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Overview

Obesity in Rhesus and Cynomolgus Macaques: A Comparative Review of the Condition and Its Implications for Research

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Obesity is an increasingly important health issue in both humans and animals and has been highly correlated as a risk factor for hyperglycemic conditions in humans. Naturally occurring obesity has been extensively studied in nonhuman primates with a focus on the development of biomarkers for characterizing overweight individuals and tracking the progression of obesity to conditions such as type 2 diabetes mellitus. Animal models have provided a basic understanding of metabolism and carbohydrate physiology, and continue to contribute to ongoing research of obesity and its adverse health effects. This review focuses on spontaneous obesity in rhesus and cynomolgus macaques as a model for human obesity and type 2 diabetes mellitus, including associated risk factors for the development of obesity and obesity-related health conditions. Little is known about preventive measures to minimize obesity while maintaining a healthy colony of macaques, and numerous complexities such as social status, feeding behaviors, timing of feeding, food distribution, and stress have been identified as contributing factors to overweight body condition in both single and group housed nonhuman primates. As in humans, increased body weight and obesity in macaques affect their overall health status. These conditions may interfere with the suitability of some animals in various studies unrelated to obesity.

Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus.

Obesity has been defined as "a disease in which excess body fat has accumulated such that health may be adversely affected"[67] and can be measured by numerous tools, most of which are based on morphometry, such as height and weight ratios, body size and shape, and percentage body fat. All have benefits as well as limitations. In humans, obesity has become an increasingly important health issue with worldwide ramifications. More than 30,000 articles on this topic are published annually, and peer-reviewed scientific journals, such as *International Journal of Obesity*, are dedicated specifically to obesity animal models and research in humans. In addition, the prevalence of obesity in companion animals has increased to near-epidemic proportions, and the veterinary community struggles to find solutions and satisfactory preventative measures. A recent report[39] outlined specific disease entities associated with obesity in companion dogs and cats, of which approximately 22% to 40% are estimated to be obese, that mirror those of humans and macaques, and included metabolic disorders, endocrinopathies, orthopedic disorders, cardiorespiratory disease, urinary and reproductive disorders, neoplasia, dermatologic conditions, and anesthetic complications.

Several animal models have been used to study overweight body condition and include dogs, pigs, hamsters, rats, mice, and nonhuman primates, such as macaques and baboons.[22,101] Obesity can be induced experimentally in these species by using high-fat diets or surgical force-feeding and through genetic modification.[119] In captive nonhuman primates, particularly rhesus and cynomolgus macaques,[21,62] obesity occurs spontaneously, making these species excellent models for the condition in humans.

Because of their close genetic relatedness to humans, similar physiologic changes and obesity-related health conditions, including increased abdominal fat, body mass index, and alterations in various serum chemistry parameters, for example, increased serum glucose levels, much of the scientific literature to date has focused on describing physiologic characteristics and subsequent disease in spontaneously obese macaques. Rhesus and cynomolgus macaques are used in a wide array of research models exploring the pathogenesis and treatment of a range of human diseases. The scientific validity of research results requires the use of healthy animals. In both Canada and the United States, husbandry guidelines promote the physical and psychologic wellbeing of nonhuman primates used in research.[20,50] In addition to basic maintenance of appropriate standards of living conditions, the guidelines also address preventing and treating disease. Therefore, in contravention to existing guidelines, spontaneous obesity in captive macaques could jeopardize physical wellbeing, particularly for animals housed long-term. In addition to potential adverse effects on the physical health and wellbeing of

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individual animals, obesity may influence an animal's suitability for some research protocols.

Despite the real or potential interest in maintaining normoweight (that is, at ideal weight) rhesus and cynomolgus macaques and the widespread use of these species in obesity-related and other forms of research, little information is available regarding preventive measures for avoiding obesity; the relationship between social status, feeding behaviors, and obesity; the potential confounding effects of obesity on nonobesity-related research; and refinement of feeding strategies to improve physical wellbeing of obese macaques, such as preparation of age-specific diets. These topics will be further discussed in this review and, where available, compared with similar information from human studies.

Obesity in Rhesus Macaques (*Macaca mulatta*)

Early work on growth characteristics. Early information about the growth characteristics of rhesus macaques was available only for small numbers of animals until the 1950s, when one of the first descriptions of physical growth characteristics of large numbers of rhesus macaques in laboratory colony settings was published.[105] This study focused on growth from birth to 7 y of age, and it was noted that in female macaques, body weight increased with chronologic age; after 5 y of age, the growth curve stabilized, and overall variability in weights then increased due to poorly defined factors, such as obesity, pregnancy, and illness. Therefore, it is noteworthy that more than 60 y ago, 'obesity' was being observed in colony rhesus macaques. In male macaques, the growth weight curve continued beyond 5 y of age and did not plateau through the sixth and seventh years, as it did in female macaques.[105] In addition, male macaques showed a distinct growth spurt in their adolescent years (between ages 3 and 4 y). When male macaques were rested between breeding periods, their physical activity decreased, and weight gain was noted. This previous work[105] pioneered the characterization of typical growth patterns in captive rhesus macaques, highlighted sexual dimorphism in rhesus body weights and growth, and established early observations of obesity in macaques maintained in captivity.

Characteristics of spontaneous obesity in macaques. Because of the continued use of macaques in research and restrictions on importation from parts of Asia since the mid1970s, captive long-term colonies of rhesus macaques have been developed and maintained in the United States. This action provided opportunities to study middle-aged rhesus macaques and further characterize spontaneous obesity in animals older than 10 y. Standard physical guidelines for categorizing overweight monkeys were developed, and descriptions of the effects on body condition were reported.[62,64] This work largely involved 14 individually housed male rhesus, ranging in age from 11 to 24 y, with body weights ranging from 7.7 to 16.3 kg. These studies[62,64] were intended to confirm the association between obesity and glucoregulatory abnormalities in adult male rhesus macaques and to illustrate other characteristics of spontaneous weight gain. Body composition measurements, sucrose preference tests, and glucose tolerance tests were evaluated, and animals were categorized as 'very obese,' 'moderately obese', and 'nonobese,'; only 5 of 14 animals were noted as being nonobese.[61,62] Measurements of body fat content, body mass index (BMI), abdominal circumference, and abdominal skin fold thickness were significantly and highly correlated with obesity. In addition, 'very obese' monkeys presented with significantly elevated fasting serum insulin levels and exaggerated insulin responses to glucose loading. Further investigations indicated that excess body fat was located primarily in the abdominal region, and glucoregulatory abnormalities were present in both sexes of obese rhesus macaques.[65] These findings in macaques have subsequently been noted to be similar to the central body fat distribution patterns in obese humans and their susceptibility to metabolic syndrome, including insulin resistance.[56,57]

As in humans, body weight shows great variability in adult rhesus macaques, indicating that body weight alone is not adequate to strictly categorize an animal as being normal weight or obese.[64,107] In captive primates, periodic morphometric measurements, such as percentage body fat, are necessary to accurately monitor the physical health and growth of individual animals. The relationship between various morphometric measurements and percentage body fat was examined in 13 female rhesus macaques.[116] Animals were grouped according to their reproductive status, with nulliparous macaques having a mean age of 3.2 y, and multiparous animals having a mean age of 8.8 y. Measurements of crown–rump length (height), weight, abdominal subcutaneous fat, and total body water were used to calculate percentage body fat in sedated animals. Although all of the morphometric measurements were significantly interrelated, skin fold thickness was the best predictor of percentage body fat.

Ensuring adequate interobserver correlation in data collection requires a simple but robust method for identifying obese animals. A recent study described a body condition scoring system for primates using rhesus macaques as a model.[26] Using this system involves sedating animals and palpating the hips, pelvis, paravertebral and thoracic muscle masses, and subcutaneous fat deposits. A score ranging from 1 (emaciated) to 5 (grossly obese) in half-step increments is given to each animal. The results of the cited study suggested that such a scoring system can be an effective tool to identify animals with poor body condition (emaciated or obese) that may compromise their overall health and suitability for participation in other research programs.

Several studies of aging in primates have examined body composition and its relationship with energy expenditure, metabolic parameters, and glucoregulation.[40,83,85,105] Technologic advancements including X-ray absorptiometry to measure body composition and indirect respiration calorimetry chambers to measure oxygen and energy expenditure have provided additional accuracy in correlating and confirming body measurements.[83] In rhesus macaques, the age range between 10 to 17 y has proven to be the period when body fat and its effect on body mass are most significant.[83,85,105] As animals age beyond 20 y, lean body mass and energy expenditure begins to decrease.[83,85,105] One study interpreted body weight data from 65 diabetic and 88 nondiabetic rhesus macaques and found both groups tended to gain weight as they aged, with peak weight gain noted between 14 to 18 y of age.[105] In nondiabetic subjects, fasting plasma glucose was virtually unchanged, even with weight gain; however, it increased with age in the diabetic group.

Monitoring macaque health in the laboratory environment is enhanced through assessment of various serum biochemistry parameters, such as blood glucose levels, which typically are increased due to handling stress during annual physical examinations.[112] Specific properties of food consumed just prior to blood collection can affect glucose concentrations, and the metabolic response to simple carbohydrates has been shown to affect glycemic responses in individual animals. Extrapolating these findings to group-housed macaques suggests that some animals will consume more chow and fruit items than will other animals, and this difference may affect individual glycemic responses, leading to erroneous interpretations.

Given the noted variation in blood glucose levels, including serum fructosamine levels in annual biochemistry panels of captive and wild macaques may facilitate identification of animals with sporadic compared with persistent hyperglycemia. Fructosamines are formed when glucose molecules are bound to proteins through glycation.[3] Fructosamine levels reflect mean glucose concentrations in the blood over the preceding 2- to 3-wk period.[3,121] In humans and cats, serum fructosamine has proven to be a reliable adjunct measurement to glucose and an indicator of the diabetic condition and adequacy of glycemic control.[55,70] In cats, increased fructosamine levels are highly correlated with persistently elevated blood glucose levels and are not elevated for experimentally induced transient hyperglycemia.[70] These findings suggest that fructosamine is effective in identifying persistent hyperglycemia in many species and that levels do not increase due to transient hyperglycemia. Routine use of fructosamine levels as a marker in macaques would require establishing age- and species-specific references ranges.

Similarly, evaluation of hemoglobin glycation has been used to identify persistent hyperglycemia in humans and nonhuman primates.[51,100] Hemoglobin A1c is the predominant fraction formed after glycation of the N-terminus of hemoglobin β chains.[79,89] Hemoglobin A1c levels reflect long-term exposure to elevated glucose levels (8 to 12 wk), considering that the lifespan of a macaque erythrocyte is approximately 85 d.[76] However, acute or chronic blood loss, hemolytic anemia, hemoglobin variants, elevated urea levels, and pregnancy all can influence hemoglobin A1c levels, which must be interpreted with these conditions in mind.

Although a growing body of reference ranges for serum biochemistry parameters is available specifically for cynomolgus macaques, continued work with significant numbers of 'normal' age-, sex-, and species-matched animals is required for accurate data interpretation and reference interval establishment. Furthermore, some parameters may be useful in defining obesity and insulin resistance in small numbers of research subjects or clinical cases, yet may be too expensive and time-consuming for routine monitoring of large numbers of macaques.

Identifying the characteristics of obesity in rhesus and cynomolgus macaques has been an important contribution to obesity research in other nonhuman primate species. For example, this work has contributed to identification of spontaneous obesity and evaluation of body condition in species including Japanese macaques (*Macaca fuscata*), bonnet macaques (*Macaca radiata*), chimpanzees (*Pan troglodytes*), pigtail macaques (*Macaca nemestrina*), and African green monkeys (*Chlorocebus pygerythrus*).[17,21,61,104,110,111,123]

Obesity in free-ranging rhesus macaques. The previously described studies[62,64] in macaques were conducted under controlled laboratory conditions in individually housed animals, to ensure accurate measurement of food intake. These results may not be applicable to animals housed in large colonies or troops. Furthermore, when working with nonhuman primates, minimally invasive methods should be used to assess physical wellbeing. This practice not only minimizes animal stress and associated transient hyperglycemia but enhances safety for the humans working with them. Provisioning is defined as "offering food beyond the natural supply and/or quality of the animals' environment."[4] Evaluations of a nonintrusive method for determining body fat in a provisioned colony of free-ranging rhesus macaques by using a 7-point visual scale has been described.[8] Macaques were evaluated by 5 human observers, who rated each animal from thin to extremely fat. The macaques then were trapped and weighed, and morphometric measurements, such as crown–rump length and abdominal skin fold thickness, were taken to compare with the observer scores. The results indicated that the 7-point scale system was reliable and correlated with measures of body weight and body fat.[4] Further research to validate a noninvasive system such as that described[4] could greatly assist general management practices for captive primates and might easily be implemented as a frequent observation (that is weekly, monthly) to prospectively identify macaques that are overweight. Another important finding from the cited study[4] was that obesity occurs spontaneously in free-ranging rhesus macaques and that this condition is not just a problem for animals that are purpose-bred.

Body size changes were correlated with age and sex in the same colony of free-ranging rhesus macaques.[93] Morphometric measurements for subcutaneous fat were taken from sedated animals that ranged in age from infancy to 29 y, and BMI was calculated. Similar to results from studies in captive macaques, body weight and central abdominal fat accumulation were highest among 10- to 14-y-old female and 15- to 19-y-old male macaques. Therefore, obesity with central abdominal fat accumulation occurs in wild macaques with adequate access to food resources, indicating that there may be a natural propensity for this condition in aging macaques, as occurs in humans.

Obesity and Diabetes Mellitus in Rhesus Macaques

Spontaneously obese macaques provide a useful animal model to study the effects of obesity and the progression of obesity-related conditions such as type 2 (insulin-resistant) and type 1 (insulin-dependent) diabetes mellitus.[48,98] Type 2 diabetes mellitus (T2DM) and obesity are closely related, yet being obese is not sufficient alone to predict development of T2DM.[49] Studies in rhesus macaques have demonstrated that T2DM is a progressive disorder, with several sequential changes in body weight, body fat, plasma insulin levels, acute insulin response to glucose challenges, and glucose tolerance testing.[15] The earliest detectable abnormality identified is enhanced basal insulin secretion and decreased insulin sensitivity to alterations in glucose levels. Later disease includes pancreatic islet amyloid deposition and decreased numbers of islet β cells, as occurs in humans, further contributing to decreased pancreatic islet responsiveness.[35,57]

The association of central obesity in rhesus macaques with hyperinsulinemia, insulin resistance, and hypertriglyceridemia has been evaluated, and abdominal circumference was correlated more strongly with insulin resistance than with percentage body fat.[14] In addition, abdominal circumferences had a positive linear correlation with fasting plasma insulin levels.

Researchers have searched for biomarkers that precede diabetes mellitus in rhesus macaques and have attempted to detect the earliest signs of T2DM by using hepatic glucose production.[16,33] This parameter appears to be elevated only in overtly diabetic animals and is not a useful indicator of impending T2DM in monkeys overall. Diabetic monkeys develop metabolic conditions that are similar to those seen in humans, making these animals useful models of T2DM;[16,33,54] Reports in the current literature suggest that the most useful predictor of impending T2DM in rhesus macaques is central obesity.[16]

Obesity and Diabetes Mellitus in Cynomolgus Macaques (*Macaca fascicularis*)

Cynomolgus macaques (*Macaca fascicularis*) are the most widely used nonhuman primate in research in North America. For example, the Canadian Council on Animal Care Animal Use Report for 2010 states that 2765 of the 3993 nonhuman primates used in research in Canada during 2009 were cynomolgus macaques.[20] Therefore, the prevalence of obesity, hyperglycemia, and T2DM should be characterized for this species as well.

Similar to rhesus macaques and humans, cynomolgus macaques have been observed to develop spontaneous obesity in adulthood,[25,62] and as with rhesus macaques, many studies on cynomolgus macaques have focused on the relationship between body weight and body fat with other biologic parameters.[24,25,68] In humans and other animals, expression of the *ob* gene, which encodes leptin (a protein intimately involved with body weight regulation), and serum leptin levels are positively correlated with percentage body fat.[31] In one of the earliest studies conducted on leptin in cynomolgus macaques, a positive correlation was identified between increased serum leptin levels and body weight in female macaques.[25] Additional studies investigated the relationship between alterations in serum chemistry parameters and the quantity of body fat, to help define the degree of obesity in individual cynomolgus macaques.[24] The sample population for this work included 44 female and 40 male macaques. As in the previous study,[25] plasma leptin levels were positively correlated with percentage body fat, and leptin and adiponectin levels were also found to be significantly correlated with insulin levels.[24]

Adiponectin is another hormone produced by white adipose tissue that is thought to be involved with metabolic regulation of energy. Levels of this adipokine are inversely correlated with obesity in humans and rhesus macaques and are associated with insulin resistance.[47] The ratio of leptin:adiponectin was significantly elevated in animals with greater than 40% body fat.[24] Interestingly, leptin levels in female macaques were significantly higher than those in male animals. The authors concluded that the leptin:adiponectin ratio may be an important index for identifying obesity in cynomolgus macaques. Further research into the role of leptin and adiponectin in regulating macaque weight is necessary, given that this ratio seems to be a promising indicator of excessive weight gain tendencies. Unfortunately, these parameters are not routinely available for serum chemistry evaluation at this time.

Naturally occurring T2DM has also been reported to occur in cynomolgus macaques.[51,56,113,114] In one study, 6 hyperglycemic cynomolgus macaques demonstrated severe degenerative pancreatic lesions consistent with islet amyloidosis,[113] correlating with human findings in many cases of T2DM. All animals had increased ratios of central to peripheral adiposity as well as hyperinsulinemia, which preceded the development of overt T2DM. Further work sought to compare carbohydrate and lipid metabolism in naturally occurring and experimentally diabetic cynomolgus macaques.[114] Of the 6000 animals evaluated, 36 were identified as having naturally occurring T2DM, whereas another 5 animals had type 1 diabetes mellitus. Typically those animals with T2DM were obese. The study also found that as the glycemic profile deteriorated due to hyperinsulinemia and hyperglycemia, T2DM monkeys began to lose weight. In cynomolgus and rhesus macaques, the development of T2DM can take years to progress, indicating that glucose and triglyceride levels can be increased long before therapeutic intervention with insulin is required.[22]

Measurement of Obesity and Diabetes Mellitus in Humans

Obesity in humans has been defined in numerous ways, most simply as the presence of excess body fat or adipose tissue that leads to impaired health.[57,125] Several classification schemes and measurement methods have been developed and are categorized by the general principle on which they are based, including density-based (hydrodensitometry; air displacement plethysmography), body imaging (computerized tomography; magnetic resonance imaging; dual-energy X-ray absorptiometry), bioelectrical impedance, and morphometric (skin fold; waist circumference; waist–hip ratio) methods.[103] These methods can be complicated and cumbersome and generally are relegated to research settings. BMI is a simple index of weight-for-height that is used commonly to classify underweight, normoweight, overweight, and obese conditions in adults; however, BMI has some limitations in regard to interpretation. BMI is calculated as weight (in kilograms) divided by the square of the height (in meters; that is, kg/m^2), and in 2000, the World Health Organization used this method to define overweight (preobese) humans as those with a BMI between 25 and 30 kg/m^2 and obese persons as those whose BMI exceeded 30 kg/m^2.[125] BMI values are age- and sex-independent but may not correspond to the same degree of body fat in different people, due to different body proportions, exercise levels, and fat distribution. Although the health risks associated with increasing BMI are continuous and undeniable, the interpretation of BMI levels in relation to health risk factors may vary for different populations. Therefore, the exclusive use and reliance on BMI in obesity classification is limited.

The search for a reliable and consistent method to identify and classify obesity in humans has recently been focused on serum and plasma biomarkers of obesity and their significance as risk factors in the development of future adverse metabolic conditions, such as T2DM, polycystic ovary syndrome, and cardiovascular disease.[57] Adipose tissue is a specialized short- and long-term storage tissue for excess energy; however, it also acts as an important endocrine organ with systemic effects.[94] Adipose tissue releases numerous substances including steroid hormones, growth factors, various cytokines, eicosanoids, complement and complement-binding proteins, vasoactive factors, regulators of lipid metabolism (that is, adipokines), and numerous other factors.[93] Harnessing the varied array of substances released by adipose tissue has led to the identification of several useful obesity biomarkers, including leptin, adiponectin, and resistin, which correlates with the findings of the nonhuman primate studies described previously. Other promising biomarkers include proinflammatory mediators, since epidemiologic studies have demonstrated a strong correlation between the levels of C-reactive protein, IL6, and TNFα with perturbations in glucose homeostasis, obesity, and atherosclerosis.[126] Even though these factors may be promising adjuncts for definitive measurement of obesity, many can be produced and released by tissues other than adipose tissue, as well as during infection and tumor growth and progression. Therefore, they are not specific biomarkers for obesity. Serum levels must always be interpreted in light of other ongoing health issues. Levels of free fatty acids may also be associated with increased insulin resistance and subsequent T2DM,[12] representing another useful target for monitoring of diabetes development and progression.

In their 2011 Position Statement, the American Diabetes Association outlines current definitions and descriptions of diabetes mellitus in humans.[2] A fasting plasma glucose level greater than 5.6 mmol/L in overweight subjects is defined as an indication of hyperglycemia and considered a prediabetic condition, whereas a fasting plasma glucose greater than 7.0 mmol/L is associated with a provisional diagnosis of diabetes mellitus.[1] Definitive diagnosis of diabetes mellitus often relies on interpretation of several concurrent diagnostics and is patient-specific, and the decision to call a patient 'diabetic' (or not) is at the discretion of the attending physician. The oral glucose tolerance test is a standard, highly specific, although cumbersome, measurement of the current diabetic status of a patient,[2] and the test evaluates fasting plasma glucose as well as levels of plasma glucose 2 h after a specific oral dose of glucose. Increased fasting and 2-h postchallenge plasma glucose levels are recognized measures of poor glycemic control[2] Further, much emphasis has been placed recently on the accurate measurement of hemoglobin A1c (HbA1c) and serum fructosamine as a reflection of the previous 2 to 7 wk of glycemic control, and these parameters are thought to better reflect the diabetic state of a subject than does plasma glucose.[2] HbA1c has been suggested as an assessment of "risk-associated glycemia" for establishing population prevalence figures.[117] Further characterization of biomarkers of diabetes mellitus in humans may allow for a standard diagnostic process in the future. In addition, new research into the genetics of disease may help researchers further define a simple 'gold standard' test to diagnose obesity and diabetes mellitus.

Genetic discoveries have provided extensive information into the clinical classification of obesity and diabetes mellitus. A recent review[73] highlighted genome-wide association of genetic variants influencing BMI, obesity, and subsequent development of diabetes mellitus in humans. This work is promising for the future of targeted disease treatments. A thorough review of recent genetic studies is beyond the scope of the current report. The human obesity literature also indicates that parental influence may play a role in determining feeding behaviors of children.[53,80]

Feeding behavior in humans. The association between aspects of behavior and obesity in humans may relate to obesity considerations in nonhuman primate species. Some researchers have used an ethologic approach to examine obesity in humans. Proximate causes of obesity that have been studied in humans include energy balance, genetic factors, dietary composition, physical activity level, feeding behavior, and psychologic factors.[118] Regarding epidemic levels of obesity, some research suggests that increasing levels of maternal fatness may be exposing children in utero to a metabolic trend that may be difficult for future generations to cope with.[118] Identified risk factors and predictors of obesity in children include high energy-dense diets, large portion sizes, specific eating patterns, high levels of sedentary behaviors, and decreased levels of physical activity. Parental obesity and the human tendency toward dietary variety are strongly associated with predicting weight gain in children, which has both genetic and environmental components.[87] In addition, the ever-growing number of sweet, high-energy, and high-carbohydrate foods that are introduced into the North American food market parallels and predicts the increasing prevalence of obesity.[9,74]

Stress and body condition in humans. The relationship between chronic stress and obesity in humans is another area of active research.[34,82] Chronic stress is characterized by prolonged activation of the hypothalamic–pituitary–adrenal axis. In rodents and humans, binge eating of 'comfort foods' (high-fat, high-carbohydrate foods) may be a coping mechanism to reduce the effect of chronic stress on the body.[34] During periods of adverse stress, the hypothalamic–pituitary–adrenal axis releases glucocorticoids, and excess release of glucocorticoids has been found to suppress the ability of the growth hormone system to metabolize adipose tissue. This process leads to development of central visceral fat, which is associated with hyperinsulinemia, insulin resistance, and metabolic diseases in humans and other species, including rhesus and cynomolgus macaques.[82]

The benefits of physical activity continue to be demonstrated in various studies; intensity, duration, and frequency of aerobic exercise training all play key roles in the treatment of insulin resistance in obese elderly adults.[27] In contrast, physical inactivity may affect gene regulation, decreasing metabolism. Potentially related to decreased basal metabolic levels, mitochondrial densities are decreased with physical inactivity in healthy subjects and in patients with obesity and T2DM,[18] and these findings may also be applicable to captive nonhuman primates. Further research in both humans and nonhuman primates is warranted and should focus on examining how the body adapts metabolically at a subcellular level to physical inactivity.

Social status and obesity in humans. In humans, social status can be measured in terms of income, education level, and occupational position. In the literature, this characteristic typically is referred to as 'socioeconomic status.' The relationship between socioeconomic status and obesity is extremely complex and may vary by country and gender. An extensive epidemiologic literature review in 2007 examined this phenomenon.[75] In general, in highly developed countries, low socioeconomic status is associated with larger body size in women; the association between socioeconomic status and body condition in men is less clear.[75] The suggested reasons for this dimorphism are the weight-based stigma and discrimination that affects women, whereas larger body size may be associated with power and dominance in men.

Psychosocial stress categories include social class, marital status, and education level. Psychosocial stress and obesity in humans living in a developed country was investigated recently. The results showed that social stress was positively related to an increase in overall levels of body fat, and the strongest predictor of obesity in this study was poor education.[42]

Social Status and Body Condition in Rhesus and Cynomolgus Macaques

Social status and stress. Both behavioral and physiologic factors are likely to contribute to the etiology of spontaneous obesity in captive macaques. As for humans, potential associations between various physiologic parameters and the social status of individual animals is an important consideration when assessing root causes of obesity in nonhuman primates. Cynomolgus and other macaque species live in complex social hierarchies, in which there are dominant and subordinate animals.[78,102] Social status influences access to food resources, which can affect body condition.

A growing body of evidence supports the ideas that social subordinance in nonhuman primates may be a cause of chronic stress and that social rank influences quality of life.[91,92,95] In olive baboons, subordinate animals have higher basal glucocorticoid levels (a measure of active stress response) than do dominant animals.[91] In long-term studies of wild baboons, social rank within a specific society affects the individual animal's basal hypothalamic–pituitary–adrenal gland function and also affects the individual experience of each animal.[91] For example, periods of social instability, such as the addition of a new male animal into a troop, can affect stress responses in specific animals of both dominant and subordinate ranks and yet not affect others at all.[91] After experimental reorganization of stable groups of captive adult female cynomolgus macaques, subordinate animals spent more time alone and received more aggression than did dominant animals, and social isolation was correlated with increased basal cortisol levels.[95] These studies suggest that the relationships between social rank, social stress, and obesity should be explored in captive macaques, particularly as the movement toward pairing and group-housing of macaques continues.

Social status and obesity. A study of captive male African green monkeys examined the potential relationship between social status and fat distribution.[32] The authors determined that lower-ranking male monkeys were heavier than were dominant male animals (for example, all male monkeys at the 85th percentile or higher for body weight were low-ranking males) and that, after new groupings of male monkeys were formed, the overall incidence of obesity increased from 11.8% to 16.7%, suggesting that the stress associated with social instability resulted in an increased propensity for obesity.[32] Experimental work with social reorganization in male cynomolgus macaques fed a high-fat diet demonstrated a similar relationship between social rank and production of atherosclerosis in dominant animals.[58] Dominant animals living in unstable social groups exhibited significantly greater coronary artery atherosclerosis than did subordinate monkeys housed in the same conditions, and dominant animals had more extensive arterial lesions than did dominant monkeys housed in the stable group condition. This factor may be sexually dimorphic, because socially housed female cynomolgus macaques fed an atherogenic diet resulting in higher intraabdominal:subcutaneous fat ratios were more likely to be subordinate.[97] The proposed mechanism underlying this observation is that visceral fat (white adipose tissue) has enhanced receptor sensitivity for glucocorticoids; basal plasma glucocorticoid levels are increased in subordinate female cynomolgus macaques; glucocorticoids stimulate fatty acid uptake and lipid deposition; and T-cell activation and proinflammatory cytokines induced by visceral fat induce HPA activation. Together, all of these steps lead to exacerbation and perpetuation of visceral fat deposition in subordinate animals.[96] In another study, subordinate female cynomolgus macaques were more prone to both injury and hyperglycemia, consistent with the hypothesis that increased social stress arising from a lower social status may predispose animals to metabolic syndrome and T2DM.[5]

A promising approach to collecting feed intake data in socially housed rhesus macaques is a custom-built, automated feeder designed to dispense a pellet of food when activated by a radiofrequency chip subcutaneously implanted in the wrist of a subject. This feeder was used to quantify food intake in 2 stable social groups of female rhesus macaques (n = 4 and n = 5). Animals were given access to control, low-fat, and high-fats diets over a 3-wk period. The social status of each animal was recorded, and observation sessions were used to collect data on affiliative, agonistic, and anxiety-like behaviors. The results indicated that the subordinate female macaques consumed significantly more of both the low-fat and high-fat diets and fed throughout the night. The dominant animals did not monopolize the feeders or restrict the access of the subordinate animals.[124] The cited study[124] raises interesting questions about feeding socially housed macaques in the future. Perhaps similar technology could be used to customize diets for individual animals in a group-housed setting, to minimize the development of obesity and its related health problems.

Feeding Behavior in Wild Nonhuman Primates

Feeding behavior is a major factor contributing to the development of obesity in captive macaques, yet much of what we know about feeding behavior in primates comes from observations of wild populations.[8,93] In the wild, access to resources influences the nature of feeding behaviors displayed by macaques and other primate species.[4,38,66,77,90,102] In a wild troop of Japanese macaques, interindividual distance was an important factor during feeding bouts.[38] Widely distributed food sources allow increased interindividual distance, perhaps thereby decreasing the incidence of agonistic interactions. When food distribution is restricted to smaller areas, competitive interactions increase; however, when food is presented in small batches, submissive behaviors increase.[90] Low-ranking animals are easily startled while feeding, but this response does not affect their food intake rate as compared with that of high-ranking animals. When a highly valued food item was not available, low-ranking female animals compensated by eating other food items.[90] Similarly, in cynomolgus macaques, subordinate females were observed to feed away from the majority of the troop; this behavior appears to reduce aggression from higher ranking animals and allow for similar food intakes in subordinate and dominant animals.[66]

Observations of wild brown capuchin monkeys suggest that group members with high dominance ranks feed significantly more at resources where competition is increased.[52] Large differences in food intake by dominant animals were not related to differences in metabolic need due to body size. For example, a dominant female monkey consumed more food than did 3 lower-ranking male animals, even though she was much smaller in body size.[52] Subordinate animals may wait to feed if they lose a fight to a dominant animal; however, this behavior does not occur if the subordinate is tolerated while feeding near a dominant animal. Another important observation from the cited study[52] is that during periods of nonfeeding, adult female monkeys spent a large amount of time grooming the dominant male animal. This behavior may serve to increase the male's tolerance of their presence near him during feeding, allowing them to increase their food intake.[52]

Provisioning or supplementation of food resources by humans has been used in the field to facilitate observational time and assist with identification of wild primates. Adverse effects of this feeding practice, such as increased aggression, have been reported in Japanese macaques, rhesus macaques, olive baboons, and chimpanzees.[4] Whether this effect is due to the resource being clumped or restricted or to the forced decrease in interindividual distance is unclear. In Japanese macaques and chimpanzees, provisioned groups show an increase in agonistic interactions; this effect is an important consideration when observing feeding behaviors in captive macaques.[4,90] Captivity may alter normal feeding behavior in macaques and has the potential to add stress to the social cohesion of group-housed macaques. Furthermore, captive macaques may be prone to obesity in part due to limited motivation for physical activity associated with a reduced need for foraging and avoiding predators in the supportive and protective artificial environment.

Feeding Behavior in Captive Macaques

Effects of food distribution on the behavior of captive macaques. In the captive environment, the effects of provisioning by humans are generally easier to observe than in the wild. In one study examining the association of varying food distribution on captive bonnet macaque behavior, clumped distribution of food significantly affected the troop's behavior as compared with equal distribution of food.[11] Clumped distribution was described as food placed in a box that allowed restricted access, and equal distribution involved dispersing the food in a manner such that all animals could feed simultaneously. Clumped distribution caused an increase in dominance displays and agonistic interactions, and affiliate and play behaviors decreased steadily. Dominance status determined priority of access to the food during clumped distribution, suggesting that the group's social stability was stressed by restricting food access to a specific location.[11]

Studies evaluating feeding competition in captive rhesus macaques have shown that feeding behavior of dominant animals does not change dramatically whether food is clumped or dispersed evenly but that behavior of subordinate animals is modified to suit the food distribution.[7,19,36,81] For example, when food items such as bananas and carrots were either clumped or dispersed, the dominant animals' latency to feed was relatively unchanged, regardless of the method of distribution. Subordinate animals had to wait significantly longer to feed, and sometimes were unable to feed at all, at the clumped pile. Although subordinates tended to avoid provoking higher-ranking animals, subordinate macaques were less likely to demonstrate cautious behavior and more willing to risk aggression when a highly valued food item (banana) was presented.[7] This effect was observed further in a subsequent study in which food item dispersion was manipulated, with the addition of snake 'dummies' to further compromise resource availability.[19] Subordinate animals displayed variations in their feeding tactics. Dominant macaques were hesitant to approach snake-guarded food piles and threatened other macaques only when individual animals approached where dominant macaques were feeding. In contrast, subordinates would risk the snake dummies if the food item was highly valued (banana), and less-valued food did not warrant this risk, as demonstrated by a pile of carrots with 2 snakes that went untouched by all macaques.[19] Therefore, decision-making processes and the value of the food item both play a role in determining what risks subordinate animals will undertake in situations of clumped food distribution.

Feeding behaviors were observed in a group of juvenile rhesus monkeys for which the feeding area was restricted.[81] During the 56-d study period, feeding occurred 6 times daily by means of a single trough placed outside the enclosure but within reach of animals. High-ranking juveniles accessed the feeding area more often and for longer periods. Subordinate animals had reduced access to the feeding area and optimized feeding opportunities by filling their cheek pouches quickly and eating their food away from the feeding area. While in the feeding area, subordinate monkeys displayed increased startle behaviors, which disrupted feeding bouts. Juvenile male animals tended to be tolerated for less time and were driven from the area by dominant monkeys more often than were juvenile female macaques.[81]

Food size and meal patterns. Another factor to consider in the feeding behavior of captive macaques is the size of the piece of food that is given. Food size may be more important in predicting aggression during feeding than is the distance between food items in a stable group of rhesus macaques. Using a valued food item (apple) of varying sizes, researchers assessed aggressive responses, and results showed that large food size was a better predictor of elicited aggressive behavior than was interfood distance.[72]

Feeding behavior and meal patterns have been studied in individually housed obese and nonobese rhesus macaques.[43,88] Obese normoinsulinemic and obese chronic hyperinsulinemic monkeys were fed ad libitum diets to compare food intake and meal patterns, and there were no significant differences in total food consumed or meal patterns between the 2 groups. These results suggest that if obese macaques in a chronic hyperinsulinemic state do not alter food intake or meal patterns when fed ad libitum, other ways to monitor their overall health may be more appropriate. In captivity, individually housed rhesus macaques tend to eat most of their caloric intake in meals (food consumed in greater than 2-min bouts), following a circadian rhythm.[43,88] However, in group-housed macaques where spontaneous obesity is occurring, little has been documented about feeding behavior and food intake patterns.

Husbandry Strategies for Feeding Primates

Unless obesity itself is being studied, captive macaques in most institutions in North America are fed a nutritionally balanced diet consisting largely of commercial primate biscuit supplemented with fresh fruits, vegetables and other food treats. Although overfeeding of enrichment food items could contribute to obesity, colony veterinarians report that most food supplements are fed on a restricted basis and comprise less than 10% of the daily diet.[6] In general, institutions that house primates work on a structured routine, and feeding times are often highly regulated. Several studies have shown that this predictability has both positive and negative influences on animal behavior.[10,106,115] In captive stumptail macaques, experimentally varying feeding times led to increased animal stress. As the animals waited to be fed, overall activity levels decreased but activities such as abnormal self-directed behaviors and agonistic interactions increased.[115] Comparable results were found in a similar study using captive brown capuchin monkeys.[106] In chimpanzees, using a variable feeding schedule that the animals could not anticipate led to a reduction in abnormal behavior and inactivity.[10] These studies suggest that anticipation of feeding time may be a highly important event in a captive primate's day and may affect animal welfare in a species-dependent fashion. In short, a highly variable schedule may be useful for reducing negative anticipatory behaviors, such as aggression, but a strict feeding schedule might be better to minimize psychologic stress.

Psychologic stress associated with food access insecurity, even when the total food amount provided is essentially ad libitum, has been shown to induce central adipose fat deposition, weight gain, and increased BMI; persistent shifts in function of the hypothalamic–pituitary–adrenal axis; and proinflammatory immunologic modulation in adolescent bonnet macaques, particularly those born to subordinate dams.[60] The authors did not follow the animals over their lifetime to determine whether obesity was maintained later in life, but these findings suggest that stress associated with early maternal feeding experiences may be important in determining later susceptibility to obesity in nonhuman primates. Many institutions currently housing and breeding large numbers of rhesus and cynomolgus macaques maintain animals in large troops of 100 animals or more. The role of food access insecurity in these settings with subsequent effect on propensity for offspring obesity bears further investigation, given that obesity is an acknowledged and widespread problem in captive macaque colonies.[6] Furthermore, food distribution must be planned to ensure that subordinate animals have appropriate access to food and enrichment items, similar to that for all members of the group.

Typical institutional troop settings and management practices for captive group-housed macaques do not permit for differential feeding practices or dietary composition based on age or caloric need.[6] Such strategies increase the time required for colony management but may be necessary to optimize overall animal health in these captive settings. A recent review of husbandry procedures for nonhuman primates acknowledged the problems that may come with providing food free-choice.[86] In the wild, a cynomolgus macaque may spend up to 50% to 70% of its waking hours feeding and foraging, and the use of enrichment strategies to encourage species-typical behaviors, such as food foraging, is becoming standard. Many foraging items can be small, such as sunflower seeds or grains, and only small quantities are required to captivate a primate’s attention. In addition, provision of food rewards for enrichment and positive reinforcement training is common. A review of positive reinforcement training techniques provides ample evidence of new opportunities to create a working relationship with primates used in research, where cooperation between human and primate is the goal.[69] Positive reinforcement training often involves (especially at the outset) the repeated use of food rewards.[69] The use of such food rewards plausibly could promote weight gain in animals being trained. Current guidelines advise caution when supplementing a nutritionally balanced diet but do not offer specific guidance regarding calories or quantity of food rewards.[50] Investigation into the possible association between using food rewards and weight gain should be explored if an obesity problem is noted within a colony. In addition, personnel involved in providing food rewards and food enrichment must be educated about the potential for obesity development, in that these persons may be involved in inadvertent overfeeding of animals.

Prevention of Obesity in Rhesus and Cynomolgus Macaques

Prevention of obesity by calorie restriction. The current literature does not contain extensive research about preventing obesity in macaques; however, longitudinal calorie-restriction studies of rhesus macaques initiated in the late 1980s are providing interesting results concerning the health benefits of maintaining a normal body weight with age.[28,63,84] Spontaneous obesity and subsequent adverse health conditions have been well-documented in mature (older than 10 y) macaques and pose management challenges as captive primate colonies age and continue to be maintained for breeding and research purposes.[6] Not only is animal health compromised, but as indicated, overweight body condition also may affect the suitability of animals for certain areas of research and alter fertility. The foremost strategy to prevent obesity in macaques has been caloric restriction.[23,30,46,45] Calorie restriction involves placing a mature animal on a strict feeding protocol (for example, typically up to 30% less than ad-libitum–fed control animals) to stabilize body weight through weekly caloric adjustment. This practice results in reduced serum insulin levels and increased glucose tolerance in food-restricted animals.[40,46,45] In addition, caloric restriction has been shown to produce significant changes in metabolism by increasing efficiency of calorie use.[45] Furthermore, brain volume and fine motor skills are preserved with calorie restriction.[59,122] Overall, calorie restriction appears to significantly affect survival in rhesus macaques, with one study identifying a median survival age of 25 y for ad libitum–fed macaques compared with 32 y for calorie-restricted animals.[13] This outcome is in large part due to decreased incidence of metabolic diseases such as diabetes and cardiovascular disease, decreased degeneration of CNS function, and reduced incidence of neoplasia.[29,63]

However, body weight changes are not associated with a decrease in appetite. When calorie-restricted, individually housed monkeys are given the opportunity to return to a nonrestricted diet, they can and will revert back to an overweight state.[44] Total body fat in rhesus macaques was evaluated indirectly via plasma leptin levels and was found to be significantly lower in restricted-feeding animals. These animals also had lower body weight and total body mass than did control animals.[30] Similar findings have been noted in male cynomolgus macaques, in which calorie restriction significantly reduced central abdominal fat and intraabdominal fat mass compared with those of controls.[23]

Prevention of obesity in group-housed macaques. Whether individual calorie restriction could be implemented effectively in a group-housing paradigm is unclear, given that the aforementioned studies only evaluated individually housed animals. Social housing is a necessary means of managing macaque colonies and caloric restriction may not be appropriate or feasible. Strategies to individualize calorie intake may need to be implemented in captive colonies. Information available for the care of aging primates at zoos might be a useful resource. For example, at the Louisville Zoo, the diets of gorillas are modified to accommodate overweight and geriatric members.[37] Some of these diet changes include adding omega-3 and -6 fatty acids, glucosamine, and chondroitin supplements; creating individual quantities of biscuits for calorie restriction; and varying feeding times during the day. In the laboratory setting, single-purpose commercial monkey chows have been developed to satisfy all nutritional adult requirements and provide a controlled variable for research protocols. These chows are fed to animals for their entire postweaning lives, often with fresh fruit, vegetables, and other food treats provided on a supplementary basis. Chows for different age periods of a macaque’s life may be necessary to match life stages with caloric needs, as has been done for companion animals and food animals.

That little information is available on preventive measures or interventions to address obesity in macaques and that calorie restriction does not appear to be a practical option for large colonies highlights the possibility that the prevalence of obesity in captive macaques used for research will continue to increase. The various measurements and body condition scoring systems described in the previous section (see *Characteristics of Spontaneous Obesity in Macaques*) provide options for characterizing obese animals but do not assist in prevention or treatment of obesity. Reliance on a specifically designed, nutritionally balanced, conveniently fed diet in the form of monkey chow may have led to an unintentional complacency with respect to obese macaques, and a shift in thinking is needed to explore possible solutions. For example, investigation into the motivation behind physical activity in captive macaques is warranted because it may lead to ways to encourage overweight animals to engage in species-appropriate 'exercise.' Finally, the lack of information available on prevention and treatment of obesity in macaques reinforces the complexities involved in its causes.

The Use of Obese Rhesus and Cynomolgus Macaques in Nonobesity Research

Obesity is widespread in captive colonies of rhesus and cynomolgus macaques and, as has been described, spontaneously obese rhesus and cynomolgus macaques are excellent models for human obesity, demonstrating similar physical and biochemical alterations and subsequent propensity for metabolic diseases, such as T2DM. However, out of necessity, the use of these animals in nonobesity research is far more common and may confound results. For example, in one study, the effects of excessive body fat on pulmonary function and gas exchange was examined in cynomolgus macaques.[127] Functional residual capacity and percentage body fat showed a strong and significant negative correlation, in that increased abdominal fat was noted to result in a reduced chest volume. The authors suggest that obesity may have serious adverse effects on pulmonary research, particularly lung function studies.[127] These results raise further questions about possible confounding effects when using obese macaques in other research areas.

In addition, obese animals usually are less preferred for preclinical safety studies that base dose administration on body weight, given that increased fat stores may result in altered drug metabolism, blood drug levels, and responses to higher doses compared with leaner subjects. Although these animals are often 'randomized' into the control groups for some experimental studies, obesity still represents a significant confounding variable, potentially leading to altered patterns of carbohydrate metabolism, neuroendocrine signaling, proinflammatory modulation, coronary heart disease, and decreased reproductive performance.

To illustrate the importance of this issue, one only needs to expand this topic into the realm of studies on wild primates and even other species. A recent study examined reproduction and associated serum leptin levels in wild populations of vervet monkeys in Africa.[120] The researchers weighed and calculated a BMI for all animals on this study. Mean body masses of the wild adult male and female monkeys were significantly lower than those typically reported in captive vervets; BMI values also were lower than those reported for captive rhesus macaques and wild baboons. Leptin was not significantly correlated with BMI in male and acyclic female animals, and serum leptin levels were markedly lower in acyclic female monkeys compared with values reported for captive Old World monkeys. The authors concluded that leptin may have evolved to be effective at lower levels, but the cited study[120] also suggests an altered underlying metabolic difference in captive primates compared with wild counterparts.

Numerous examples regarding the adverse effects of obesity on the physiology of other species may be relevant to nonhuman primate models. Obesity significantly elevates serum leptin levels and induces estrus cycle disturbances in mares.[109] In mice, diet-induced obesity results in significantly increased mortality and decreased inflammatory response when compared with lean mice.[99] In a study of companion dogs, levels of serum C-reactive protein, an acute-phase protein, were significantly lower in obese dogs compared with nonobese controls.[108] Rats that became overweight after feeding of a high-fat diet for 3 mo had significantly impaired cognitive function when animals were required to participate in spatial memory, operant tests, and blind-alley maze tasks, compared with animals fed standard rodent chow.[41] Finally, a recent article discusses the problems that are associated with using obese mice and rats as controls in research for similar reasons that have been suggested herein for macaques, including increased risk for insulin resistance, impaired glucoregulation, and impaired cognitive and immune functions.[71] These animals provide good models for obese humans but may not be ideal when used as models for normoweight humans.

Because nonhuman primates represent such a valuable resource for research projects, many studies use minimal numbers of animals. This practice coupled with a lack of active management of obesity in captive colony settings may lead to increased variability in results for nonobese research projects that incorporate the use of obese animals as study subjects. For this reason, the routine use of obese macaques as control or experimental subjects in projects studying nonobesity-related issues is not recommended.

Conclusions

Obesity has been studied extensively in rhesus and cynomolgus macaques, with recent focus on developing biomarkers for characterizing overweight subjects and following the progression to adverse health conditions, such as obesity, in at-risk animals. Similar to overweight humans, obese macaques are at increased risk for developing hyperglycemic and adverse metabolic conditions, including T2DM. Little is known about preventive measures that can be taken in maintaining an aging colony of macaques while minimizing obesity. The feeding behaviors of group-housed primates can be affected by complexities such as social status, predictability of feeding time, the caregiver doing the feeding, and the manner in which the food is distributed. Adverse health consequences can be aggravated by the social status of an individual animal within the group and potentially by regrouping animals for experimental or breeding purposes. For example, in large captive breeding colonies, where new groups are formed to increase genetic diversity or due to fallout from another social group, animals that become subordinate in new groups may be at increased risk for becoming obese. An interesting question is whether animals held in a large field cage with increased inter-individual space have the same obesity rate as does a similarly sized group with less space. A higher density setting would seem likely to increase adverse social pressure on subordinate animals, possibly leading to increased risk of obesity.

In light of documented changes in various serum biochemistry parameters and other systemic effects in obese macaques, obesity may introduce confounding variables into nonobesity-related research. Furthermore, the welfare of animals that develop obesity may be compromised because of potential progression to further adverse health events. Not only are adverse health problems harmful to the animal's physical wellbeing, but these animals may be removed from their social grouping to stabilize their body weight, monitor or reduce food intake, and facilitate monitoring of serum insulin and glucose levels. Removal of an individual animal from its social grouping counters the regulatory imperative for social housing in macaques, and potential long-term detrimental consequences should be examined carefully before implementing this measure.

Just as obesity has become a serious health issue in human and companion animals, ample evidence suggests that the same view applies to obesity in long-term captive rhesus and cynomolgus macaque colonies. Further research is warranted and necessary with regard to diagnosing obesity, preventing obesity, monitoring overweight animals for development of adverse metabolic conditions, and developing programs to humanely combat obesity in aging macaques while enhancing colony health and wellbeing.

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