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Long-Term Effects of Castration on the Skeleton of Male Rhesus Monkeys (*Macaca mulatta*)

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Abstract

While osteopenia (OPE) and osteoporosis (OPO) have been studied in various species of aging nonhuman primates and extensively in ovariectomized rhesus and cynomolgus macaques, there is virtually no information on the effects of castration on the skeleton of male nonhuman primates. Most information on castrated male primates comes from a few studies on the skeletons of eunuchs. This report used a subset of the Caribbean Primate Research Center's (CPRC) Cayo Santiago (CS) rhesus macaque skeletal collection to qualitatively and quantitatively compare the bone mineral density (BMD) of castrated and age-matched intact males and, thereby, determine the long-term effects of castration (orchidectomy) on bone. Lumbar vertebrae, femora and crania were evaluated using dual-energy X-ray absorptiometry (DEXA or DXA) and digital radiography augmented, when fresh tissues were available, with autoradiography and histology. Results confirmed physical examinations of long bones that castration causes changes in the skeleton of male rhesus macaques similar to those found in eunuchs, including OPE and OPO of the vertebrae and femora, thinning of the skull, and vertebral fractures and kyphosis of the spine more severe than that caused by normal aging alone. Also like eunuchs, some castrated CS male rhesus monkeys had a longer life span than intact males or females. Based on these results and the effects of castration on other tissues and organs of eunuchs, on behavior, hormone profiles and possibly on cognition and visual perception of human and nonhuman primates, and other mammals,

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castrated male rhesus macaques should be used with caution for laboratory studies and should be considered a separate category from intact males. Despite these caveats, the castrated male rhesus macaque should make an excellent animal model in which to test hormone replacement therapies for boys and men orchidectomized for testicular and prostate cancer.

Keywords

Aging; orchidectomy; eunuch; longevity; bone density; Cayo Santiago

INTRODUCTION

The castration of human males has a long history and has been performed for various purposes over the centuries: occupational (i.e., harem and security guards, servants and choir/opera singers), punishment for sex offenders, self-cleansing and religious purification, eugenics programs, medical (i.e., treatment of testicular and prostate cancers) and, most recently, for sexual reassignment surgery [Hamilton & Mestler, 1969a, 1969b; Tsai, 1996; Jenkins, 1998; Scholz, 2001; Scott and Holmberg, 2003;]. There is a wealth of information on the sociosexual behavioral impacts of the castration of boys and on their reduced male secondary sex characteristics such as smaller heads, higher-pitched voices, lack of facial hair and reduced muscle mass [Eng et al., 2010], however, only a handful of studies have addressed the effects of orchidectomy on the skeleton. These are limited to three historical bone collections of eunuchs from the Skoptzy Christian sect in Russia, Imperial China and the Ottoman Empire [Wilson & Roehrborn, 1999; Zitzmann & Nieschlag, 2001; Eng et al., 2010]. Without the testicles, the production of testosterone is greatly reduced and has a significant impact on skeletal development and integrity [Silberberg & Silberberg, 1971]. Depending upon the age at castration and duration thereof, the effects on the skeleton include failure of the epiphyses to close resulting in increased stature or height, osteoporosis (OPO), thinning of the long bones and skull, kyphosis of the spine and pathological fractures [Wilson & Roehrborn, 1999; Eng et al., 2010]. Other organs and tissues are also affected, most notably the pituitary gland undergoes hyperplasia, the breasts enlarge (gynecomastia) and the prostate becomes hypoplastic or atrophic [Wilson & Roehrborn, 1999]. More recently, bone health after castration, either through physical (i.e. bilateral orchidectomy) or chemical sterilization, as a therapy for prostate or testicular cancer, has become the subject of clinical research on OPO and epidemiological studies on the risk of fractures [Daniell, 1997; Melton et al., 2003; Morote et al., 2007; Ondrusova et al., 2009]. These gonadectomized men are at high risk for developing OPO [Anderson et al., 1998]. In fact, OPO and fractures in these eunuchs are as severe and common as in women five to seven years younger [Seidlova-Wuttke et al., 2008]. Importantly, these men are three times more likely than women to die from hip fractures [Todd et al., 1995]. Despite these serious health risks facing castrated men, a recent study on Korean eunuchs based on historical records found that eunuchs lived 14.4 to 19.1 years longer than intact men of similar socioeconomic status [Min et al., 2012]. This confirmed an earlier report by Hamilton and Mestler [1969a] showing that some eunuchs in a mentally-deficient population outlived intact males by 13 years.

Osteoporosis is a naturally-occurring disorder of aging humans and it has been well documented in aging female and male Cayo Santiago (CS) rhesus macaques through studies of living animals [Aguilo & Cabrera, 1989] but mostly using their skeletal remains [DeRousseau, 1985; Grynepas et al., 1989, 1993a, 1993b; Cerroni, 2000; Cerroni et al., 2000, 2003; Turnquist et al., 2012]. Bone loss with age has also been reported in male rhesus monkeys from other populations [Pope et al., 1989; Colman et al., 1999; Black et al., 2001] and in male baboons [Kammerer et al., 1995].

Experimentally, nonhuman primates and several other animal species have been used to study the effects of castration in both males and females. Early investigations involving male nonhuman primates focused almost exclusively on the effects of castration on hormones and behavior. Briefly, behavioral changes from lack of testosterone include reduced aggression and sexual activity [Wilson & Vessey, 1968; Resko & Phoenix, 1971; Phoenix, 1974; Buhl et al., 1978; Phoenix, 1978; Chambers & Phoenix, 1983; Schenck & Slob, 1986; Davis-daSilva & Wallen, 1989; Zumpe et al., 1996, 1997]. Ovariectomized rhesus and cynomolgus macaques were also used for hormone and reproductive behavior studies and first developed as models for post-menopausal osteopenia (OPE) and OPO in the 1980s [Miller et al., 1986]. These studies have been reviewed in a number of reports [Jerome et al., 1994; Cerroni et al., 2000; Smith et al., 2009; Pritzker & Kessler, 2012; Turnquist et al., 2012]. Ovariectomized female macaques, particularly cynomolgus models of post-menopausal OPO, have been used extensively for testing new drugs such as anabolic steroids, bisphosphonates and selective-estrogen-receptor modulators to prevent or treat OPO [Smith et al., 2009; Pritzker & Kessler, 2012]. Other animal species including mice [Inada et al., 2011], rats [Wink & Felts, 1980], ferrets [Mackey et al., 1995], and pigs, goats, sheep and dogs [Reinwald & Burr, 2008] have been promoted as models for human post-menopausal bone loss but the ovariectomized macaque remains the model of choice [Smith et al., 2009].

On the other hand, there have only been a few published reports on the effects of orchidectomy on bone in nonhuman primates. A chimpanzee born in 1934 was castrated at two years of age [Clark, 1945] and a second chimp born in 1945 was castrated as an infant at two months of age [Clark & Gavan, 1962]. The first chimp lived to 22 years of age and the second to 15 years. The skeletons of these two apes, the only known prepubertally-castrated male anthropoids as of 1962, were found to have delayed closure of the epiphyses compared to control animals [Clark & Gavan, 1962]. However, they were not examined for signs of OPE or OPO. Seidlova-Wuttke and colleagues [2008] published the only other known report. This covered a short-term study on orchidectomized common marmosets (*Callithrix jacchus*) using quantitative computer tomography. They found OPE in the young marmosets and borderline OPO in the older animals.

The purpose of our study was to determine the long-term effects of castration in the skeletons of castrated CS male rhesus macaques (*Macaca mulatta*) curated in the Caribbean Primate Research Center (CPRC) Skeletal Collection using various methods including dual energy x-ray absorptiometry (DEXA or DXA) and digital radiography. These skeletons were first noted as being abnormally light in weight years ago but it was not until recently that they were subjected to DEXA analysis and digital radiography to validate these

observations and to test the hypotheses that due to the significant decrease in testosterone production, [1] OPE and OPO would occur in young castrated male rhesus macaques, and [2] the severity of these conditions in old castrated males would be greater than in their age-matched intact male controls that develop senile OPE and OPO.

METHODS

All research utilizing CS monkeys is (1) approved by the CPRC and the Institutional Animal Care and Use Committee of the University of Puerto Rico, Medical Sciences Campus, (2) performed in accordance with USDA regulations and USPHS policies and guidelines, and (3) adheres to the American Society of Primatologists Principles for the Ethical Treatment of Nonhuman Primates.

The Cayo Santiago rhesus macaque colony

Cayo Santiago, a 15.2-ha island located 1 km off the southeast coast of Puerto Rico (18°09'N, 65°44'W), has been home to a free-ranging colony of Indian-origin rhesus macaques (*Macaca mulatta*) since late 1938. All monkeys on this island are descendants of the 409 founders and the population is considered the most homogeneous large Indian-origin rhesus colony in the U.S.A. [Kanthaswamy et al., 2010]. The animals are maintained under semi-natural conditions for behavioral and noninvasive biomedical research and are provisioned with a commercial monkey diet (0.23 kg/monkey/day). They also forage on the natural vegetation and are geophagic. Purified rain water is available ad libitum from automatic waterers located around the island. All individuals are identified by ear notches and a unique alphanumeric tattoo [Rawlins & Kessler, 1986]. A daily census was initiated in mid-1956 [Altmann, 1962] so that births, deaths, changes in group membership and losses of monkeys are generally noted within two days of occurrence. The number of naturally-formed social groups has varied between two and eight. The now-computerized demographic database is updated by monthly reports and includes identification, birth date, sex, group fissions, group memberships, maternity, maternal genealogy, parity (if applicable), death date and cause of death (if known). Paternity has been determined genetically for more than four thousand individuals and maternity, as derived from behavioral observations, has been confirmed genetically for almost as many. Based upon these data, pedigrees can be reconstructed covering several rhesus generations [Albers & Widdig, 2013; Widdig et al., 2015b]. Moribund and severely injured animals are either removed from the island for treatment or are euthanized in accordance with guidelines of the American Veterinary Medical Association [2013]. Due to the free-ranging conditions of the colony, direct veterinary intervention has always been minimal except during the annual trapping period when monkeys are humanely-captured, given physical examinations, have blood drawn and, since 1985, vaccinated against tetanus [Kessler et al., 2014].

The Cayo Santiago rhesus macaque skeletons

The systematic collection of complete skeletal remains of CS rhesus macaques began in 1971–1972 and over the course of the past four decades has become an unparalleled resource for osteological research [Rawlins, 1979; Sade et al., 1985; Turnquist & Hong, 1989; Yellen, 1989; Dunbar, 2012]. All skeletons were prepared using a standardized water

maceration process that has been in effect since the early 1970s [Turnquist & Hong, 1989]. The collection, often referred to as the CPRC Skeletal Collection, is currently housed in the CPRC's Laboratory of Primate Morphology (LPM), formerly known as the Laboratory of Primate Morphology and Genetics (LPMG). The collection has continued to expand and, as of November 2013, there were 2,676 CS and CS-derived rhesus skeletons (from rhesus born on CS and moved to the CPRC's Sabana Seca Field Station or the former La Parguera Primate Facility in Puerto Rico), 2,394 of them accompanied by complete demographic records including age at death, sex, identity, maternity (observed or observed and verified by maternity testing), matriline, and social group. Many also have additional associated information including dominance rank, dental records and radiographs [Wang, 2012; Wang et al. 2015]. Paternity and genotype are also known for many of the individuals in the skeletal collection [Widdig et al., 2004, 2015a]. These skeletons, all of which are derived from the same closed Indian-origin population, provided the osteological resources for this study [Rawlins & Kessler, 1986; Turnquist & Hong, 1989; Cerroni, 2000; Cerroni et al., 2000, 2003; Dunbar, 2012].

Castrated males

The skeletons of all five castrated male CS rhesus monkeys in the collection were used for this study and categorized as Prime Age or Old Age Group depending upon their age at death and scanned with age-matched intact controls (see Table I). The monkeys were castrated at three months to seven years of age (two at 3–4 months, two at age 4 years and one at age 7 years). These individuals died from 10 to 30 years after being castrated. Two monkeys castrated as infants died at 10.3 and 11.1 years of age and were castrates for approximately 10 and 11 years, respectively. When these two males died, they were in the age range for peak bone mass for CS males of about 7.0 to 18.5 years and in “prime adulthood” (10.0–14.9 years) [Cerroni et al., 2000], and were categorized as Prime Age Group animals. The other three castrates, ranging in age from 26 to 33.8 years when they died, were classified as members of the Old Age Group. Among these three were two monkeys who were castrated as adolescents (4 years of age) and one as a young adult (7 years of age). These three Old Age Group monkeys were castrated for approximately 19 to 30 years prior to death.

Intact males

For the assessment of vertebral bone mineral density, data on bones from the skeletons of 128 intact male CS monkeys [Cerroni et al. 2000] were compared with those from castrated animals. These specimens ranged in age from one to 26 years.

For femoral and calvarial assessment, bones from 21 skeletons were selected and grouped into the two age categories with intact controls selected randomly for comparison. The Prime Age Group of controls consisted of 11 individuals ranging in age from 10.3 to 11.4 years. The Old Age Group controls consisted of 10 individuals. The controls in the Old Age Group ranged in age from 20.4 to 29.1 years and represented all of the skeletons of intact males in the collection that were greater than 20.4 years of age.

Measurement of bone mineral density

For the vertebrae, dual-energy X-ray absorptiometry (DEXA or DXA) measurements of the last lumbar vertebra were obtained using a DPX-L Lunar Bone Densitometer (GE-Lunar Corp., Madison, WI) at high resolution (76kVp, 150 μ A, 1/64 sample interval, fine collimation 0.84 mm) and analyzed with Lunar DPX-L X-ray Bone Densitometer Small Animal software version 1.0c, 1992 as described in Cerroni and colleagues [2000, 2003]. All the vertebrae were scanned in Toronto at Mount Sinai Hospital. For the femora and calvaria from the 5 castrates and 21 intact controls, areal bone mineral density of the femoral neck, mid-shaft femur and parietal boss of the parietal bone in the cranium were scanned using a Norland Eclipse DEXA (Cooper Surgical, Inc., Trumbull, CT) at the Yerkes National Primate Research Center Field Station. All measurements were done on the right femur except for one individual who had gross evidence of right femoral osteopathy. All specimens were placed in a transparent polyvinyl chloride container (2.36 cm x 1.57 cm x 4.33 cm for vertebrae and 9.50 cm x 15.70 cm x 27.50 cm for femora and calvaria) and scanned in a caudo-rostral direction at high resolution. The femoral neck bone mineral density was measured using the small body hip automated software. The shaft portion, consisting mainly of cortical bone, was defined by a 6 mm x 19 mm manual digital box (region of interest) located approximately 4 cm from the trochanter minor. To scan the right parietal boss, the cranium was angled at approximately 20 degrees from a horizontal plane. Parietal bone scans were acquired and analyzed using Norland's Illuminatus small animal software (version 4.2.3). The parietal boss was captured in a 6 x 6 mm region of interest using manual selection. Coefficients of variation were less than 1.8% for each of the scans performed in this study. For the purpose of this study, these data sets were treated separately in our analyses, as they were derived from two different DEXA machines; the vertebral data on BMD was analyzed separately from the BMD data on the femora and calvaria.

Radiographs

Digital radiographs of the last lumbar vertebra, femur and skull of all castrates (n=5) and age-matched controls were taken at the CPRC using a Vet APR system with Eureka Linear MC 150 collimator radiograph machine (GTR Labs, Inc., Gassaway, WV) at 60 KVP, 200 MA, 0.02 second exposure and 400 MAS. The software used was Maxxvue Vet by E.B. Medical (Chantilly, VA).

Data analysis

The DEXA measures the quantity of hydroxyapatite in bone, as bone mineral content (BMC) in grams, and calculates the areal bone mineral density (BMD), expressed as grams of mineral per unit area scanned (g/cm^2). The BMD of vertebrae from the castrated males was assessed by DEXA using the same methods as control animals in the study by Cerroni and colleagues [2000]. The definition of OPE and OPO established for women by the National Osteoporosis Foundation of the United States, the European Foundation for Osteoporosis and Bone Disease, and the World Health Organization was followed for this study as in previous ones of the CS rhesus skeletons [Cerroni et al., 2000, 2003]: 1) *Normal*: a value for BMD or BMC not more than 1 standard deviation (SD) below the average value of young (Prime Age) adults; 2) *Osteopenia (low bone mass)*: a value for BMD or BMC

more than 1 SD below the young adult average, but not more than 2.5 SD below; 3) *Osteoporosis*: a value for BMD or BMC more than 2.5 SD below the young adult average value; and 4) *Severe osteoporosis (established osteoporosis)*: a value for BMD or BMC more than 2.5 SD below the young adult average value, plus the presence of one or more fragility fractures [Kanis, 1994; Wasnich, 1996]. In the CS rhesus macaques, the areal BMD of female rhesus monkeys peaks at approximately 9.5 years, remains constant until 17.2 years, and then subsequently declines [Cerroni, 2000]. The average peak BMD value for intact CS males occurs at about 7.0 years and remains constant until 18.5 years. The mean BMD ($\pm$ 1SD) for “prime adulthood” (Prime Age Group) adults (10.0–14.9 years) was 0.788 gm/cm² ($\pm$ 0.120) [Cerroni et al., 2000]. These values were used to assess osteopenia [BMD < 0.668 (peak minus 1 SD)] and osteoporosis [BMD < 0.488 (peak minus 2.5 SD)].

For DEXA of the femora and calvaria, Student’s one-tailed *t*-tests were used to compare Prime Age and Old Age Groups and intact males versus castrates of the same age group. Statistical significance was set at $\alpha < .05$. Statistical analyses were done using IBM SPSS Statistics 22 (Armonk, NY), and related images were generated using Slidewrite Plus 7.0 (Advanced Graphics Software, Inc., Rancho Santa Fe, CA).

RESULTS

1. Vertebrae

BMD of vertebrae—As reported by Cerroni and colleagues [2000], the L7 vertebrae (or the last lumbar vertebra in some individuals with numerical variability) of intact male CS rhesus had a peak BMD from 7.0 to 18.5 years (Fig. 1). Among the five castrates (see Table I), one in the Prime Age Group (NO/355) was above the average peak value and one in the Old Age Group (KB/830) was osteopenic. The remaining three castrates [one in the Prime Age Group (NP/341) and two in Old Age Group (CN/647 and 056/2038)] were osteoporotic. Thus, all three castrates in the Old Age Group, representing 60% of all castrates, either had OPE or OPO. In comparison, only 3.8% ($n=4$) of intact males older than 7 years ($n=104$) were osteoporotic and only 11.5% ($n=12$) were osteopenic. In contrast to the castrated males, the vast majority (84.6%, $n=88$) of intact males older than 7 years had normal BMD values.

Table I also shows a comparison of the BMD of the L7 (or last lumbar) vertebrae of age-matched intact and castrated CS males. The 25- to 26-year-old intact males averaged 0.835 gm/cm² (SEM=0.146), higher than their castrated counterparts, having an average BMD of 0.516 gm/cm² (SEM=0.061) but the difference was not statistically significant ($P = 0.107$). The oldest male monkey in the collection (056/2038), a castrate for 30 years, was almost 34 years of age at death; the BMD value of its L7 vertebra was 0.460 gm/cm². Unfortunately, there was no intact adult male skeleton close to this age in the collection for a direct comparison. The oldest intact male skeleton was from a monkey that died at age 29 years but this individual had severe spinal arthritis and, therefore, its lumbar vertebrae were not suitable for DEXA scanning. As noted in Cerroni and colleagues [2000], many of the older adult animals in this collection exhibit extensive osteophytosis and degenerative disc disease which may lead to elevated BMC readings and BMD values, and thus biased results. These

individuals were not included in the control sample derived from this previous investigation and used in this study.

Morphology—All three castrated males with OPO demonstrated characteristic features of the disorder in humans. In the Prime Age Group, NP/341 had less radiodensity in its L1 and L7 vertebral body and processes (Fig. 2). In L7, compared to age-matched specimens, NP/341 not only had thinner cortical bone, but also less total bone mass and trabecular bone. Likewise, CN/647 in the Old Age Group had remarkable porosity in the cortical bone of L7, compared to LT/1161, an age-matched intact male (Fig. 3). There was increased porosity of the vertebrae with wedge and fragility (pathological) fractures, eventually causing severe osteoarthritis and kyphosis (Fig. 4). Occasionally, Dowager's hump was observed in senescent CS rhesus monkeys (see Fig. 5; [Cerroni et al., 2000; Pritzker & Kessler, 2012; Turnquist et al., 2012]).

2. Femora and Calvaria

BMD—Overall, the femoral bone mineral densities (BMD) of intact males in the Old Age Group were significantly lower than in the Prime Age Group (*t*-test: femoral neck, $P = 0.004$; mid-shaft femur, $P < 0.001$; calvarium, $P = 0.053$), indicating the presence of age-related OPE or OPO, especially evident in the femur (Table II, Fig. 6). Bone mineral density was lower in the femora of castrated males compared to intact male controls of the same age group at both the femoral neck (*t*-test: Prime Age: $P = 0.005$; Old Age: $P = 0.062$) and the mid-shaft femur (Prime Age: $P = 0.003$; Old Age: $P = 0.038$). The BMD values of all the castrated males were lower than the mean values, and for the mid-shaft femur, the values were outside the low range for bone density in the intact male controls (Table I, Figs. 6 & 7).

There were no significant measureable differences in BMD of the calvaria between the castrated and intact males (Prime Age: $P = 0.347$; Old Age: $P = 0.495$) (Table II, Fig. 6). In addition, the variation in bone density, measured by the Coefficients of Variation (CV), were considerably higher in the calvaria compared with the femora in both Prime Age and Old Age groups (Prime Age: 0.48 vs. 0.08–0.09; Old Age: 0.37 vs. 0.24) (Fig. 6).

Morphology—In the femora, there was loss of trabecular bone in the femoral neck and cortical bone in the femoral shaft as evidenced by thinning. However, in external morphology the femora in castrated males generally were larger or longer than those of normal specimens (Figs. 7 & 8). Failure of closure of the epiphyses and avulsion were found in at least one male castrated as an infant e.g. femoral specimen of monkey NO/355 (age at death, 10 years). In this monkey, the distal growth plate was not yet fused (indicated by a dark arrow in Fig. 8). Note the remarkable thinning of the shaft of the femur in the aged male castrate. Figure 9 shows a fresh para-sagittal section of the distal femur and a specimen auto-radiograph of this section, respectively, for aged castrate CN/647. Note the thinning of the distal femoral shaft indicating OPO. Figure 10 shows a photographic comparison of the mid-shaft femur of an aged castrate (CN/647) with an aged intact male (LT/1161). Histologically, this femur had an abnormally large number of empty lacunae with increased porosity of the cortex that was consistent with OPO (Fig. 11).

The skulls of castrates in both Prime and Old Age Groups were smaller and more rounded than those of intact individuals, in addition to having thinner cortical bone and decreased calvarial thickness both on physical examinations and DEXA scans (Fig. 12). Again the differences in bone density are quite remarkable between the castrated and intact male rhesus skulls on both DEXA (Fig. 12) and radiography (Fig. 13).

DISCUSSION

Based on DEXA, digital radiographic and physical examinations of all castrated male CS skeletons compared to a large sample of intact male skeletons and age-matched controls from the same collection, it is concluded that castration results in the thinning of cortical bone and OPE/OPO over time in rhesus macaques impacting both internal and external bone morphology and mechanical qualities. Both vertebrae and femora in castrated males were of low bone density and within the range of OPE or OPO. In addition, the femora of castrated males may have lower total bone mass than do the controls. Gross, auto-radiologic and histologic findings in available necropsy tissue from at least one of the five castrated male rhesus monkeys (CN/647) were consistent with DEXA and digital radiographic findings of OPO in its skeletal remains e.g. femur, L7 and calvarium. However, the calvaria from the skeletons of castrated monkeys, in general, had BMD comparable to controls, although the total bone mass in the castrates might be lower than controls as well, and qualitative DEXA scans, radiographs and physical examinations of the calvaria indicated thinning of the skull compared to intact males (Fig. 12 & 13) as occurs in eunuchs [Wilson & Roehrborn, 1999; Eng et al., 2010]. The calvaria demonstrated higher variation in BMD than did the femora; e.g. some were thin, while others were normal. The crania vary considerably in size and shape after skeletal maturation and this could adversely impact the assessment of BMD using DEXA.

This rare sample of castrated male nonhuman primate skeletons revealed the importance of testosterone in the maintenance of bone health measured by both bone density and bone mass, especially in the postcranial skeleton (vertebral column and lower limb). The long-term effects of orchidectomy on rhesus bone are similar to findings in previous studies on humans and other castrated mammals (males or females) [Schot & Schuurs, 1990; Torres de la Riva et al., 2013; Hart et al., 2014] and to the short-term study on osteoporosis in castrated male marmosets [Seidlova-Wutte et al., 2008].

Osteoporosis and arthritis are the two most common age-related conditions of the musculoskeletal system leading to an increased risk of fracture, immobility or death in humans. These conditions are also seen in the CS rhesus macaques [Buikstra, 1975; DeRousseau, 1978; Cerroni, 2000; Cerroni et al., 2000, 2003; Pritzker & Kessler, 2012; Turnquist et al., 2012]. Although the symptoms may be managed, the causes of arthritis and OPO in the general human population and the ability to prevent these conditions remain elusive. It is noteworthy that in the CS rhesus macaques, osteoporotic spines generally tend to be relatively free of osteophytes, or, if OPE/OPO is present, are either free of vertebral osteophytosis and vertebral osteoarthritis, or express milder forms of the disease [Cerroni, 2000], a phenomenon that warrants further investigation, especially in castrated animals.

Despite all of the underlying health risks associated with castration in humans [Wilson & Roehrborn, 1999; Eng et al., 2010], those orchidectomized as children, adolescents or young adults (4 years of age or older), lived longer than intact, normal males of the same socioeconomic level [Min et al., 2012] and so did Caucasian eunuchs with mental disabilities [Hamilton & Mestler, 1969a, 1969b]. It is intriguing to note that the two CS males castrated as infants only lived to about 10 years of age, yet all three individuals castrated at older ages lived more than 26 years. In the CS population, 29.7% of males lived longer than 10 years, only 4.1% lived beyond 20 years, and only 1.5% lived beyond 25 years [Wang, 2012]. By November 2013, there were only 6 intact males and 2 females who survived beyond 25 years (25.190 to 28.301 yrs in males, 29.260 to 31.444 yrs in females). On CS, the oldest intact male was 28.301 years, and the oldest intact female lived to 33.444 years, both younger than the oldest castrated male (33.753 yrs). Although this represents only a small sample, these findings in castrated CS rhesus macaques are consistent with those on Korean eunuchs [Min et al., 2012] and in other populations of eunuchs [Hamilton & Mestler, 1969a] and some animal species [Hamilton & Mestler, 1969b].

In conclusion, the long-term effects of castration on the skeletal system in male CS rhesus macaques, including OPE and OPO, are similar to those historically found in eunuchs and to those in men therapeutically orchidectomized for cancer who are deprived of hormone replacement therapy [Morote et al., 2007]. Based on these results and the effects of castration on other tissues and organs of eunuchs, castrated male rhesus macaques should be used with caution for long-term laboratory studies and should be considered a separate category from intact males as the lack of testosterone not only affects bone and other tissues and organs, hormones and behavior, but also may be linked to cognitive impairment [Alexander et al., 1998; Barrett-Connor et al., 1999; Hart, 2001; Hart et al., 2014] and the processing of visual stimuli [Little, 2013]. Despite these caveats, the castrated male rhesus macaque should make an excellent model in which to test hormone replacement therapies for boys and men orchidectomized for testicular and prostate cancer as well as other reasons.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

Figure 7.

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Figure 8.

Figure 9.

Figure 10.

Figure 11.

Figure 12.

Figure 13.

Table 1

Results of DEXA scans of L7 vertebrae of castrated and selected normal (intact) age-matched control male Cayo Santiago rhesus macaque skeletons by age category (Prime Age Group and Old Age Group)

Monkey/Skeleton #	Age Cast'd	AAD (yrs)	Years Cast'd	BMD L7	BMD L7 Peak Mean	BMD L7 Peak SD	BMD SD Units	Diag
Prime Age Group								
NP/341	3 mo	11.12	11	0.467	0.788	0.120	-2.68	OPO
591/713	N/A	10.49	N/A	0.983	0.788	0.120	1.62	N
NO/355	4 mo	10.29	10	0.886	0.788	0.120	0.82	N
UP/303	N/A	10.33	N/A	0.713	0.788	0.120	-0.62	N
Old Age Group								
CN/647	4 yr	26.96	23	0.472	0.788	0.120	-2.63	OPO
LT/1161	N/A	24.68	N/A	0.544	0.788	0.120	-2.03	OPE
KB/830	7 yr	26.04	19	0.615	0.788	0.120	-1.44	OPE
JG/1210	N/A	25.19	N/A	0.995	0.788	0.120	1.72	N
056/2038	4 yr	33.75	30	0.460	0.788	0.120	-2.73	OPO
EE/846	N/A	26.49	N/A	0.967	0.788	0.120	1.57	N

Note: Age Cast'd, age at castration; AAD, age at death; Years Cast'd, years castrated; BMD, bone mineral density (g/cm²); BMD peak mean, and BMD Peak SD, mean peak bone mineral density and standard deviation, respectively, for intact males; BMD SD units, standard deviation units for each specimen scanned. Diagnoses, based on WHO criteria, are given in the far right column: N, normal; OPE, osteopenia; OPO, osteoporosis.

Table II

Results of DEXA areal bone mineral density measurements (g/cm^2) on femora and calvaria of castrated male Cayo Santiago rhesus macaques by age category compared with age-matched intact male controls

Age Group	Monkey/Skeleton #	AAD (yrs)	Fem Neck	Fem mid-shaft	Calvarium (Parietal boss)
<u>Prime Age Group</u>					
	NP/341	11.12	0.493 (OPO)	0.663 (OPO)	0.744
	NO/355	10.29	0.628 (OPE)	0.752 (OPE)	0.958
Age-Matched Control	Range	10.32–11.40	0.604–0.832	0.815–1.074	0.258–1.694
Fem & Calv N=11	Mean	10.87	0.707	0.915	0.992
	SD	0.40	0.056	0.079	0.476
	CV	0.04	0.08	0.09	0.48
<u>Old Age Group</u>					
	056/2038	33.75	0.405 (OPO)	0.424 (OPO)	0.327
	CN/647	26.96	0.363 (OPO)	0.379 (OPO)	1.108
	KB/830	26.04	0.517 (OPO)	0.585 (OPO)	0.649
Age-Matched Control	Range	20.40–29.12	0.308–0.794	0.366–0.912	0.320–1.249
Fem N=10; Calv N=9	Mean	24.49	0.571	0.651	0.690
	SD	2.84	0.138	0.153	0.254
	CV	0.12	0.24	0.24	0.37

Note: AAD, age at death; Fem Neck, femoral neck; Fem Mid-shaft, mid-shaft of femur; Fem, femur; Calv, calvarium; OPE, osteopenia; OPO, osteoporosis.