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Age-Related Structural and Metabolic Changes in the Pelvic Reproductive End Organs

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In this work, we provide preliminary data and a review of the literature regarding normal structural and functional changes that occur in the aging uterus, ovary, testicle, and prostate gland. It is expected that such knowledge will help physicians to distinguish physiologic changes from pathologic changes at an early stage. We retrospectively reviewed pelvic magnetic resonance imaging (MRI) scans of 131 female and 79 male subjects ages 13 to 86 years to determine changes in volume of the uterus, ovary, and prostate gland with age. Scrotal ultrasound examinations of 150 male subjects ages 0 to 96 years also were analyzed retrospectively to determine changes in testicular volume with age. In addition, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scans of 145 male subjects ages 11 to 90 years were analyzed retrospectively to assess for changes in maximum standardized uptake value (SUV_{max}) of the testicles with age. The uterus had a mean volume of 38.55 ± 3.68 cm^3 at 17 to 19 years of age, increased to a peak volume of 71.76 ± 19.81 cm^3 between 35 to 40 years, and then declined to 24.02 ± 8.11 cm^3 by the eighth decade of life. The maximal ovarian volume per subject maintained a relatively stable size in early life, measuring 9.46 ± 3.25 cm^3 during the second decade of life, 8.46 ± 3.32 cm^3 in the mid-fourth decade of life, and 7.46 ± 3.33 cm^3 at 45 years of age, after which it declined to 4.44 ± 2.02 cm^3 by the late fifth decade of life. The ovaries were not identifiable on MRI in subjects beyond the sixth decade of life. The volume of the prostate increased from 23.45 ± 6.20 cm^3 during the second decade of life to 47.5 ± 41.59 cm^3 by the late eighth decade of life; the central gland of the prostate increased from 9.96 ± 3.99 cm^3 to 29.49 ± 28.88 cm^3 during the same age range. Mean testicular volume was 11.2 ± 5.9 cm^3. Testicular volume increased with age from birth to 25 years. After age 25, there was a significant decline in the testicular volume. The mean SUV_{max} for the testicles was 1.9 ± 0.5. Testicular metabolic activity demonstrated an increasing trend until the age of 35 years. A plateau in SUV_{max} was observed after the age of 35 years until the age of 65 years. A slight decrease in SUV_{max} was observed after the age of 65 years. The pelvic structures of men and women change both structurally and functionally over the lifespan, and such changes can be quantified using ultrasound, MRI, and ^{18}F-FDG-PET.

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Many studies have reported the physiological and hormonal changes of the male and female reproductive organs with age.[1-7] It is important to supplement this knowledge with a description of how the appearances of these organs change over the lifespan using both structural and functional imaging techniques. With this knowledge, nuclear medicine physicians and radiologists will be better able to differentiate early pathology from changes of normal aging. In addition, geriatricians may gain a better understanding of the aging process in these organs and be better able to care for our aging population. To this end, we provide quantitative preliminary data of the age-related changes in volume of the uterus, ovary, prostate gland, and testicle based on retrospective analysis of pelvic magnetic resonance imaging (MRI) or testicular ultrasonography (US) examinations, and changes in testicular metabolism with age based on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET). We

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also provide a review of the literature regarding age-related structural and functional changes in these organs.

Materials and Methods

Institutional review board approval for retrospective data collection and image analysis along with a HIPAA waiver were obtained from the Hospital of the University of Pennsylvania's and the Children's Hospital of Philadelphia's Institutional Review Boards before study initiation.

Pelvic MRI

MRI examinations of 58 female subjects (age range, 13-59 years) were retrospectively reviewed to study the ovaries, MRI examinations of 72 female subjects (age range, 17-82 years) were retrospectively reviewed to study the uterus, and MRI examinations of 84 male subjects (age range, 20-84 years) were reviewed to study the prostate gland. All subjects underwent routine pelvic MRI examinations at the Hospital of the University of Pennsylvania (HUP) during the period of 2000 to 2006 and were retrospectively analyzed for this study. Female subjects with a history of pelvic infection, pelvic inflammatory disease, malignancy, chemotherapy, pelvic radiation therapy, uterine fibroids, and ovarian cysts were excluded. Male subjects with a history of pelvic infection, pelvic malignancy, chemotherapy, and pelvic radiation therapy were excluded. Routine female pelvic MRI studies were performed at 1.5 T with a phased-array torso coil using axial T1-weighted fast spin echo, axial fat-suppressed T1-weighted gradient-recalled echo, axial, sagittal, and fat-suppressed coronal T2-weighted fast spin echo, and delayed postgadolinium contrast-enhanced axial fat-suppressed T1-weighted gradient-recalled echo images. Routine pelvic MRI studies were performed in the male subjects at 1.5 T using axial T1-weighted fast spin echo and multiplanar T2-weighted fast spin echo images, sometimes with delayed postgadolinium contrast enhanced axial fat-suppressed T1-weighted gradient-recalled echo images.

Testicular US

One hundred fifty male subjects (age range, 1 month to 90 years) underwent routine testicular ultrasound examinations at HUP and Children's Hospital of Philadelphia. Exclusion criteria included presence of a varicocele, large hydrocele, testicular trauma, testicular cyst, testicular infection, testicular inflammation, undescended testicle, testicular torsion, testicular dysgenesis, testicular infection, pelvic malignancy, chemotherapy, or pelvic radiotherapy. Multiple axial, sagittal, and coronal grayscale images had been obtained through each testicle, and maximal long axis dimensions were recorded in three perpendicular directions for each testicle.

^{18}F-FDG-PET

This study also retrospectively included 145 male subjects ages 11 to 90 years who had ^{18}F-FDG-PET whole-body imaging at HUP during February 2002 to November 2006. Most PET scans were performed for the staging of melanoma, lymphoma, or neuroblastoma, or for hip prosthesis assessment before therapy; however, all subjects with a history of pelvic metastasis, previous chemotherapy, and pelvic radiotherapy were excluded.

Subjects fasted for at least 4 hours before receiving ^{18}F-FDG intravenously and their serum glucose levels were <140 mg/dL. All subjects were asked to empty their bladders immediately before being scanned. PET scanning was performed in these subjects with dedicated whole-body PET scanners (Allegro; Philips Medical Systems, Bothell, WA, or C-PET; ADAC UGM Medical Systems, Milpitas, CA). PET was initiated 60 min after the intravenous administration of a dose of ^{18}F-FDG adjusted to the body weight (130 μCi/kg [4.8 MBq/kg] for the Allegro and 68 μCi/kg [2.5 MBq/kg] for the ADAC camera). Sequential overlapping scans were acquired to cover from the base of the skull to the mid thighs, including the neck, chest, abdomen, and pelvis. Transmission scans obtained with a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed with an iterative reconstruction algorithm, and both attenuation-corrected and nonattenuation-corrected images were utilized.

Image Analysis

Volume of the Uterus, Ovary, and Prostate Gland

Regions of interest (ROIs) were manually traced about the outer contour of each organ of interest on multiple consecutive slices using our picture archiving and communications system workstation (Centricity; GE Health care, Milwaukee, WI), which automatically provided area values. Area values were then summed and totals were multiplied by slice thickness to obtain organ volumes. For the uterus, sagittal or coronal T2-weighted images were used depending on ease of visualization of the uterus, and contours were restricted to the uterine corpus with exclusion of the cervix. For the ovaries, axial T2-weighted images were used, and the larger of the 2 ovarian volumes were recorded for each subject. For the central gland of the prostate and the overall prostate gland, axial T2-weighted images were used for measurement purposes. The low signal intensity surgical capsule of the prostate gland, which is located between the low-intermediate signal intensity central gland and the high signal intensity peripheral zone, was used as the outer contour of the central gland.

Volume of the Testicle

Long-axis diameters of the testicles were obtained from axial, sagittal, and coronal views based on data reported in radiology reports. The volume of each testicle was then estimated using the formula for a prolate ellipsoid: width $\times$ length $\times$ height $\times$ 0.523. The bilateral testicular volumes were then averaged to provide a mean testicular volume for each subject.

Maximum Standardized Uptake Value (SUV_{max}) of the Testicle

The SUV_{max} of the testicle was obtained from axial views of the PET images in all subjects. An ROI was drawn about each

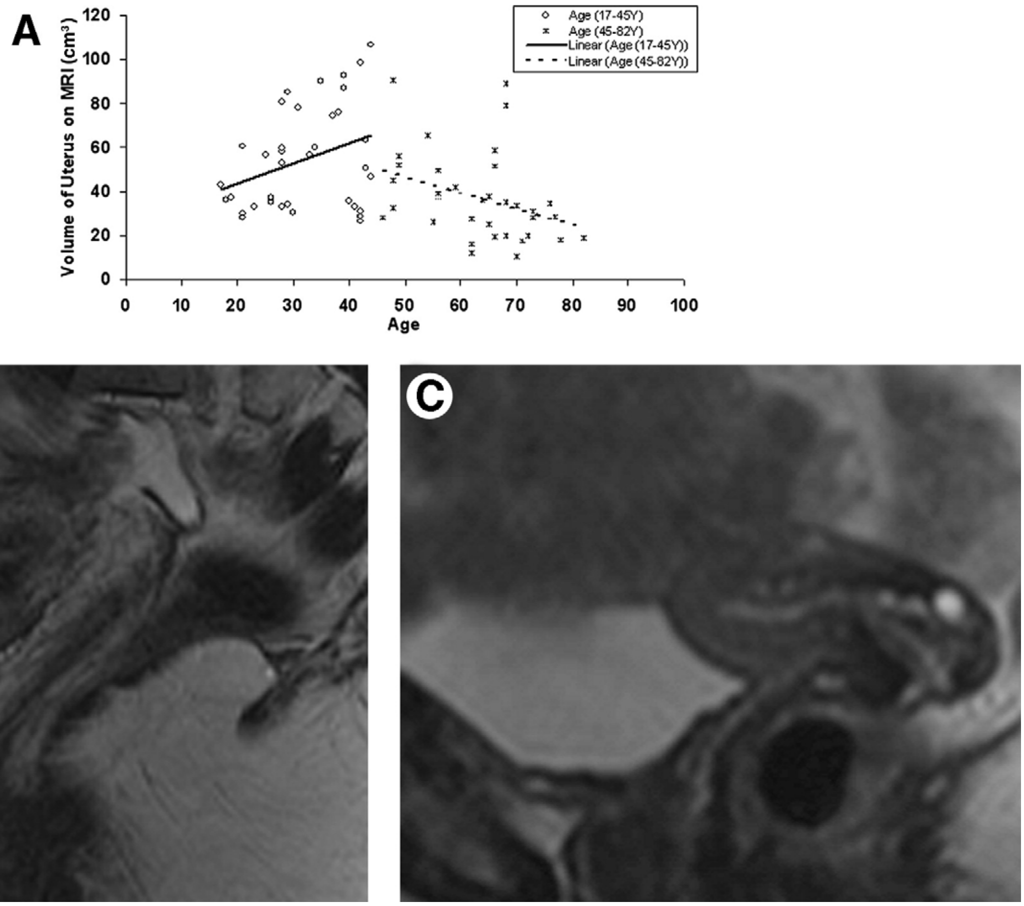

Figure 1 (A) Effect of age on uterine volume as measured on T2-weighted MRI. Sagittal T2-weighted MR images of uteri of 28-year-old woman (B) and 78-year-old woman (C) demonstrate age-related decrease in uterine volume.

testicle on three separate axial slices. SUV_{max} was calculated by the computer for each ROI drawn. The overall SUV_{max} for each subject was then determined by averaging the two highest SUV_{max} values of the 2 testicles.

Data Analysis

The volumes of the uterus, ovary, prostate gland, and testicles, and the SUV_{max} of the testicles were each correlated with age. The data were plotted with Microsoft Excel software (Microsoft Corporation, Redmond, WA). Linear regression curves and statistical analyses were performed with SPSS software version 14.0 (SPSS Inc., Chicago, IL). Pearson correlation coefficients (r), 95% confidence intervals (CI), and 2-tailed P values also were calculated. P values of less than 0.05 were considered to be statistically significant.

Results

Uterus

The MRI volume of the uterus increased from 38.55 ± 3.68 cm^3 at 17 to 19 years of age and reached a peak of 71.76 ± 19.81 cm^3 at 35 to 40 years of age ($P = 0.0009$). This increase with age approached statistical significance ($r = 0.3245$; 95% CI 0.0046 to 0.5902; $P = 0.0535$). After women reached the age of 45, the uterus began a progressive decline in volume with age to reach 24.02 ± 8.11 cm^3 by the eighth decade. This decrease represents a 60% reduction from peak volume. Overall, the uterine volumes statistically significantly decreased with increasing age on MRI of 72 female subjects ($r = -0.33$; 95% CI −0.052 to −0.1063; $P = 0.047$; Fig. 1).

Ovary

The ovaries were visualized bilaterally in 41 of 59 adult subjects ages 13 to 59 years (69.5%) and unilaterally in 18 of the 59 subjects (30.5%). The larger ovary maintained a relatively stable size in early life. It had a volume of 9.46 ± 3.25 cm^3 during the second decade of life and 8.46 ± 3.32 cm^3 by the mid-fourth decade, which were not statistically significant different ($P = 0.2786$). After age 45, ovarian volume declined from 7.46 ± 3.33 cm^3 to 4.44 ± 2.02 cm^3 by the late fifth decade ($P = 0.0039$). The ovaries were not well visualized on MRI in the remaining 72 subjects after the sixth decade of life. Overall, the volume of the larger functional ovary significantly decreased with increasing age ($r = -0.4396$; 95% CI −0.63 to −0.2; $P = 0.0006$; Fig. 2).

Prostate Gland

The total volume of the prostate gland increased from 23.45 ± 6.20 cm^3 during the second decade of life to 47.5 ±

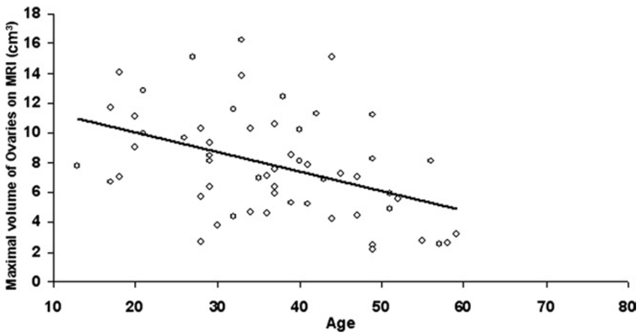

Figure 2 Effect of age on maximal ovarian volume as measured on T2-weighted MRI. Please note that ovaries could not be well-visualized after age 60.

41.59 cm^3 by the late eighth decade. The increase in volume with age was noted to be statistically significant ($r = 0.5054$; 95% CI 0.32 to 0.6535; $P < 0.0001$; Fig. 3). The volume of the central gland of the prostate increased from 9.96 ± 3.99 cm^3 to 29.49 ± 28.88 cm^3 during the same age range, representing a statistically significant increase with age ($r = 0.4232$; 95% CI 0.2229 to 0.5892; $P = 0.0001$; Fig. 3).

Testicle

The mean testicular volume was 11.2 ± 5.9 cm^3. Testicular volume rapidly increased with age from birth to 25 years of age ($r = 0.7108$; 95% CI 0.75 to 0.89; $P < 0.005$). After age 25, there was a significant decline in the volume ($r = -0.24$; 95% CI -0.5 to -0.1; $P < 0.05$; Fig. 4A). The mean SUV_{max} for the testicles was 1.9 ± 0.5. Testicular metabolic activity demonstrated an increasing trend until the age of 35 years ($r = 0.6$; 95% CI 0.2 to 0.78; $P < 0.05$). A plateau in SUV_{max} was observed after the age of 35 years until the age of 65 years ($r = -0.1$; 95% CI -0.35 to 0.17; $P > 0.05$). Subsequently, a slight decrease in SUV_{max} was observed after the age of 65 years ($r = -0.1$; 95% CI -0.38 to 0.1; $P > 0.05$; Fig. 4B).

Discussion

Female Reproductive Changes

The reproductive changes that women undergo with age are well-recognized and documented. Although women's life expectancy has increased significantly in the 21st century, the average time of menopause has not changed from approximately 50 years of age.[8] Thus, women now spend more than one-third of their lifetime in the menopausal period. Menopause and the consequent decrease of estrogen levels are associated with a variety of problems, which can be divided into the following groups (1) vasomotor symptoms including sweating, hot flashes, and palpitations[9]; (2) decreased mental and physical functions, including fatigue, depression, panic disorder, cognitive problems, and decreased libido[10]; (3) car-

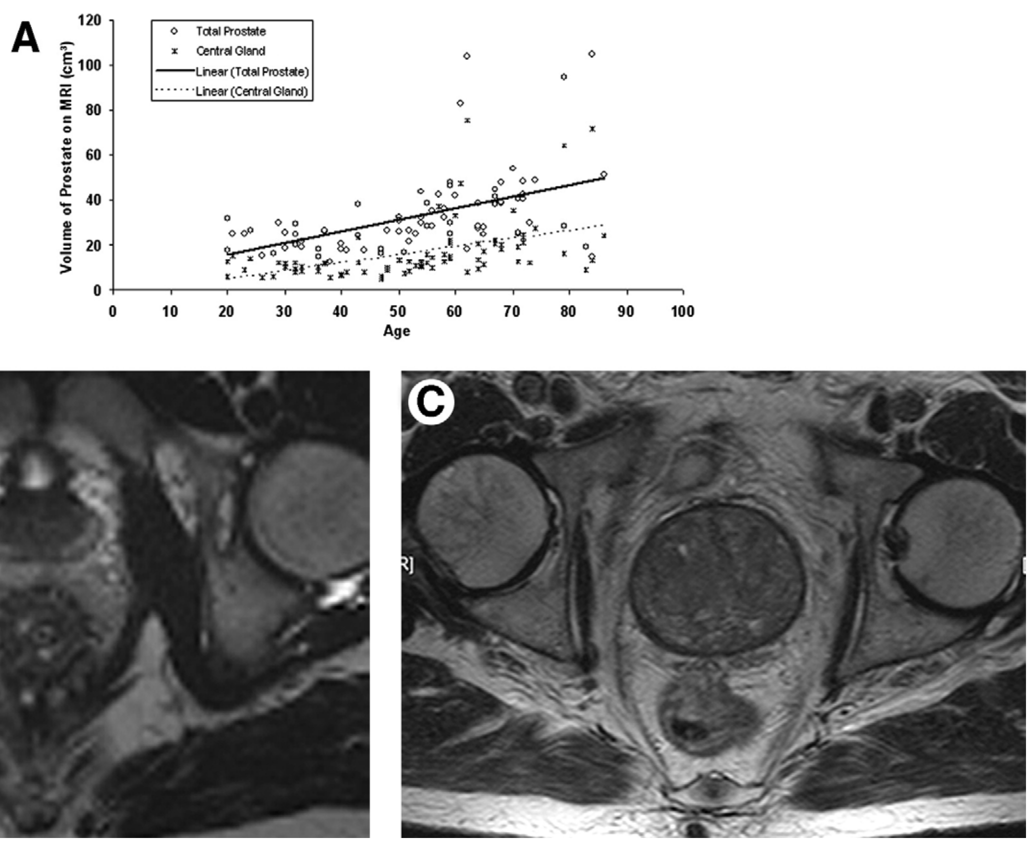

Figure 3 (A) Effect of age on central gland volume and total prostate gland volume as measured on T2-weighted endorectal coil MRI. Axial T2-weighted MR images of prostate glands of a 24-year-old man (B) and a 79-year-old man (C) demonstrate age-related increases in central gland and total prostate gland volumes.

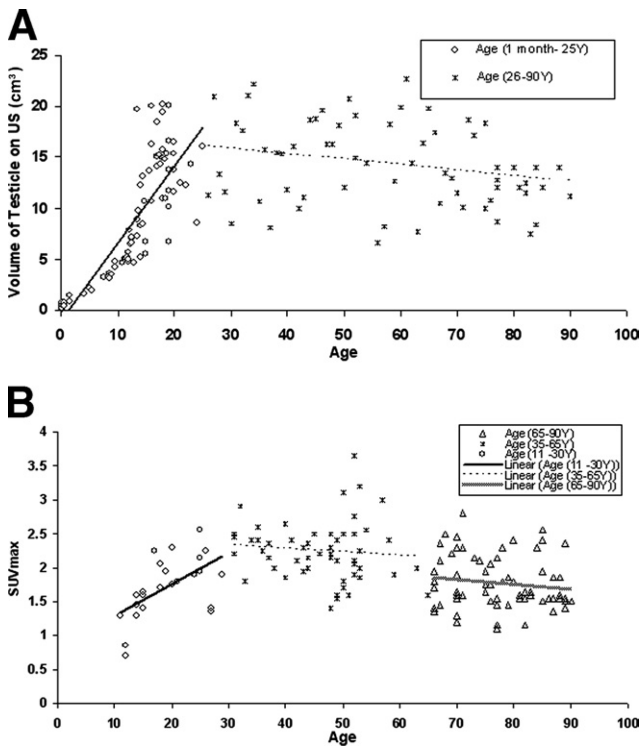

Figure 4 (A) Effect of age on testicular volume as measured by testicular US. (B) Effect of age on SUV_{max} of testicles as measured by ^{18}F-FDG PET.

diovascular disease, including ischemic heart disease[8,11,12]; (4) structural alterations, including endometrial atrophy and osteoporosis[8]; and (5) urogenital symptoms, such as vaginal dryness, incontinence, and cystitis.[13] Aging also increases a woman's risk of developing medical, gynecologic, or obstetric conditions that may impair her fertility. Knowledge of these effects of aging on a woman's reproductive function is important so that physicians and other health care providers can appropriately advise and treat the growing number of women seeking to become pregnant at an advanced reproductive age.[14]

Reproductive function in female mammals requires the precise regulation and coordination of the hypothalamus, pituitary, and ovary. The best characterized aspect of this hormonal axis is the dramatic change in ovarian function, the result of which is a precipitous loss of estrogen and alterations in progesterone secretion with menopause.[15-26] Not as well characterized are the hypothalamic and pituitary level changes that accompany menopause.[27,28] The hormones secreted by the hypothalamus and pituitary may play an important role in the initiation and progression of menopause; for example, gonadotropins have been found to change before ovarian failure and continue to decline after menopause.[27-29]

An increase in miscarriage rates also is evident with advancing age, despite similar implantation rates of donated oocytes and appropriate action of progesterone on the endometrium. The secretion of estradiol and progesterone has been found to occur earlier in pregnancy in women younger than 40 years of age, and points to the changing uterus as a possible source for this increase in miscarriage rates.[30]

Uterus

First-line examination of the uterus can be accomplished with endovaginal US.[31] In some women, this technique may not provide accurate visualization secondary to a vertical orientation of the uterus, marked enlargement of the uterus, or the presence of leiomyomas or adenomyosis.[32] In young girls, the measurement of uterine volume generally has been accomplished using US, and the size of the uterus has been found to increase with chronological age, bone age, and Tanner stage.[33,34]

The use of MRI has become more common as a second-line imaging tool because it provides better tissue contrast and imaging quality, is operator independent, and often allows for a more specific diagnosis to be made.[32] A number of investigators have described the ability of MRI to delineate the normal morphology of the uterus and the layers of the uterine wall.[32,35-40] MRI of the normal uterus and cervix is typically best demonstrated on T2-weighted images,[32,39] and sagittal T2-weighted images without fat suppression provide the best delineation of the zonal anatomy of the uterus. On these images, the endometrium demonstrates high signal intensity, whereas the outer myometrium shows an intermediate-to-slightly high signal intensity. Between these 2 zones, a low signal intensity inner myometrium or junctional zone is visible.[31,32,39] The premenopausal endometrial stripe varies in thickness with the menstrual cycle up to about 16 mm, and the postmenopausal endometrial stripe is typically ≤4 to 5 mm in thickness.[36,38,41-46] The junctional zone is normally ≤12 mm in thickness and is an important landmark to delineate the margins of malignant tumors such as endometrial carcinoma.[32,47-49] Leiomyomas, or fibroids, frequently are seen, particularly in women in their reproductive years, as they are the most common benign neoplasm of the uterus.[32] However, in our analysis, we decided to exclude women with any uterine pathology including leiomyomas, as we felt that inclusion of subjects with leiomyomas would have increased uterine volume measurements, particularly in women in their reproductive years of life. On MRI, leiomyomas are typically well-marginated and low in signal intensity on T2-weighted images.[32,50]

Hauth and coworkers used MRI to examine the uteri of 100 healthy women between 21 to 73 years of age.[32] They found no age-related changes in the uterine position, which typically was anteflexed. The mean volume of the uterus in women with leiomyomas or adenomyosis (MA) was significantly larger (88 cm^3) than in women with neither leiomyomas nor adenomyosis (the NMA group; 48.9 cm^3). The mean volume of NMA uteri increased until the fifth decade and then decreased. In a similar fashion, we found uterine volume to peak in the latter half of the fourth decade of life. Furthermore, they found the cervix to follow the same pattern as the uterus, increasing in volume with age until the fifth decade, and then decreasing after that. More specifically, the cervix had a mean volume of 11.3 cm^3 in the third decade of life, increased in size to 23.1 cm^3 in the fifth decade, and then decreased to 18.4 cm^3 by the sixth to eighth decades. Hauth and coworkers were also able to characterize how volumes of the endometrial, inner myometrial, and outer myometrial zones of the uterus changed with age. The endometrial and inner myometrial zones both increased in thickness in the NMA group until the fifth decade of life to a maximum mean diameter of 7 mm and 8 mm, respectively, and then decreased after that. The outer myometrium did not change significantly with age.[32] These findings contrast with those of Brown and coworkers who found that the inner myometrium maintains its thickness after menopause, whereas the other zones decrease in size.[35]

These results concerning the age-dependent differences in the volume of the uterus and cervix and the thickness of the endometrium and inner myometrium are well explained by the hormonal status of these women. The increase in size of these structures until the fifth decade correlates with the cumulative hormonal effects of estrogen, progesterone, and other hormones over the reproductive years. Conversely, the decrease in volume of the uterus and cervix and a decrease in the thickness of the endometrium and inner myometrium can be explained by the decreasing serum levels of these hormones after menopause.[32] Sonographic studies have revealed similar results. Merz and coworkers found a parity-related increase in uterine size in premenopausal women. After menopause, a significant reduction in the size of the uterus and in the corpus/cervix ratio was found. The amount of reduction in uterine volume was related to the number of years since menopause.[51]

Hauth and coworkers failed to find a change in the volume of the uterus, inner myometrium, or outer myometrium between the follicular and luteal phases of the menstrual cycle.[32] However, others have described an increase in endometrial thickness during the menstrual cycle, and have found it to be significantly thicker in the luteal phase, ranging from 7 to 16 mm in thickness.[36,38,41] Haynor and coworkers reported a significant increase in the myometrium during the follicular phase and a continued, but slower, increase during the luteal phase.[36] However, there did not seem to be any difference in inner myometrial thickness between the follicular and luteal phases.[32,38,39]

Studies using ^{18}F-FDG-PET have found metabolic activity of the uterus to vary with the menstrual cycle as well as decreased uterine metabolic activity after menopause. Lerman and coworkers[6] examined 285 women, of whom 126 were premenopausal and 159 were postmenopasual. In the premenopausal women, 2 peaks of increased endometrial ^{18}F-FDG uptake were identified during the 4-phase cycle. Mean SUV values were 5 ± 3.2 and 3.7 ± 0.9 in menstruating and ovulating patients, respectively, and 2.6 ± 1.1 and 2.5 ± 1.1 in patients in the proliferative and secretory phases, respectively. The mean endometrial SUV in postmenopausal patients not receiving hormonal therapy was 1.7 ± 0.5. Nishizawa and coworkers reported similar findings.[52]

Ovary

Ovarian size changes over the lifespan and has been most extensively studied with US. One study from Cohen and coworkers analyzed ovarian volume in relationship to menstrual status, age, height and weight, pregnancy history, phase of the menstrual cycle, presence of a leiomyomatous uterus, and current pregnancy status.[53] Data were gathered by pelvic or abdominal US, and 725 patients were included in the analysis. Ovarian volumes were determined with the formula for a prolate ellipsoid. Mean ovarian volumes were statistically different for premenarchal, menstruating, and postmenopausal women at 3.0, 9.8, and 5.8 cm^3, respectively. Ovarian volume also was found to significantly differ based on decade of life. The mean volume in the first decade of life was 1.7 cm^3, increased to 7.8 cm^3 in the second decade, and achieved a maximum of 10.2 cm^3 in the third decade. Mean ovarian volume then began to gradually diminish in size to 6.0 cm^3 by the seventh decade. These results are consistent with are own findings of decreasing ovarian size beginning in the fourth decade of life.

Multiple studies have results similar to those of Cohen and coworkers and have found the ovaries to increase in volume with age from premenarche to the menstrual period.[33,34,54] Interestingly, Herter and coworkers noted higher ovarian volumes during the neonatal age and puberty in contrast to those in subjects between 1 month and 7 years of age. In later life, although the ovaries do become smaller with both age and menopause, it seems that menopause is the more decisive factor and that age contributes little over menopause status in predicting ovarian volume.[55]

Nevertheless, a large study found that other significant predictors of ovarian volume other than age and menopause were years since menopause, age at menopause, weight, parity, history of hormone replacement therapy, and history of breast cancer.[56] Cohen and coworkers reported that mean ovarian volume for pregnant women (11.1 cm^3) was found to be significantly larger than for nonpregnant women (9.4 cm^3) and that ovarian volume was found to increase significantly with patient height although without statistical significance.[53] They also reported that mean ovarian volume was not found to differ significantly with respect to the phase of the menstrual cycle, presence of a leiomyomatous uterus, or patient weight.

Hauth and coworkers used MRI to study ovarian changes over the lifespan similar to our analysis. They found the mean volume of both ovaries to increase until 31 to 40 years of age and then continuously decrease. In addition, they found that the mean volume of the largest ovarian follicles increased until 41 to 50 years of age and then decreased. The highest mean numbers of ovarian follicles was seen on the left side in the 21 to 30 year old women, and on the right in the 31 to 40 year old women.[32] Unfortunately, there are disagreements with respect to the size of the normal ovary as well as trends over the lifespan. Although the study by Cohen and coworkers found mean ovarian volume to decrease from 9.8 cm^3 in menstruating women to 5.8 cm^3 in postmenopausal women, reported volumes are lower in other studies. One study examined 115 Swedish women and found the mean volume to decrease from 4.1 cm^3 in menstruating women to 1.2 cm^3 in postmenopausal women.[57]

Unlike the study of Cohen and coworkers, which did not find ovarian volume to differ significantly with phase of the menstrual cycle, another study of 428 women aged 14 to 45 found a difference. It reported that in women not using oral contraceptives, the larger ovary increased in size from the start of the cycle through day 19 after which it declined. In addition, this study found that compared with women who were not using contraceptives, those using intrauterine devices had larger ovaries and those using oral contraceptives had smaller ovaries.[58]

We are not aware of studies using ^{18}F-FDG-PET to compare SUVs of the ovaries over the lifespan. It has been noted that elevated SUVs are not uncommon in premenopausal women for benign reasons, especially with changes in the menstrual cycle.[6,52,59-61] In particular, the SUV of an ovary can normally be elevated during the late luteal and early follicular phases of the menstrual cycle.[52] Such fluctuations in ovarian SUV tend to make interage comparisons difficult. In addition, malignant and functional ovarian lesions often have overlapping SUVs, but increased ovarian uptake in postmenopausal women is often associated with the presence of malignancy.[6]

Male Reproductive Changes

In the past few decades, hormonal and physiological changes with age have been observed in men as well, and have been given the name "andropause" or "androgen decline in the aging male" (ADAM).[62-67] In contrast to women, in whom ovarian failure is predictable and clinically obvious, the signs in men are variable and have a more subtle clinical manifestation. Observed changes include loss of libido and erectile function[68,69]; loss of lean body mass[70]; a decrease in insulin sensitivity[71]; a decrease in bone mineral density resulting in osteoporosis[72,73]; depression, irritability, loss of memory[74]; fatigue[75,76]; anorexia[77,78]; and vasomotor symptoms. True andropause is more clinically obvious and is frequently seen in patients receiving either surgical or chemical androgen ablation therapy for prostate cancer.[79] In these patients, signs and symptoms were treated through the administration of testosterone.[1]

In men, hypothalamic–pituitary–gonadal function progressively declines with age. Studies describe decreases in serum testosterone, free testosterone, and the ability of the testes to secrete testosterone after stimulation as well as increases in luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), and estradiol concentrations with age.[80-84] Although testosterone production increases rapidly at the onset of puberty and then remains stable, it dwindles quickly after age 50 to 20 to 50% of peak levels by age 80.[1,63] During the period of decline, longitudinal studies have shown that total testosterone concentration decreases by up to 1% per year.[85,86] A double-blind, placebo-controlled, randomized clinical trial of recombinant human chorionic gonadotropin improved muscle strength and physical function and activity in older men with partial age-related androgen deficiency, supporting the concept of andropause.[2]

Nevertheless, alterations in sex steroid and hormone levels with age are not ubiquitously found. A study by Carreau and coworkers evaluated the hypothalamic–pituitary–gonadal axis in 3 groups of men aged 60 to 69, 70 to 79, and 80 to 91 years by measuring the intratesticular concentrations of several steroids (pregnenolone, progesterone, dihydroepiandrosterone, testosterone, and estradiol) and serum levels of FSH, LH, testosterone, estradiol, and SHBG. No significant changes in serum hormone and SHBG concentrations or in testicular steroid contents among the three groups of patients were found. However, the mean serum SHBG level was three times higher in the oldest men than in the other groups, and a positive correlation between patient age and serum SHBG was observed.[87]

Testicle

Our findings regarding age-related changes in testicular volume and metabolism correlate with those of the concept of andropause. Decreases in metabolic activity beginning in the sixth decade of life and decreased testicular volume in the early seventh decade may well be due to the observed hormonal changes which occur in this time period. Other studies also point toward testicular changes over the lifespan. A large study by Beres and coworkers analyzed data from 1985 males aged 0 to 28 years. Data for comparison were obtained from a Hungarian gypsy sample and a nongypsy sample. Whereas at the ages of 0 to 9 years testicular volume did not show any notable variation, there was a conspicuous and rapid (approximately 10-fold) increase in volume between 10 to 15 years. The maximum testicular size was attained among the nongypsies at ages 17 to 18 and among the gypsies at ages 21 to 22 years. The average testicular volume for every age group older than 19 to 20 years was greater in the gypsy sample than in the nongypsy sample, and in each group from the start of puberty, the right testis was bigger on average than the left.[88] Aside from illustrating the rapid increase in testicular size that occurs with puberty, Beres and coworkers also showed that differences may exist between different ethnic groups and environments. Studies of men of other ethnicities have noted differences as well.[89,90]

There are other differences between the testicles of prepubertal and pubertal men. The echogenicity of the prepubertal testis appears markedly reduced compared with the medium level echogenicity of the mature testis.[91] The mean testicular arterial impedance was found to be decreased in pubertal and postpubertal boys in comparison to prepubertal boys as well.[92]

Ng and coworkers determined that older men tended to have lower semen volume and total sperm output than younger men. In addition, older men had more abnormal sperm morphology with fewer normal forms and reduced vitality as well as more cytoplasmic droplets.[93] Pasqualotto and coworkers conducted a study with 889 normal men to evaluate how sperm production, hormone levels, and testicular volume change with age.[94] The youngest patients were 24 to 30 years old, and thereafter were grouped in 5-year age range increments with the oldest group being those older than 45. There were no differences between patients of various age with respect to levels of LH, testosterone, or testicular volume. Changes noted with increasing age included increases in serum FSH and decreases in sperm concentration, sperm motility, and semen volume. Normal semen morphology, by World Health Organization criteria, was significantly lower in men older than the age of 45 than in younger men. It should be noted that although a variety of other studies have similarly found decreases in semen volume with age,[93,95-97] several others have differed from Pasqualotto and coworkers in finding no association or even an increase in sperm concentration with age.[95,97-100]

A variety of changes may explain the age-associated decreases in semen quality. Cellular and physiological changes with age have been described in the testicles, seminal vesicles, prostate gland, and epididymis.[94] Age-related narrowing and sclerosis of the testicular tubular lumen decreases spermatogenic activity and increases degeneration of germ cells, and fewer and less functional Leydig cells have been reported in autopsies of men who died from accidental causes.[101] Other age-related changes in the human testicle include reduced tubular length, increased thickness of tubular boundary tissue, focal mononuclear orchitis, and dilation of the rete testis. Testicular parenchymal weight, proportion of testicle occupied by seminiferous epithelium, and volume of seminiferous epithelium are significantly reduced in aged men.[81] There also may be decreases in the Sertoli cell population.[102] Smooth muscle atrophy and a decrease in protein and water content, which occur in the prostate gland with age, also may contribute to decreased semen volume and sperm motility. Also, the epididymis, a hormonally sensitive tissue, may undergo age-related changes. This hormonal or epididymal senescence may lead to decreased sperm motility in older men.[94]

Although the study by Pasqualotto and coworkers did not find testicular volume to change with age, there were very few patients who were older than the age of 50. Our study and others, by including subjects in their eighties and nineties, have found testicular volume to decrease with age as well as with malnutrition, alcoholism, malignancy, and chronic terminal illness. Diabetes mellitus, drug use, and pelvic injury were not associated with decreased volume.[103,104]

Our study found the SUV_{max} of the testicles to increase through to the mid-50s, after which point it declined. A previous study using only 8 patients similarly found an inverse correlation between age older 50 years and testicular SUV.[105] Knowledge of the metabolic activity of the testicle is important because testicular carcinoma is the most common solid malignancy in male adults younger than age 30. The differentiation of pathology from normal metabolic change at an early stage is very important because early therapy may result in long-term survival of 50 to 90%.[106] Our results regarding the age-related testicular metabolism in young adults as quantified on ^{18}F-FDG-PET can be used as a normative baseline reference for future studies regarding testicular metabolism.

Prostate Gland

In men of reproductive age, the prostate gland functions by providing nutrients and optimizing the ionic and pH environment for sperm in the seminal fluid. The normal prostate gland reaches a weight of approximately 20 g in men aged 21 to 30 years, and unless benign prostatic hypertrophy (BPH) develops, this weight remains essentially constant.[107,108] As the individual ages, there is an increased likelihood of BPH and of problems which accompany this age-related nodular transitional zone enlargement and prostatic overgrowth.[109] BPH is present in 20% of men at 40 years of age and progresses to 70% at 60 years of age.[110] Often, this interferes with urination and causes lower urinary tract symptoms in up to 50% of elderly men. Other complications of urodynamic compromise include bladder hypertrophy, urinary tract infections, postvoid residuals, upper urinary tract changes, and urinary retention. As such, one of the most frequent interventions in elderly men is transurethral resection of the prostate, with a lifetime risk for surgery of approximately 25% to 30%.[109]

The prostate is a fibromuscular gland surrounding the prostatic urethra at the bladder base within the extraperitoneal space.[111,112] It has an apex and a base, where the prostatic apex is inferiorly located and the prostatic base is superiorly located. Furthermore, the prostate gland may be separated into several zones. The peripheral zone is located posteriorly within the prostate from the base of the verumontanum to its apex, the transitional zone surrounds the proximal prostatic urethra, and the central zone surrounds the transitional zone at the prostatic base and the ejaculatory ducts. The peripheral zone, central zone, and transitional zone constitute 70%, 25%, and 5% of the prostate gland, respectively, and the central gland of the prostate is composed of the central zone and transitional zone.[111,113,114]

Histologically, the prostate can be divided into the fibromuscular part (stroma) and the parenchymal or glandular part (epithelium plus lumen).[115,116] BPH is typified by hyperplasia of glandular and stromal tissues surrounding the urethra with nodular growth where the ejaculatory ducts enter into the transitional or periurethral zones of the prostate.[109] There are a variety of alterations at the cellular level as well including basal cell hyperplasia, enhanced extracellular matrix deposition, reduced elastic tissue, increased infiltrating lymphocytes around ducts, acinar hypertrophy, and more luminal corpora amylacea and calcifications in the form of prostatic calculi, along with increased stromal mass, particularly of the amount of smooth muscle cells.[117]

Although the exact etiology of BPH remains poorly understood, it is generally accepted that the presence of circulating androgens and advancing age both play a role. A variety of other observations have been made in an attempt to explain its etiology. There are alterations of the autonomic nervous system in the aging prostate gland, including a decrease of nerves of the enkephalinergic and nitrinergic systems, both of which mediate smooth muscle cell relaxation.[109,118-121] Local sex-steroid hormones may play a role as well. Studies indicate that bioavailable prostatic testosterone levels decrease with age and that the prostatic estradiol/bioavailable testosterone ratio increases in patients with BPH.[122,123] 5-alpha reductase type 2 converts testosterone to the more potent dihydrotestosterone, is found in the prostate gland in stromal fibroblasts and in basal epithelial cells, and has been found to show greater activity in BPH than in normal tissue.[124] Other factors reviewed by Untergasser and coworkers include alterations in epithelial/stromal cell interactions, alterations in luminal/epithelial cell interactions, and increased inflammation.[109]

Our findings of increased prostate gland volume with age are in agreement with a number of studies based on histological,[115] MRI,[125,126] and US measurements of volume.[127-130] Arenas and coworkers studied the prostate glands at autopsy of 281 men aged 20 to 84 years who died in traffic accidents, which were classified as histologically normal ($n = 182$), with nodular hyperplasia ($n = 42$), with intraepithelial neoplasia ($n = 40$), or as carcinomatous with low Gleason grade ($n = 20$). Each prostate gland was divided into three regions (periurethral, central, and peripheral), and the volume of each region, as well as the average volume occupied by stroma and epithelium in each region, was quantified. There were no histologically normal prostate glands in men over 70 years of age. Prostate glands with prostatic intraepithelial neoplasia (PIN) and carcinoma were observed in subjects in as early as the third decade of life, and nodular prostatic hyperplasia was seen in subjects starting in the fourth decade. Among the normal prostate glands, total volume was found to increase from about 24 cm^3 to 36 cm^3 between the third and fifth decades of life, and decreased to about 29 cm^3 in the sixth decade. The periurethral and peripheral regions followed a similar pattern, increasing through the fifth decade and then decreasing in the sixth decade, whereas the central region increased through the sixth decade. The volume of the stroma in the peripheral and central regions increased progressively with advancing age, while the stroma of the periurethral region increased only through the fifth decade. The volume of the epithelial tissue as well as the abnormal tissues followed a more complicated course. The histologic data from Arenas and coworkers point toward a decrease in the total volume of the prostate gland in late life, which differs from our findings.[115]

Other imaging studies support our finding that prostatic volume increases in elderly men as well. An MRI study by Williams and coworkers suggests that there is an age-related increase in prostatic growth rate that peaks between 56 to 65 years of age, and which declines thereafter. The mean overall prostatic growth rate between subjects ages 30 to 71 was found to be 2.36 cm^3 per year whereas between 56 to 65, it was 4.15 cm^3. They found that the growth rates of the central zone followed a similar trend.[126]

In a study of 1601 males (1301 normal subjects and 300 BPH patients) ranging from birth through 92 years of age, Xia and coworkers used US to further refine the growth stages of the prostate gland. They found that prostatic volume growth could be categorized into 4 life stages: (1) the first slow-growing phase (from 0 to 9 years) during which the prostate grows slowly at a rate of 0.14 g per year; (2) the first rapid-growing phase (from 10 to 30 years), during which the prostate grows at a rate of 0.84 g per year; (3) the second slow-growing phase (from 30 to 50 years), during which the prostate grows at a rate of 0.21 g per year; and (4) the second rapid-growing phase (from 50 to 90 years). This study also reported that the prostate gland growth rate was 0.50 g per year in normal subjects and 1.20 g per year in patients with BPH.[130]

Allen and coworkers used MRI to study the prostatic volume of 40 men between 17 and 74 years of age and found that both the central and peripheral zones enlarged with age. As in our study, they found that the central gland expanded more rapidly than the peripheral zone. Between the second and eighth decades of life, the central gland enlarged by 175% and the peripheral zone grew by 67%. In addition, they found that the anterior fibromuscular stroma decreased and became thinner with increasing gland size, and that the periprostatic venous plexus became less prominent with increasing age.[125] A study by Vesely and coworkers used transrectal US to measure the size of the prostate gland. A statistically significant-but-weak correlation was found between prostate volume and age. Prostatic volume was found to increase from 27.53 cm^3 in subjects measuring 54 to 48.24 cm^3 in those older than 80 years.[127]

In patients with BPH, increases in prostate volume have been found to correlate with an increased risk of disease-specific morbidity such as acute urinary retention and the need for surgery.[127,131] Serum levels of prostate-serum antigen have been found to correlate directly with prostate gland volume in patients with lower urinary tract symptoms and BPH.[127,132-134] Nevertheless, it seems that the association between lower urinary tract symptoms and prostate gland volume is weak.[127,135]

We are not aware of studies using ^{18}F-FDG-PET to compare SUVs of the prostate gland over the lifespan, which may in part be due to difficulties in measuring the SUV of the prostate related to excreted ^{18}F-FDG within the adjacent urinary bladder.

Limitations

Limitations of our preliminary data include their retrospective nature, a small study sample, a potential for sampling error in our measurements, and the inability to obtain height, weight, menstrual cycle, and hormone-replacement therapy status information in the majority of subjects. Despite these limitations, we believe that our data provide useful information for those interested in studying changes in the reproductive end organs with normal aging and provide a basic methodological approach for future study of normal structural and functional changes in these organs with aging.

Conclusions

We have presented preliminary quantitative data regarding changes in volume of the uterus, ovaries, prostate gland, and testicles across a large age range through use of MRI and US, as well as age-related changes in the metabolic activity of the testicles with age as detected by ^{18}F-FDG PET. Such data can be used as a normative baseline to assess subjects of any age in the clinical setting who undergo pelvic US, MRI, or ^{18}F-FDG PET, and may serve as an aid to those investigators involved in research related to the aging process. We have also reviewed the literature with regards to the normal age-related changes in structure and function of these pelvic reproductive end organs. It is our hope that this information will be useful to clinicians and investigators as a starting point to evaluate the structure and function of these organs for clinical and research purposes.

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