models when exposed to hypercaloric diets, reports of spontaneous obesity are common among NHPs, specifically rhesus and cynomologos macaques, vervet monkeys, and squirrel monkeys [10-12]. Along with their close genetic relatedness, NHPs have obesity-related physiologic changes that are very similar to humans, making NHPs a valuable research model for obesity and aging [13]. These animals also carry similar rates of metabolic diseases and spontaneously develop T2DM at rates which increase with age [14, 15].

In contrast, caloric restriction (CR) is associated with a decreased risk of age-associated pathologies in humans and NHPs [16-18]. CR is studied with regard to its potential benefits, increasing health-span and extending life-span, while obesity has been linked to diminished health and accelerated aging. NHP studies have shown that CR lowers insulin levels and results in decreased incidence of T2DM compared to controls [19, 20]. Human studies have shown similar beneficial metabolic effects in overweight individuals after 6 months of CR, improving cardiovascular health along with other biomarkers of aging [21-23]. These results suggest that CR may provide protection against development of T2DM and insulin resistance and, therefore, provides a useful tool for investigating mechanisms of aging and age-associated diseases. In fact, there are currently parallel longitudinal studies, at the National Institute on Aging (NIA) and the Wisconsin National Primate Research Center (WNPRC), using NHPs to investigate this phenomenon [17, 24]. Preliminary findings from

these studies have mixed results with regards to CR and extension of life-span, but both have found an association between CR and extended health-span [17, 24]. In practice, CR is a difficult intervention to implement among the human population. As such, obesity and diabetes remain a prevalent health concern in the aging population.

In this review, the contributions made by NHP models of obesity and metabolic dysfunction are summarized.

Characterizing Obesity & MetS

Obesity

In humans, obesity is defined as BMI of ≥ 30 kg/m², yet a BMI of 25.0 to 29.9 kg/m² has been associated with an increased risk of death [3]. Defining obesity in monkeys is a similar process, though two measures are commonly used, 1) measures of abdominal fat folds, BMI, and abdominal circumference, or 2) waist-hip ratio (WHR) and the circumference of the thigh (waist/thigh ratio) [25]. When compared to radioisotope methods in a cross-sectional analysis, both methods for defining obesity in rhesus monkeys was found to be highly correlated with body fat [25]. However, this analysis did not take weight across the lifespan into account [25].

Though fairly straightforward in young and healthy humans and NHPs, age-related changes in body composition make defining obesity in the aged population quite challenging [26]. For example, aging is associated with decreases in fat free mass (termed sarcopenia), increases in fat mass, kyphosis, and compression of vertebrae leading to loss of height [26]. These variances, along with gender differences are not taken into account when using BMI and body weight to determine obesity. Similarly, comparable difficulties are faced when assigning body condition scores [27] (a subjective measure of body fat) in an aged rhesus monkey colony.

Another factor complicating the story of obesity and aging is the obesity paradox. Here, obesity is thought to serve as a protectant of sorts after a certain age because elderly obese individuals seem to live longer and have fewer and shorter hospital stays compared to age-matched people of normal weight [26, 28]. However, more recent studies have shown a much stronger association between obesity and morbidity in the elderly when various confounding factors are controlled (e.g. cohort factors and duration of life spent obese) [1, 29]. The existence of an obesity paradox is a controversial topic with mixed findings to date [30]. Further human and NHP studies in this area are warranted.

Metabolic syndrome

MetS occurs as a consequence of complex genetic and environmental factors [7]. McNeill et al. [31] found that, within the elderly population, individuals with MetS had increased incidence of coronary heart disease and CVD, with high blood pressure being the most strongly associated factor. Results indicate that MetS was associated with a 2-fold increase in risk of experiencing CVD, CVD mortality, and stroke [32]. However, beyond the age of 75 the relationship between MetS components and CVD is lost, similar to the obesity paradox. It has been proposed that this decrease in predictability with age may be due to an

increase in the existence of competing risk factors (e.g. unhealthy diet, lack of exercise, insulin resistance, diabetes, etc.) once an individual reaches 75 years of age [31]. These are indications of the relative difficulty of describing obesity and the MetS in individuals of advanced age.

Zhang et al. [33], used a population screening approach to identify a model of spontaneous MetS in rhesus monkeys in order to investigate early pathogenesis and relation of the syndrome to vascular difficulties. Screening parameters for MetS were based on those used in human medicine [8] and included waist and hip circumference, body weight, blood pressure, fasting plasma glucose, insulin, triglycerides, high- and low-density lipoprotein cholesterol and total cholesterol. Animals scoring the highest on these measures were deemed to be pre-disposed to MetS and followed for 18 months. Similar to humans, pre-disposed NHPs in this study were overtly obese and had higher body weight and waist circumference compared to similarly aged control animals and had significantly higher insulin levels, showing evidence of insulin resistance [33].

Type II diabetes mellitus

As is common in human medicine, diabetes is evaluated in monkeys with measures of fasting blood glucose and insulin levels, glycated hemoglobin (HbA1c) values, arginine stimulation test, intravenous glucose tolerance test (IVGTT), and oral glucose tolerance test (OGTT). Fasting glucose concentrations are generally lower in macaque monkeys compared to humans (50 – 80 mg/dl and 70.2 – 100.0 mg/dl, respectively) [34, 35]. A >106 mg/dl glucose concentration suggests overt diabetes in NHPs, where humans require >126 mg/dl for overt diabetes diagnosis (table 1) [34, 35].

Effects of Obesity

Metabolic and endocrine factors

Diabetes and obesity are recognized causes of accelerated aging [36, 37]. For example, obesity (high BMI) is associated with an accelerated rate of epigenetic changes associated with age of human liver, which may play a role in insulin resistance or liver cancer [38]. Obesity affects the adipose tissue and influences hormones, inflammation, and glucose homeostasis, which can lead to the development of diabetes and subsequent characteristics of accelerated aging. In obese states, macrophages infiltrate adipose tissue, elevating cytokine levels (e.g. TNF- α and IL-6) and may result in insulin resistance and T2DM[39].

Serum lipids, cholesterol, and triglycerides are positively related to body fat distribution in obese and non-obese humans and NHPs [40]. Lipoprotein changes are observed in association with the development of diabetes in rhesus monkeys [40]. Specifically, these changes include increases in plasma triglycerides, total cholesterol, and very low-density lipoprotein, and decreases in high-density lipoprotein cholesterol [41].

Spontaneous T2DM in NHPs presents with similar clinical and pathological features as humans and the same risk factors have been identified [42, 43]. Similar to humans, NHPs exhibit a pre-diabetic period of obesity-associated insulin resistance[44]. This period leads to compensatory insulin secretion along with subsequent detrimental changes in plasma lipid

and lipoprotein concentrations, composition, and glycation. Fasting glucose concentrations increase following a deficiency in pancreatic insulin production [45].

In addition, inflammation plays a crucial role in the development of insulin resistance, diabetes, and cardiovascular disease associated with obesity [46]. Adiponectin, a hormone secreted by adipose tissue, is an anti-inflammatory molecule responsible for regulating lipid and glucose metabolism, increasing insulin sensitivity, regulating food intake and body weight, and protecting from chronic inflammation. Levels of adiponectin are inversely proportional to fat content, therefore, decreases in plasma levels of adiponectin are seen in obese diabetic NHPs and humans, contributing to the development of insulin resistance [47]. It is negatively associated with CVD risk factors (blood pressure, low-density lipoprotein cholesterol, and triglycerides) in humans [48] and with body weight and BMI in humans and NHPs [47, 49].

Experimental Nonhuman Primate Models

Spontaneous models

Nonhuman primates develop T2DM in an age-dependent manner, which is influenced by obesity and characterized by insulin resistance, hyperinsulinemia, and progressive hyperglycemia similar to humans [50]. This makes them a valuable resource for intervention studies, novel therapies, disease pathogenesis studies, studies of nuclear and cellular mechanisms, as well as the mechanisms of diabetic complications, like cardiovascular disease [51]. In addition, NHP's disease progression occurs in a much shorter timeframe compared to humans but in a longer timeframe compared to rodent models, allowing for study of disease pathogenesis. However, studies using spontaneous NHP models are limited due to the unpredictability of disease onset and the ability to conduct large scale studies.

When given food *ad libitum*, captive born animals may develop obesity-associated diseases in an age-dependent manner[41]. Elevated serum glucose and triglycerides have also been described in free-ranging primate colonies[52]. Tattersall et al. [52] describe a high-carbohydrate diet with excesses of sugar cane and molasses as likely contributing to these instances of diabetes in a crab-eating macaque colony. The development of obesity and diabetes has also been described in the free-ranging rhesus monkeys on the island of Cayo Santiago[25].

Importantly, female Old World primates have menstrual cycles that closely approximate that of humans. For this reason, female monkeys provide useful models for the study of reproductive aging, menopause, and hormonal dysregulation along with its association with increased risk for developing metabolic syndrome. Also, pregnancy, menopause, and/or sex hormone treatments can affect the development of insulin resistance and T2DM[53] in female monkeys. Endogenous gestational diabetes occurs in some species of NHPs along with complications similar to those observed in human females with the same disease [54]. Though rare, a NHP model of gestational diabetes provides a unique opportunity to study this disease and potential treatments, as ethical considerations constrain study in a human model.

Secondary models

Obesity can be induced in a NHP model after administration of a Western diet (high-fat/high-cholesterol) [55]. T2DM and its associated metabolic perturbations can also be successfully induced in rhesus monkeys. For example, Bremer et al. [56] proposed that increases in dietary fructose consumption may have attributed, in part, to increased incidence of insulin resistance seen in the human population. To test this theory, a fructose sweetened solution was administered daily to male monkeys for 6 – 12 months. In this short amount of time, a high fructose dietary additive was able to produce many features of metabolic syndrome including central obesity and T2DM in their animals [56]. Trans fatty acids (TFA) in foods have been regulated by the Food and Drug Administration due to their association with the development of abdominal obesity, cardiovascular disease, and T2DM. To assess this phenomenon, Kavanagh et al. [57] administered a long-term diet high in TFA to healthy African Green monkeys. They found that this diet lead to significant weight gain and was associated with insulin resistance in this NHP model [57].

Contrary to human studies which often rely on self-reporting of eating habits, NHP studies offer precise dietary control and valid measures of food consumption. With this model, the metabolic effects of specific dietary parameters can be assessed. Using this method, Astuti et al. [58], assessed the metabolic effects of 4 different diets over a 12 month period in cynomologos monkeys and developed a reliable method for inducing atherosclerosis, a comorbidity of T2DM, in a NHP model. These important empirical advantages provided by NHP studies aid future exploration into biological mechanisms, disease progression, and novel interventions.

Streptozocin (STZ), a specific β -cell toxin, has been used to create a reproducible model of diabetes in monkeys and other animals [59, 60]. This method specifically targets β -cells resulting in hyperglycemia but produces pancreatic islet pathology more closely resembling type 1 diabetes [45]. Here, monkeys are not insulin resistant, just insulin deficient, unless aged or obese and the induction protocols can be modified to accommodate for this. In doing so, overweight animals can be made to convert to overt diabetes through high-carbohydrate and high-fat diet, along with STZ treatment. Partial pancreatectomy with low-dose STZ is reportedly the safest and most reproducible method for inducing diabetes in a NHP model [61].

Models that target diabetic complications have also been developed. A dose and administration study determined that diabetic retinopathy could be induced in NHPs by subretinal injection with an adeno-associated virus vector to deliver human vascular endothelial growth factor (VEGF) protein to the retina [62]. This leads the way for future studies into the pathological mechanisms, developmental progression, and novel therapeutic treatment of diabetic blindness.

There are several disadvantages to a primate model; they are a long-lived species and expensive to study. Longitudinal studies in particular are costly due to specialized housing needs, trained and knowledgeable husbandry staff and veterinary care along with trained technical research staff. Induced diabetes models may show the early stages of diabetes, but do not necessarily develop all of the complications seen in overt diabetes[63].

Treatment for Obesity & Diabetes

Diabetic and pre-diabetic NHPs are clinically treated in much the same manner as humans. Diet and exercise are the first line of treatment for human patients. While dietary adjustments are easily implemented for NHPs, attempts to apply an exercise program can be much more problematic due to a variety of limitations (e.g. facility, space, staff, and individual temperaments). However, this is not an impossible task even with very limited space. In fact, treadmill exercise programs have been successfully implemented in young and old rhesus and cynomologos monkeys [64, 65].

Likewise, pharmacological treatment for spontaneous T2DM is quite similar for humans and NHPs. Exogenous insulin therapy is often administered to improve glycemic control. Other treatments include insulin-sensitizing agents, like thiazolidinedione and metformin, which are used to improve insulin resistance and glucose uptake. Sulfonylureas, glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors are also used in both humans and NHPs to stimulate insulin secretion from the pancreas [63]. During such treatments, disease progression is typically followed by periodic monitoring of blood glucose levels and HbA1C.

Parallels in Human and Monkey Aging: Conclusion

Nonhuman primates have provided an invaluable translational model in the study of human pathology [66]. Due to their phylogenetic similarities to humans, this model has been used to describe the aging process, to investigate the nature and causes of age-related illnesses, and to evaluate potential interventions [67, 68]. Attributable to their biological similarities to humans and a comparable aging process, NHPs provide an extraordinarily unique resource for scientific inquiry. Moreover, unlike clinical trials, NHP studies allow for long-term control of diet and environment, something that is almost impossible with human subjects. Normal variations seen in clinical trials (lifestyle, diet, exercise, illness, medication, etc.) are effectively removed in NHP studies.

Acknowledgments

Mini-Review: This research was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging

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Fasting blood glucose and insulin, and HbA1c values in normal and diabetic rhesus macaques and humans.

Table 1

	Monkey		Human	
	Normal	T2DM	Normal	T2DM
Fasting glucose, mg/dL	50 – 80 [34]	106 [34]	70.2 – 100.0 [35]	126 [35]
Fasting insulin, μ U/mL	70 [69]	> 70 [69]	29 [70]	> 29 [71]
HbA1c, %	3.5 – 5.0 [72]	7.9 [72]	4.0 – 5.6 [34]	6.5 [35]