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Assessment of Age-Related Changes in Abdominal Organ Structure and Function With Computed Tomography and Positron Emission Tomography

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With the size of the aged population in the United States expected to grow considerably during the next several decades, the number of imaging studies performed on such aged individuals will similarly increase. Thus, it is important to understand normal age-related changes in the structural and functional imaging appearance of the abdominal organs. We therefore present preliminary data and a review of the literature relevant to structural and functional changes in the abdominal organs of children and older adults. In a retrospective study of both adult and pediatric populations, we used computed tomography (CT), positron emission tomography (PET), and PET/CT imaging to investigate age-associated changes in size, attenuation, and metabolic function of the abdominal organs. Organs of interest include the liver, spleen, pancreas, kidneys, adrenal glands, stomach, small bowel, colon, and rectum. Although volumes of adult liver, spleen, pancreas, and kidneys do not change significantly with age, adult left and right adrenal gland volumes do significantly increase with age ($r = 0.2823$, $P = 0.0334$, and $r = 0.3676$, $P = 0.0049$, respectively). Also, the attenuation of adult liver ($r = -0.2122$, $P = 0.0412$), spleen ($r = -0.4508$, $P < 0.0001$), pancreas ($r = -0.5124$, $P = 0.0007$), and left and right adrenal gland ($r = -0.5835$, $P < 0.0001$ and $r = -0.6135$, $P < 0.0001$, respectively) decrease significantly with increasing age. Every organ studied in the pediatric population demonstrates a positive association between organ volume and age. Significant age-related changes in organ function are noted in the adult liver and small bowel, with the liver demonstrating a positive association between metabolic activity and age ($r = 0.4434$, $P = 0.0029$) and the small bowel showing an inverse association between mean small bowel standardize uptake value and age ($r = -0.2435$, $P = 0.0174$). Also, the maximum overall small bowel and colon metabolic activity in children increases with age ($r = 0.6478$, $P = 0.0008$). None of the other organs studied (ie, spleen, pancreas, adrenal glands, stomach, colon, rectum) demonstrate significant changes in metabolism with advancing age. The metabolic volumetric product (calculated as the product of organ volume and mean organ SUV) of the liver and spleen does not change significantly with age. In conclusion, various abdominal organs demonstrate differential changes in volume, attenuation, and/or metabolism with increasing age in pediatric and adult populations.

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With the possible exception of stem cells and neoplastic cells, aging is a nearly universal process that, through functional decline, leads to cell death and, eventually, death of the organism. The 77 million members of the "baby boomer" generation are beginning to enter their seventh decade of life, and age-related spending, including that related to health care costs, pension programs, and other such age-

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associated expenses, is projected to increase from 11.2% of the United States gross domestic product in 2000 to 16.7% in 2050.[1] Despite the commonness of aging and its likely future impact on the U.S. economy and health care system, relatively little is known about or agreed on regarding the causes and basic effects of normal aging.

Tietz and colleagues contend that more research is necessary to set reference values for interpreting medical information related to older individuals.[2] These researchers further suggest that changes associated with normal age may be misinterpreted as abnormal if compared with reference values derived from younger populations of individuals. Studies of changes associated with normal aging also are needed because the growing, aging population will result in an increase in the numbers of surgical procedures performed on older individuals. An understanding of the changes in organ structure and function with age is thus crucial to better understand, for instance, the amount of liver that can be resected in an elderly patient while allowing for adequate hepatic function postoperatively.

Various imaging modalities from ultrasonography (US) to computed tomography (CT) to magnetic resonance imaging (MRI) have been used in the past to evaluate the structures of single or multiple abdominal organs, with some studies comparing changes in structure with age. Several researchers have established that CT and MRI are accurate means of measuring hepatic volume in both pediatric and adult populations.[3-6] CT and MRI also have been shown to accurately determine splenic, pancreatic, and renal volumes while less accurately assessing adrenal volume.[5-8] In the current study, CT was used to evaluate the volume of abdominal organs.

Positron emission tomography (PET) enables one to evaluate tissue function that, to this point, largely has been ignored in studies formally investigating changes in abdominal organ function with age. Past studies of abdominal organ function generally have focused on one or a few organs and have judged functionality using a variety of measures such as organ blood flow or organ secretions. For example, assessments of liver function in humans and animals have relied on, among other things, hepatic blood flow measurements, liver function tests, and biliary secretions.[2,9-13] Liver scintigraphy also has been used to assess function.[14,15] Changes in splenic, pancreatic, and adrenal function have been evaluated using a variety of tests, some of which are similar to those used to evaluate liver function. In assessing the functionality of the various segments of the gastrointestinal tract, including the esophagus, stomach, small bowel, colon, and rectum in relation to age, researchers have relied not only on measurements of blood flow and secretions but also on measurements of sphincter pressure, electrical activity, and transit time. ^{18}F-fluorodeoxyglucose (FDG)-PET was used in the current study to quantitatively assess for changes in organ metabolism with age.

Overall, the aim of our study is to quantitatively evaluate for the normal changes in size, CT attenuation, and FDG-PET metabolic function of the abdominal organs from birth to old age. Organs of interest include the subdiaphragmatic hollow gastrointestinal system as well as the solid organs (liver, spleen, pancreas, adrenal glands, and kidneys) within the abdomen. The scope of organs evaluated as well as the range of the subject ages included in this study is larger than those of previous studies. Furthermore, although researchers have used CT to assess for changes in organ size with age, neither PET nor PET/CT have, to our knowledge, been previously used to assess for changes in organ function associated with normal aging. We therefore hope that this preliminary study will contribute to a better understanding of the age-related changes of size, attenuation, and metabolic function of the abdominal organs and serve as a starting point for future prospective research related to this topic of interest.

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 (HUP) and the Children's Hospital of Philadelphia's (CHOP) Institutional Review Boards before study initiation.

FDG-PET and CT Sample Population and Image Data Acquisition

Adult subjects included in this study were gathered retrospectively from subjects who were imaged at HUP from January 2005 through October 2006. Pediatric subjects were retrospectively gathered from a pool of subjects imaged at CHOP and HUP during the same time period. Each participant's age at the time of his or her imaging study was recorded. CT images were viewed and manipulated using our radiology picture archiving and communications system (PACS) workstation (Centricity; GE Healthcare, Milwaukee, WI), whereas a dedicated workstation (PETView; Philips Medical Systems, Bothell, WA) was used to work with PET images and another dedicated workstation (Syntegra; Philips Medical Systems) was used to evaluate PET/CT images.

For the evaluation of organ volume and liver and spleen function in adults, subjects whose abdominal contrast-enhanced CT and FDG-PET imaging had occurred within 90 days of each other in 2005, whose imaging studies included the entirety of each organ of interest (ie, liver, spleen, pancreas, adrenal glands, and kidneys for CT; liver and spleen for FDG-PET), and whose relevant abdominal organs were interpreted by diagnostic radiologists and nuclear medicine physicians to be normal, were included in this study as long as they had not received chemotherapy within the previous 3 months. At HUP, the abdominal CT scans used to determine the organ volumes of 57 subjects (33 men, 24 women; ages 18-81 years) were performed in a supine position with intravenous contrast material. Multidetector CT scanners with 4, 16, or 64 detector rows or single-detector CT scanners were used, and axial images were reconstructed from the multidetector and single-detector units with 5-mm and 7-mm slice thicknesses, respectively.

At CHOP, 41 pediatric subjects (ages 1 month to 17 years) whose CT scans included the entirety of each organ of inter-

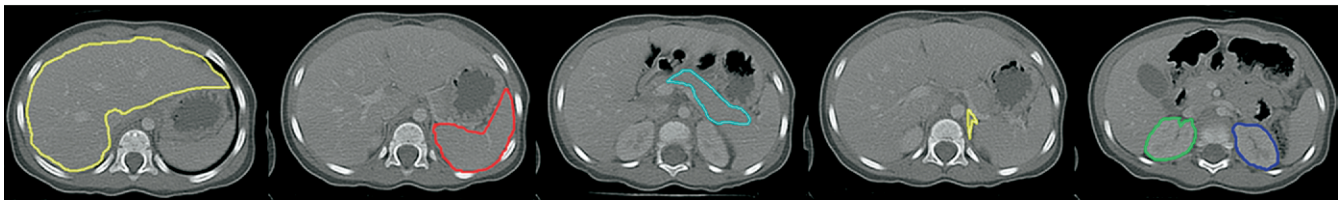

Figure 1 Axial contrast-enhanced abdominal CT images of subject demonstrating freehand ROI tracings of abdominal organ contours for volume calculation.

est (ie, liver, spleen, pancreas, adrenal glands, and kidneys), whose relevant abdominal organs were interpreted by diagnostic radiologists as normal, and who had received no chemotherapy within the previous 3 months were included in this study. The abdominal CT scans used to determine the pediatric organ volumes were performed in a supine position after the administration of intravenous contrast material. A multidetector CT scanner with 16 detector rows was used to acquire the images, and axial images were reconstructed with slice thicknesses of between 3 and 6.5 mm.

Organ Volume Calculation Procedure

Organ volumes in both adults and children were then assessed using freehand region of interest (ROI) tracings of the outer contour of each organ on axial CT slices (Fig. 1). The cross-sectional areas of each organ ROI were automatically calculated by the PACS and recorded. Sums of these cross-sectional areas were subsequently calculated for each organ and multiplied by the slice thickness to provide organ volumes. The volumes of the right adrenal gland and pancreas of one pediatric subject were not measured because of poor organ visualization secondary to poor contrast enhancement.

FDG-PET Sample Population and Imaging Protocol

FDG-PET images used to determine the metabolic function of the liver and spleen of a sample of 43 of the 57 adult subjects (22 men, 21 women; ages 19-81 years) were acquired at HUP using 1 of 2 dedicated whole-body scanners (Allegro; Philips Medical Systems, or C-PET; ADAC UGM Medical Systems, Milpitas, CA). As per the routine FDG-PET clinical protocol at HUP, all subjects fasted for at least 4 hours before their FDG-PET scan and, shortly before the injection of the FDG radiotracer and received fingerstick blood glucose measurements to ensure that their serum glucose levels were $<$140 mg/dL at the time of radiotracer injection. Subjects also were asked to empty their bladders before the PET scan. After injection of 140 μCi/kg (5.2 MBq/kg) of FDG radiotracer through an intravenous indwelling catheter inserted into an antecubital vein and during the 1-hour postinjection FDG uptake period, subjects rested in a comfortable chair. PET was then initiated after this rest period. Sequential overlapping scans were acquired from the base of the skull to the mid-thigh, including the neck, chest, abdomen, and pelvis. Transmission scans using a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed using an iterative reconstruction algorithm, and attenuation-corrected images were utilized to measure the standardized uptake value (SUV), a quantitative measure of metabolic activity, of the liver and spleen.

Solid-Organ SUV Measurement From FDG-PET

Hepatic mean SUV was measured by placing an ROI 500 $\pm$ 50 mm^2 in area in an axial slice of liver with a near-maximal cross-sectional area and whose radiotracer intensity and homogeneity were representative of those demonstrated in the liver as a whole. To measure splenic mean SUV, an ROI 100 $\pm$ 50 mm^2 in area was placed in an axial slice of spleen that had a near-maximal cross-sectional area and whose radiotracer intensity and homogeneity were representative of the characteristics of the remainder or the spleen. The metabolic volumetric product (MVP), a quantitative measure that takes into account an organ's volume and metabolism, was then calculated for the liver of each subject by multiplying the hepatic volume by the hepatic mean SUV. Similarly, splenic MVPs also were calculated for subjects in this same sample population.

FDG-PET/CT Sample Population and Imaging Protocol

To evaluate the CT attenuation in Hounsfield units of the liver, spleen, and kidneys, 93 subjects (50 men, 43 women; ages 14-83 years), each of whom had received no chemotherapy in the 3 months before their imaging study, had received whole-body FDG-PET/CT scans performed at HUP in April 2006 through October 2006 using a 16 detector row LYSO PET-CT (Gemini TF; Phillips Medical Systems, Bothell, WA) that included the entirety of each organ of interest, and had relevant abdominal organs interpreted by diagnostic radiologists and nuclear medicine physicians as normal, were evaluated. The same inclusion and exclusion criteria and equipment were used in selection of subjects for measurement of the attenuation of the pancreas (88 subjects, 47 men and 41 women; ages 14-83 years) and adrenal glands (50 subjects, 26 men and 24 women; age 14-83 years).

During each scan, a scout image was first obtained for subject localization. Then, 60 minutes after the intravenous administration of a 215 μCi/kg (7.9 MBq/kg) dose of FDG and after the administration of oral contrast material, CT images were obtained using a low-dose protocol (50-150 mAs) with a 5-mm slice thickness. Subsequently, 3D PET

data were then gathered using 3-minute table positions. The PET acquisition included time-of-flight and dead-time correction; online delayed coincidence subtraction also was used to correct for random coincidences. Rescaled CT images were applied to produce attenuation-correction values for the PET image reconstruction.

Organ metabolic activity was assessed using the same PET/CT scanning protocol and ROI placement used in determining organ attenuation, and similar inclusion and exclusion criteria applied previously in selecting subjects for organ attenuation measurement also were applied for the selection of subjects for measurement of the metabolic function of the pancreas, adrenal glands, stomach, small bowel, colon (including the ascending, transverse, descending, and sigmoid segments), and rectum. One additional exclusion criterion was applied in selecting subjects for this portion of the study: subjects with PET/CT images interpreted as showing significant diverticulosis of the colon were excluded. Overall, the SUVs of the pancreas and adrenal glands of 38 subjects, the stomach of 96 subjects, the small bowel of 95 subjects, and the colon and rectum of 97 subjects (of a total of 97 subjects; 52 men, 45 women; ages 14-83 years) were evaluated.

Organ CT Attenuation Measurement From FDG-PET/CT

CT attenuation of each organ was measured by placing ROIs in each organ while using specific guidelines to direct the size, placement, and number of the ROIs used for each organ. For the liver, 4 ROIs, each 800 ± 100 mm^2 in area, were placed on axial slices of liver, avoiding the inclusion of large vessels or ducts. An ROI was placed on a slice 3 to 5 slices inferior to the superior-most cross-sectional slice of liver, a second ROI was placed posteriorly in the slice of the liver that had a near-maximal cross-sectional area, a third ROI was placed in the slice of liver 5 slices superior to the inferior-most slice, and the last ROI was placed in the left lobe in the slice in which the left lobe had the largest cross-sectional area. The average of the attenuation values of these ROIs was then recorded.

Splenic attenuation was determined by placing 2 ROIs, each 800 ± 100 mm^2 in area, on axial slices of the spleen, with care to avoid including splenic vessels. One ROI was placed on a slice 3 to 5 slices inferior to the superior-most cross-sectional slice of spleen, whereas another ROI was placed at the level of the hilum. The average of these 2 attenuation values was recorded. Pancreatic attenuation was assessed by placing 2 ROIs, each 100 ± 10 mm^2 in area, in the pancreas, with one in the pancreatic head and another in the pancreatic body at the level of the splenic artery.

Finally, attenuation values of the adrenal glands was calculated by placing a ROI, 10 ± 2 mm^2 in area, in each of the adrenal glands at a level in which the adrenal gland cross-sectional area was near-maximal. Kidney attenuation was determined for each kidney by placing 3 ROIs, each 100 ± 10 mm^2 in area, on axial slices of the kidney with care to avoid including the renal hilum. One ROI was placed on a slice 3 to 5 slices inferior to the superior-most cross-sectional slice of kidney, while another ROI was placed near the level of the renal hilum. The final ROI was placed on a slice 3 to 5 slices superior to the inferior-most cross-sectional slice of kidney. The average of these 3 attenuation values was then recorded.

Organ SUV Measurement From FDG-PET/CT

The mean and maximum SUV measurements for the pancreas were determined by placing round ROIs, 100 ± 10 mm^2 in area, in both the head and tail of the pancreas of each subject on axial images. The mean and maximum SUV measurements for the right and left adrenal glands were determined by placing a round ROI, 10 ± 2 mm^2 in area, in each adrenal gland of each subject on the axial slice at which the cross-sectional area of the gland was near maximal. Gastric mean and maximum SUVs were determined by placing 5 freehand ROIs on axial images of the stomach, with care made to include the fundus, body, and antrum of the stomach at least once each. Small bowel mean and maximum SUV measurements were determined by placing 5 freehand ROIs in the mid-abdomen as observed on coronal views, avoiding the inclusion of colon and other surrounding abdominal and pelvic structures. Colonic mean and maximum SUV measurements also were derived from coronal images, with 5 freehand ROIs placed over each of the ascending, transverse, descending, and sigmoid colon segments. Rectal mean and maximum SUV measurements were determined from sagittal images with 5 freehand ROIs placed over the rectum.

Pediatric Bowel SUV Measurement From PET

Mean and maximum overall bowel metabolic activities also were collected from PET images of a largely pediatric group (23 subjects; ages 2-21 years, median age 13). These data were gathered by placing 5 freehand ROIs in the midabdomen, as observed on coronal views. In placing these ROIs, care was taken to avoid including the liver and other surrounding abdominal and pelvic structures.

Subject Assessment of Approximate Lumbar Spinal Height From CT

To evaluate the role of subject height on abdominal organ size, particularly because subject height was not recorded at the time of imaging for each subject, a substitute measure in place of subject height was sought that could be easily ascertained from the image data provided. The approximate height of the lumbar spine was used for this purpose because the lumbar spine was included on all abdominal CT imaging. This height was determined by measuring the distance in millimeters between the superior-most slice on which the L1 pedicle was visualized on the axial CT image and the inferior-most axial slice on which the L5 vertebra was visualized but without visualization of the sacrum. These lumbar spinal heights were determined for each of the 59 adult patients whose abdominal organ sizes were evaluated using CT. The same procedure was used to determine lumbar spinal height in the 41 children studied with CT imaging. Normalized

Table 1 Changes in Solid Abdominal Organ Volumes on Contrast-Enhanced CT With Age

Organ	Ages (Years)	Mean ± SD	Volumes (mL), Range	Pearson *r*	*P* Value
Liver	0-8	488.49 ± 295.87	131.53-1292.73	0.7523	<0.0001
	9-17	1040.66 ± 344.96	203.83-1732.54		
	18-49	1606.63 ± 386.62	1005.60-2596.17	−0.1268	0.3473
	50-81	1467.27 ± 397.77	650.13-2558.90		
Spleen	0-8	77.72 ± 64.41	10.50-259.40	0.7268	<0.0001
	9-17	174.79 ± 69.99	61.99-367.82		
	18-49	234.17 ± 84.39	101.19-439.38	−0.0528	0.6965
	50-81	213.09 ± 95.85	65.52-483.65		
Pancreas	0-8	18.32 ± 8.31	3.93-30.39	0.7763	<0.0001
	9-17	49.97 ± 18.16	23.74-88.82		
	18-49	98.79 ± 80.84	36.68-392.58	−0.0836	0.5364
	50-81	85.12 ± 57.85	24.21-365.38		
Left adrenal	0-8	0.76 ± 0.40	0.17-2.00	0.6490	<0.0001
	9-17	1.88 ± 1.14	0.37-4.08		
	18-49	3.89 ± 2.55	1.28-13.65	0.2823	0.0334
	50-81	5.42 ± 2.77	1.84-13.04		
Right adrenal	0-8	0.74 ± 0.47	0.26-2.28	0.6145	<0.0001
	9-17	1.73 ± 0.93	0.17-3.84		
	18-49	2.88 ± 1.13	0.93-4.57	0.3676	0.0049
	50-81	3.92 ± 1.66	1.87-8.36		
Left kidney	0-8	48.54 ± 23.87	12.09-106.12	0.7959	<0.0001
	9-17	126.42 ± 47.51	47.19-253.32		
	18-49	162.73 ± 37.35	70.60-274.19	−0.1102	0.4146
	50-81	154.31 ± 36.23	95.68-230.56		
Right kidney	0-8	47.61 ± 23.62	12.75-101.38	0.8384	<0.0001
	9-17	108.25 ± 38.79	20.57-182.29		
	18-49	153.12 ± 38.32	70.42-257.07	−0.0955	0.4796
	50-81	147.94 ± 37.89	87.49-224.88		

Significance at $P < 0.05$.

organ volumes and normalized organ MVPs were then calculated by dividing organ volumes and organ MVPs, respectively, by subject lumbar spinal height.

Data Analysis

Where applicable, organ volumes, organ attenuation values, and organ SUVs (both mean and maximum) were correlated with age. Also, where applicable, organ MVPs were calculated (with units of SUV − milliliter) and correlated with age. Furthermore, organ volumes and organ MVPs normalized to lumbar spinal height also were correlated with age. All scatterplots were generated with Microsoft Excel software (Microsoft Corporation; Redmond, WA), whereas linear regression curves and statistical analyses were performed using SPSS version 14.0 (SPSS Inc, Chicago, IL). The statistical analysis software was used to calculate Pearson *r* correlation values, 95% confidence intervals (95% CI), and 2-tailed *P* values. Statistical significance was considered to be present when *P* values were less than 0.05.

Results

Age-related differences in organ volumes and organ MVPs were not significantly affected by variations in subject lumbar spinal height. As such, analysis of organ volumes and organ metabolism is reported without normalization to lumbar spinal height.

Of the abdominal organs that were evaluated, a few statistically significant age-related changes in organ structure emerged. In adults, both left and right adrenal gland volumes demonstrated significant positive associations with age ($r = 0.2823$; $P = 0.0334$, and $r = 0.3676$; $P = 0.0049$, respectively; Table 1 and Fig. 2), whereas left and right adrenal gland attenuation values correlated inversely with age ($r = -0.5835$; $P < 0.0001$, and $r = -0.6135$; $P < 0.0001$, respectively; see Table 2 and Fig. 3). In contrast, every abdominal solid organ studied in the pediatric population demonstrated a positive association between organ volume and age (Table 1 and Figs. 4-8).

Liver, spleen, and pancreas attenuation values also decreased significantly with increasing age in the group studied ($r = -0.2122$, $P = 0.0412$ for liver; $r = -0.4508$, $P < 0.0001$ for spleen; and $r = -0.5124$, $P = 0.0007$ for pancreas; Table 2 and Figs. 9-11).

Similar to the results observed with adult abdominal organ volumes, the metabolic activity of most abdominal organs in the pediatric and adult subjects included in this study was not statistically significantly associated with age. Two exceptions, however, included the adult liver and the adult small bowel. The adult liver demonstrated a significant positive

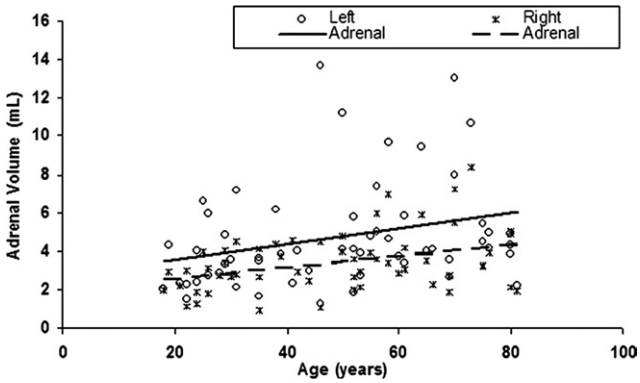

Figure 2 Change in volume (in milliliters) of adult adrenal glands with age based on contrast-enhanced CT. As noted in text, volumes of right and left adrenal glands of adults increase significantly with age.

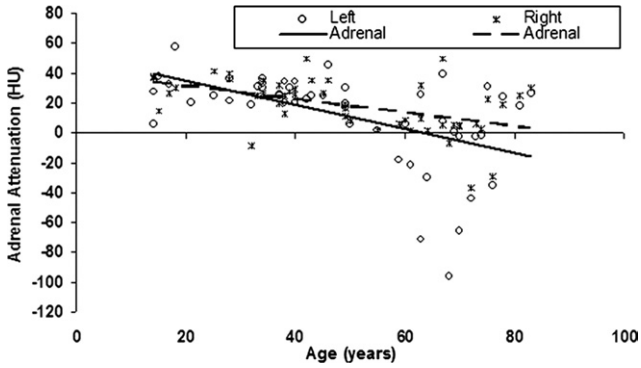

Figure 3 Change in attenuation (in Hounsfield units) of adult adrenal glands with age based on noncontrast-enhanced CT. As noted in text, attenuations of adult right and left adrenal glands decrease significantly in attenuation with age.

association between age and metabolic activity ($r = 0.4434$; $P = 0.0029$; Table 3 and Fig. 12), whereas the adult small bowel showed an inverse association between mean SUV and age ($r = -0.2435$; $P = 0.0174$; Table 3 and Fig. 13). Also, the maximum overall small bowel and colon metabolic activity of the pediatric population studied demonstrated a significant positive association with age ($r = 0.6478$; $P = 0.0008$; Table 3 and Fig. 14).

Organs SUVs that were not statistically significantly correlated with age but that had a trend toward positive correlation included splenic SUVs, mean and maximum stomach SUVs, mean and maximum ascending colon SUVs, maximum transverse colon SUVs, maximum rectum SUVs, and mean overall pediatric small bowel and colon SUVs (Table 3). Organ SUVs that were not statistically significantly correlated with age but that had a trend toward inverse correlation included maximum pancreas SUVs, maximum small bowel SUVs, mean transverse colon SUVs, mean and maximum descending and sigmoid colon SUVs, and mean rectum SUVs (Table 3).

MVPs of the liver and spleen showed no significant correlation with age (Table 4). The liver and spleen MVPs trended slightly upward with age (Figs. 15 and 16), although the trend for the spleen was nearly flat.

Discussion

Liver

Although the current study found a significant inverse relationship between liver attenuation and age in adults and a positive association between liver volume and age in children, no such significant relationship between volume and age emerged in adults. Past research has reported conflicting results regarding the relationship between liver volume and age.

In pediatric populations, researchers have found liver volume to be more significantly correlated with factors other than age. One study found that a child's weight correlated with liver volume better than did a child's age, although age and weight together correlated more strongly with liver volume than did weight alone.[14] Konuş and colleagues found that although liver size correlated positively with a child's age, liver size correlated more significantly with height.[16]

Table 2 Changes in Solid Abdominal Organ Attenuation Values on FDG-PET/CT With Age

Organ	Ages (Years)	Mean ± SD	Attenuation (HU), Range	Pearson *r*	*P* Value
Liver	18-49	54.24 ± 8.29	24.40-68.02	−0.2122	0.0412
	50-81	50.18 ± 9.71	11.77-64.94		
Spleen	18-49	46.73 ± 5.62	39.23-69.09	−0.4508	<0.0001
	50-81	40.60 ± 5.28	23.52-49.50		
Pancreas	14-53	40.20 ± 5.44	27.00-53.32	−0.5053	<0.0001
	54-83	30.06 ± 9.09	5.33-47.00		
Left adrenal	14-53	27.52 ± 0.43	6.06-57.40	−0.5100	0.0002
	54-83	−9.75 ± 36.34	−96.15-40.00		
Right adrenal	14-53	26.76 ± 11.84	−8.4-50.30	−0.5071	0.0002
	54-83	7.92 ± 19.03	−37.00-50.00		
Left kidney	14-53	26.71 ± 8.04	10.91-63.17	−0.1396	0.1819
	54-83	23.71 ± 6.50	8.72-39.73		
Right kidney	14-53	27.08 ± 6.98	6.16-49.75	−0.1567	0.1337
	54-83	23.94 ± 5.59	7.09-35.99		

Significance at $P < 0.05$.

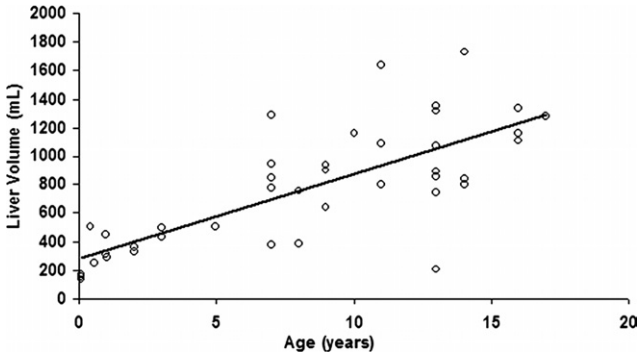

Figure 4 Change in volume (in milliliters) of pediatric liver with age based on contrast-enhanced CT. As noted in text, volumes of liver in children increase significantly with age.

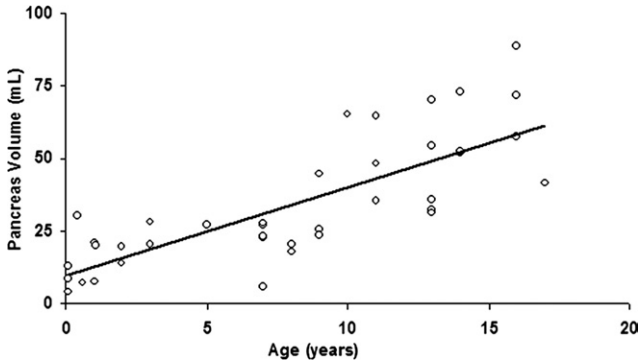

Figure 6 Change in volume (in milliliters) of pancreas with age based on contrast-enhanced CT. As noted in text, volumes of pancreas in children increase significantly with age.

Johnson and coworkers noted that body surface area was the characteristic that most accurately predicted a child's liver volume.[17] What is more, they also found that body surface area predicted adult liver volume more accurately than many other models correlating adult characteristics with liver volume.[17]

In adults, Chan and colleagues demonstrated a positive correlation between liver size (ie, weight and, accordingly, volume) and body weight and gender, with women demonstrating smaller livers than men with similar body weights.[18] Interestingly, the relationship between liver size and gender became less significant with increasing age. Zeeh and Platt[19] note that both liver weight and volume decrease with age, supporting the negative correlation between age and liver size suggested by other researchers.[20,21] Niederau and coworkers, while using US to measure midclavicular anteroposterior and midclavicular longitudinal mean liver diameters (8.1 cm and 10.5 cm, respectively), identified an inverse correlation between liver size and age.[22] In distinction to these findings, Geraghty and coworkers noted only a minor correlation between liver volume and age.[5] Similarly, although Vauthey and colleagues found liver volume to demonstrate an inverse correlation with patient age, they noted that this correlation loses significance when correcting for patient body surface area.[23] Wakabayashi and associates also concluded that liver volume determined via CT volumetry remained statistically unchanged with age when accounting for body surface area.[15] In studying 149 adults of varying ages (with a median age of nearly 50 years), Geraghty and colleagues found that the median volume of the healthy adult liver is 1710.2 mL.[5]

At the cellular level, hepatocytes themselves grow in size but decrease in numbers with age.[24] Tauchi and Sato found that mitochondria of hepatocytes change similarly, increasing in size but decreasing in overall number with age.[25] Using ^{99m}Tc-galactosyl-human serum albumin liver scintigraphy to investigate the viability of hepatocytes in livers, Wakabayashi and associates found that although corrected liver volume does not change with age, overall functional hepatocyte volume significantly decreases with age.[15] This finding of reduced hepatic functional volume with age supports previous reports of decreasing galactose elimination and urea synthesis and, thus, diminishing functional liver mass, with age.[20,26] Nitrogen clearance also decreases significantly with age.[21] A possible contributor to this reduced volume of functioning hepatocytes may be the age-associated decrease in levels of an enzyme (protein kinase CKII) involved in cellular proliferation, a finding noted in rat hepatocytes and various human tissue.[27] Additionally, the progressive accumulation of free radicals within liver mitochondria with age damages mitochondrial DNA and, along with other age-related randomly

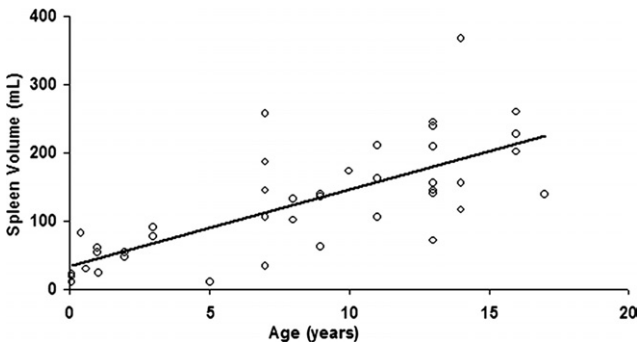

Figure 5 Change in volume (in milliliters) of pediatric spleen with age based on contrast-enhanced CT. As noted in text, volumes of spleen in children increase significantly with age.

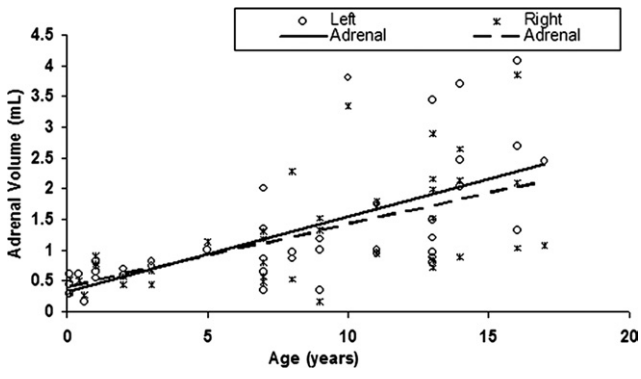

Figure 7 Change in volume (in milliliters) of adrenal glands with age based on contrast-enhanced CT. As noted in text, volumes of adrenal glands in children increase significantly with age.

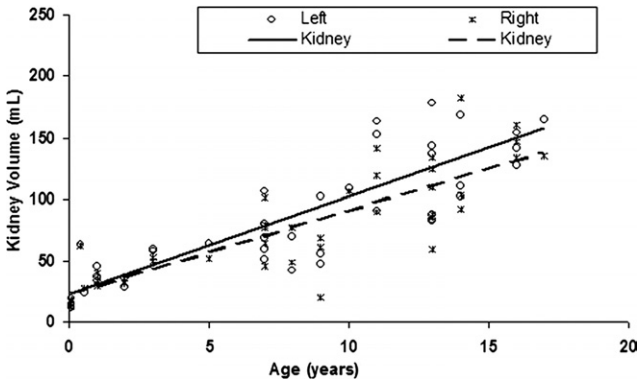

Figure 8 Change in volume (in milliliters) of kidneys with age based on contrast-enhanced CT. As noted in text, volumes of kidneys in children increase significantly with age.

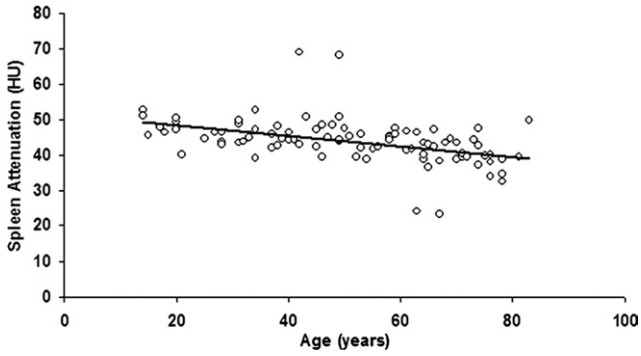

Figure 10 Change in attenuation (Hounsfield units) of adult spleen with age based on contrast-enhanced CT. As noted in text, attenuations of adult spleen decrease significantly with age.

occurring defects in respiratory chain enzymes, disrupts mitochondrial energy production and may thus limit hepatocyte function.[28-30] Grasedyck and coworkers identified further cellular-level changes associated with normal aging of the liver.[31] Specifically, they found that although the collagen content of the human liver declines after the growth period of youth, the amount of the connective tissue then remains nearly constant throughout adulthood and into old age. However, they add that in rat models, the livers of younger animals respond more robustly to toxic insults and other disturbances than do their older counterparts' livers.

The liver's function with regards to drug metabolism may be impaired beyond changes in liver size as well. In rats, certain enzymes in the P-450 pathway have been shown to lose activity in aged rats as compared with their younger counterparts, although other studies have determined that enzymes involved in phase I and phase II drug metabolism remain at relatively constant levels with aging.[32-35] Hepatic blood flow also decreases in humans with age, with Wynne and coworkers noting that decreased hepatic blood flow contributes to a reduced ability of an aged liver to clear drugs.[9,10] Zeeh and Platt suggest that the age-associated reduction in hepatic blood flow may also result in hepatic functional decline manifested as reduced bile flow and bile salt formation.[19] A similar age-associated reduction in bile flow also was noted by Handler and coworkers[36] Schmucker and coworkers, in controlling for such alterations in bile flow with age, further noted decreased secretion of immunoglobulins into the bile of older rats.[13] Overall hepatic synthesis of glucose also has been found to decrease with age.[37] In contrast to this apparent decrease in hepatic function with age, absolute hepatic protein synthesis in rats increases from youth to adulthood and then remains constant into old age.[38,39]

Also in contrast to many of these findings, the current study found the metabolic activity of the liver to increase significantly with age in adults, although the overall MVP of the liver did not change significantly. This significant increase in liver metabolism may be reflective of an increase in an aspect of hepatocyte function or other hepatic cellular function not measured by previous studies. However, the increased hepatic FDG uptake with age may also reflect cumulative inflammatory changes secondary to increasing duration of exposure to and processing of toxins by liver. Such generalized inflammatory changes, with associated increases in inflammatory cells relative to hepatic parenchymal tissue, might also contribute to an age-associated reduction in liver attenuation as noted in the current study. The observed reduction in hepatic attenuation with age may alternatively be secondary to other changes (eg, increases in collagen content,

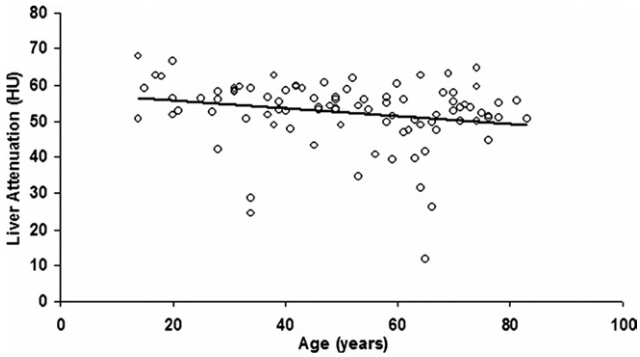

Figure 9 Change in attenuation (Hounsfield units) of adult liver with age based on contrast-enhanced CT. As noted in text, attenuations of adult liver decrease significantly with age.

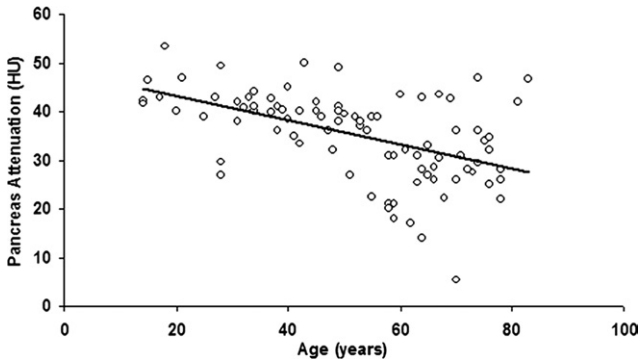

Figure 11 Change in attenuation (Hounsfield units) of adult pancreas, respectively, with age based on contrast-enhanced CT. As noted in text, attenuations of adult pancreas decrease significantly with age.

Table 3 Changes in Abdominal Organ SUV on FDG-PET and FDG-PET/CT With Age

		Mean SUV				Max SUV			
Organ	Ages (Years)	Mean ± SD	Range	Pearson *r*	*P* Value	Mean ± SD	Range	Pearson *r*	*P* Value
Liver	18-49	1.77 ± 0.34	1.3-2.7	0.4434	0.0029	–	–	–	–
	50-81	2.10 ± 0.44	1.5-3.0			–	–		
Spleen	18-49	1.41 ± 0.24	0.8-1.9	0.2214	0.1537	–	–	–	–
	50-81	1.47 ± 0.31	0.8-1.9			–	–		
Pancreas	14-53	1.30 ± 0.29	0.58-1.68	0.0747	0.6220	1.65 ± 0.43	0.88-2.93	−0.1410	0.3769
	54-83	1.16 ± 0.35	0.57-1.81			1.45 ± 0.39	0.63-2.00		
Left adrenal	14-53	1.23 ± 0.28	0.76-1.86	0.1188	0.4424	1.39 ± 0.34	0.89-2.13	0.1657	0.2828
	54-83	1.26 ± 0.39	0.71-2.20			1.44 ± 0.45	0.76-2.64		
Right adrenal	14-53	1.52 ± 0.38	0.81-2.68	0.1268	0.4121	1.68 ± 0.48	0.86-3.26	0.1337	0.3871
	54-83	1.52 ± 0.45	0.54-2.19			1.71 ± 0.49	0.55-2.38		
Stomach	14-53	1.34 ± 0.47	0.34-2.44	0.1708	0.0961	2.68 ± 1.11	1.27-5.85	0.0181	0.8614
	54-83	1.40 ± 0.39	0.45-2.20			2.73 ± 0.73	0.99-4.92		
Small bowel	14-53	1.05 ± 0.49	0.04-3.09	−0.2435	0.0174	1.60 ± 0.57	0.63-3.69	−0.1652	0.1096
	54-83	0.77 ± 0.50	0.11-1.66			1.33 ± 0.65	0.27-2.75		
Ascending colon	14-53	0.87 ± 0.25	0.46-1.41	0.1249	0.2227	2.08 ± 0.79	0.65-3.96	0.1334	0.1928
	54-83	0.89 ± 0.35	0.08-1.68			2.27 ± 0.94	0.85-5.35		
Transverse colon	14-53	0.68 ± 0.29	0.16-1.71	−0.0458	0.6557	1.59 ± 0.58	0.64-3.71	0.0951	0.3540
	54-83	0.62 ± 0.31	0.07-1.70			1.69 ± 0.82	0.62-5.37		
Descending colon	14-53	0.79 ± 0.26	0.33-1.25	−0.0957	0.3510	1.70 ± 0.54	0.75-3.54	−0.0103	0.9202
	54-83	0.70 ± 0.32	0.24-1.69			1.78 ± 0.99	0.68-7.27		
Sigmoid colon	14-53	0.87 ± 0.32	0.26-1.66	−0.0024	0.9813	2.36 ± 1.44	0.75-7.70	−0.1295	0.2061
	54-83	0.85 ± 0.37	0.11-1.80			2.15 ± 1.20	0.76-7.88		
Rectum	14-53	1.26 ± 0.42	0.45-2.56	−0.1297	0.2054	3.02 ± 1.57	0.94-9.41	0.0189	0.8538
	54-83	1.12 ± 0.44	0.33-2.55			3.16 ± 1.74	0.87-8.94		
Small bowel, colon	2-12	0.64 ± 0.12	0.42-0.82	0.2595	0.2319	1.21 ± 0.31	0.79-1.88	0.6478	0.0008
	13-21	0.76 ± 0.17	0.47-1.05			1.77 ± 0.22	1.28-2.18		

Significance at $P < 0.05$.

microscopic lipid content, or intrahepatic blood) not noted on previous studies.

Spleen

As is the case for the liver, the relationship between splenic volume and age is somewhat disputed in the literature. Our study found adult splenic attenuation to be inversely correlated with age and pediatric, but not adult, splenic volume to be positively associated with age. Although Markisz and colleagues also found splenic volume to correlate positively with age in pediatric populations, volume correlated more significantly with a child's weight.[14] Splenic length correlates well with splenic volume and also has been been used by researchers to investigate changes in splenic size with age.[40]

In one study, pediatric splenic length was found to increase linearly with increasing age, whereas a study performed by Megremis and coworkers demonstrated a significant nonlinear correlation between splenic length and age.[16,41] This latter study found that the relationship between age and spleen size was independent of body surface area,

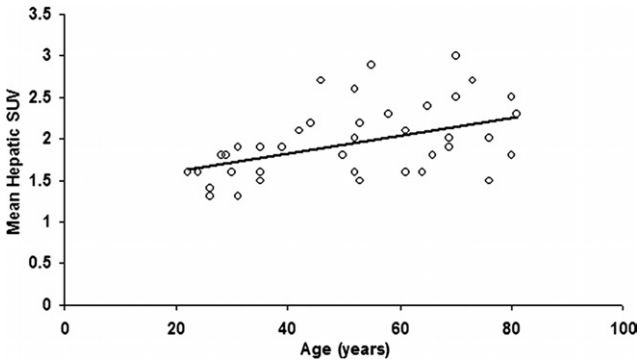

Figure 12 Change in mean SUV of adult liver with age based on FDG-PET. As noted in text, mean SUV of adult liver increases significantly with age.

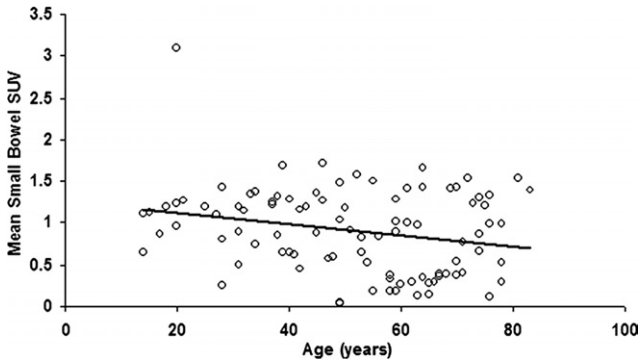

Figure 13 Change in mean SUV of adult small bowel with age based on FDG-PET. As noted in text, mean SUV of adult small bowel decreases significantly with age.

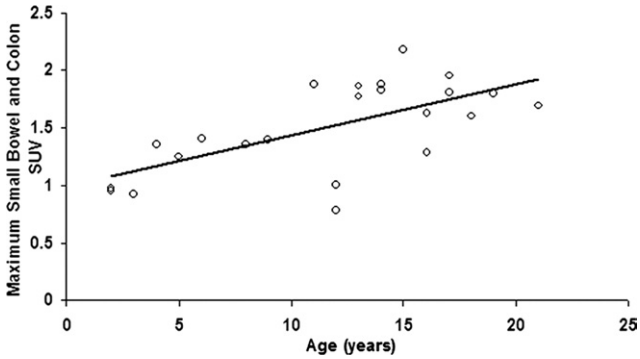

Figure 14 Change in maximum SUV of pediatric small bowel and colon (combined) based on FDG-PET. As noted in text, maximum SUV of pediatric small bowel and colon increase significantly with age.

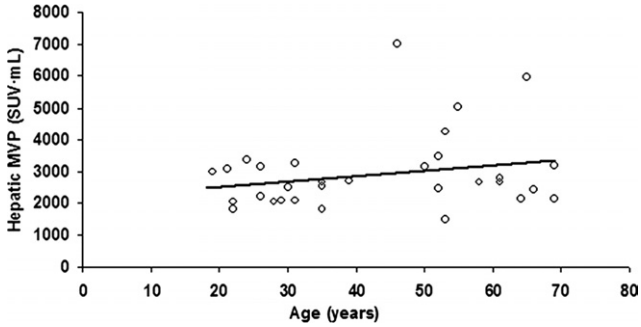

Figure 15 Change in MVP (SUV − milliliters) of adult liver with age. Liver MVP is calculated as product of liver volume (determined from contrast-enhanced CT) and liver mean SUV (determined from FDG-PET). As noted in text, MVP of adult liver does not change significantly with age.

weight, and height. Using US, Loftus and Meterweli noted a rapid increase in splenic length up to age 20 (to an upper limit of normal of approximately 12-13 cm in the Chinese population studied), followed by a slight decrease in length thereafter.[42] Rodrigues suggests that age-associated shortening, thickening, and loss of elastic fibers within the splenic capsule may contribute to a decrease in spleen size with age.[43] Although both positive and inverse significant correlations between spleen size and age have been demonstrated in other studies of adults, Geraghty and colleagues, as in the current study, noted only minimal association between splenic size and age.[5,22,44] Additionally, they noted the median splenic volume of a population with a median age of nearly 50 years to be 238.3 mL.[5] In examining splenic transverse and longitudinal lengths with US, Niederau and coworkers found mean lengths of 5.5 cm and 5.8 cm, respectively, in adults.[22]

In evaluating changes in splenic function with age, Markus and Toghill examined the percentage of pitted erythrocytes (a marker of splenic dysfunction) in a group of young and a group of elderly subjects.[45] The researchers noted a significantly higher percentage of pitted red cells in the elderly group than in the young group, suggesting diminished splenic function in the older population.[45] Although Ravaglia and colleagues also found significantly more pitted erythrocytes in subjects older than 70 years of age than in those younger than 70, only one of the more elderly subjects had a pitted erythrocyte count in line with splenic hypofunction.[46] As such, the researchers contend that splenic function decreases slightly with age but remains clinically intact. The spleen's functional state in camels also diminishes with age, as noted by its reduced role in platelet production with advancing age in adulthood. Specifically, Zidan and associates identified significantly fewer megakaryocytes in the spleens of aged versus young camels.[47]

Age-associated changes in the immunologic function of the spleen also have been investigated. Garg and colleagues found that splenic cells in older mice respond poorly to pneumococcal vaccination, with a decline in response of cells from old mice to only 10% of that of cells from young mice.[48] These researchers also noted that this vaccine-specific response could be improved by mixing the older mice's splenic cells with either irradiated splenic adherent accessory cells from young mice or a relatively larger number of these irradiated splenic adherent accessory cells from old mice. This finding suggests that, with age, splenic immunologic function declines resulting from a quantitative decrease in a specific splenic cell type. Itzhaki and coworkers, in studying a variety of cells derived from the spleens of young and old mice, found trends suggestive of increased apoptotic cell death in the spleens of older mice but with an age-related decrease in proliferative capacity of splenic cells in all but the oldest mice.[49] This increased loss of splenic cells, combined with a decreased ability of the remaining splenic cells to proliferate, may contribute to some of the functional losses noted in aging spleens by various researchers. Such a cellular loss, with a resultant greater ratio of blood to soft tissue in the spleen, also may contribute to the age-related decrease in splenic attenuation noted in the current study. What is more, the reduced flow of blood through the liver noted by some researchers may lead to functional congestion of the spleen, further boosting the ratio of blood to soft tissue in the spleen

Table 4 Changes in Hepatic and Splenic Metabolic Volumetric Products (Mean SUV − mL) Using FDG-PET and Contrast-Enhanced CT With Age

Organ	Ages (Years)	Mean ± SD	MVP (Range)	Pearson *r*	*P* Value
Liver	18-49	2915.72 ± 1218.84	1798.21-7009.65	0.1705	0.2743
	50-81	3147.92 ± 1250.73	1170.23-5962.03		
Spleen	18-49	358.88 ± 152.83	145.71-703.01	0.0512	0.7442
	50-81	330.26 ± 164.57	72.07-686.99		

Significance at $P < 0.05$.

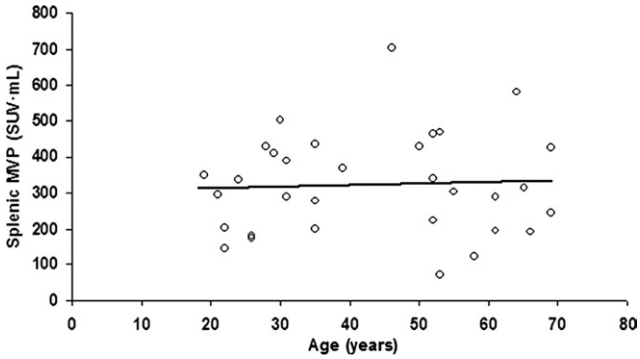

Figure 16 Change in MVP (SUV − milliliters) of adult spleen with age. Spleen MVP is calculated as product of spleen volume (determined from contrast-enhanced CT) and spleen mean SUV (determined from FDG-PET). As noted in text, MVP of adult spleen does not change significantly with age.

and further decreasing the attenuation of the spleen with age. However, our findings of no significant change in either splenic FDG uptake or splenic MVP with age differ with the finding of a decrease in splenic function as noted in the previously discussed research. This may reflect that cells within the spleen continue to metabolize glucose despite a waning ability to contribute to hematological, immunological, or other such functioning as indirectly measured by other researchers.

Pancreas

Researchers undertaking studies of age-related changes in pancreatic structure have reported contradictory findings. Anande and colleagues, undertaking an endoscopic retrograde pancreatographic study of static pancreatic duct diameter, found the accessory pancreatic duct and portions of the main pancreatic duct to be significantly more dilated in older individuals (with a mean diameter of 3.78 mm in the head and 2.86 mm in the midbody) than in younger persons (with a mean diameter of 2.97 mm in the head and 2.36 mm in the midbody), although the length of the ducts were similar across age groups.[50] Using US in 1,000 men and women ages 18 to 65, Niederau and coworkers found a mean maximal pancreatic head diameter of 2.2 cm and further noted a significant positive correlation between age and pancreatic size.[22] Other researchers, using CT to study pancreatic volume, found no such significant associations between pancreas size and age, similar to the findings of the current study.[5] Gilbeau and coworkers found that, although the pancreas becomes increasingly lobulated with age (especially in diabetics), the pancreases of nondiabetic subjects demonstrate no correlation between size and age.[51]

Gilbeau's group also found that diabetic subjects' pancreases were smaller than those of nondiabetic individuals (a conclusion supporting the findings of Migdalis and coworkers) and did demonstrate an inverse correlation between pancreatic size and age in individuals with diabetes.[51,52] The greatest decrease in pancreatic volume was noted in those diabetic subjects treated with insulin.[51] Although the pancreatic body is smaller in diabetic subjects than in their nondiabetic counterparts, the size differential between the larger pancreases of nondiabetic subjects and the smaller pancreases of diabetics is particularly prominent in subjects' pancreatic heads and tails.[51] No differences in pancreatic attenuation were noted between the organs of nondiabetic and diabetic subjects.[51] In the current study, pancreatic attenuation significantly decreased with age. This inverse relationship with age may be secondary to the fatty replacement of pancreatic tissue, which is not uncommon in aging individuals.

In attempting to draw a connection between pancreatic structure and function, Tsushima and Kusano noted that pancreatic attenuation as determined with CT shows no correlation with pancreatic parenchymal perfusion.[53] Tsushima and Kusano also found no change in parenchymal perfusion with age.[53] Glaser and Stienecker, in evaluating pancreatic exocrine function by looking at pancreatic duct dilation in response to secretin stimulation, found that the changes in duct diameter were similar between younger and older adults.[54] This finding suggests stability in this marker of pancreatic function and is in agreement with our finding of no significant change in pancreatic FDG uptake, and thus of metabolic function, with age. Gullo and coworkers, using the fluorescein dilaurate test (a noninvasive test of pancreatic exocrine function), also found no correlation between age and pancreatic function.[55] In contrast to such findings of stable pancreatic exocrine function with age, Vellas and coworkers found that duodenal aspirates from older subjects contained significantly reduced concentrations of pancreatic enzymes than did those from younger individuals, suggesting reduced pancreatic function with age.[56] Laugier and colleagues arrived at a similar conclusion, noting that although pancreatic flow rate and enzyme secretion increased through to the third decade, they decreased thereafter to a statistically, albeit not clinically, significant degree.[57]

Similar to these pancreatic exocrine studies, many investigations of pancreatic endocrine function have identified an inverse correlation between age and function. Glucose-stimulated insulin secretion decreases linearly in pubertal children, although this association disappears when controlling for differences in insulin sensitivity.[58] Pancreatic β-cell function has been shown to decrease with age independent of the effects of intraabdominal fat on β-cell function.[59] Kahn and associates, in studying differences in the insulin secretion of younger and older individuals in response to glucose infusion, identified a significant reduction in insulin secretion in older subjects when compared with younger counterparts despite an equal glucose sensitivity of the β-cells across age groups.[60] Ihm and coworkers similarly noted a more robust glucose-stimulated release of insulin from the islets of adolescent and young adults than from islets of adults older than 40 years of age.[61] Bourey and coworkers also found that some members of an older group of subjects demonstrated a significantly diminished insulin response to glucose infusion; however, the researchers noted that others among the older subjects demonstrated insulin responses that were similar to those of younger individuals.[62] This similarity in insulin re-

sponse between younger and older subjects supports the findings from a previous study of the effects of aging on glucose response.[63] Gumbiner and his associates did note a higher basal level of insulin secretion in the elderly versus the young subjects, though.[63]

Adrenal Glands

The current study demonstrates that in both children and adults, the adrenal glands grow in volume to a statistically significant degree with increasing age. A previous study of neonates and infants found the adrenal glands of neonates to be larger than those of infants, which differs from the current study's findings, but it focused on only a small age segment of the current study's population.[64] In children, the adrenal cortex expands in width with age, and in about the seventh year of life, the inner zone of the adrenal cortex, the zona reticularis, begins to develop, in agreement with the increase in volume noted in this study's pediatric population.

Regarding adults, past research in rats has similarly found adrenal cortical volume to be larger in older rats than in younger adult rats.[65] Others have found no significant association between age and adrenal size in human adults, whereas still others have found significant inverse associations between age and adrenal microstructural size.[5] Hornsby asserted that, in older adults, the adrenal cortex begins to mildly atrophy and commonly develops areas of hyperplasia (ie, nodules).[66] This latter theory could help explain the increase in volume noted in the current study. What is more, the fatty nature of the adenomatous changes often seen in adrenal glands of elderly individuals may contribute to the significant age-associated decrease in adrenal gland attenuation noted in the current study.

Data regarding age-related changes in baseline and stimulated activity of the adrenal glands is also conflicting in the literature. Lashansky and coworkers found that the adrenal glands of infants produce more 17-hydroxyprogesterone at baseline and when stimulated with adrenocorticotropic hormone (ACTH) than do the adrenal glands of children ages 1 to 5 years.[67] Baseline levels of this 17-hydroxyprogesterone then increase again, attaining significantly elevated levels in late-pubertal children. This older pediatric group also demonstrated higher baseline and ACTH-stimulated levels of dehydroepiandrosterone (DHEA), possibly secondary to presence of an established zona reticularis (the inner region of the adrenal cortex that produces adrenal androgens like DHEA and its sulfate, DHEA-S) for several years. Additional subtle yet significant age-related differences in pediatric baseline and ACTH-stimulated adrenal activity were noted by the researchers, some of which were sex-dependent.

Roberts and associates noted that such purely age-associated changes in adrenal gland response to ACTH stimulation are not maintained into adulthood.[68] Although some significant differences in adrenal gland response emerge when considering both gender and age (eg, the adrenal glands of young men respond less to 60 ng of ACTH stimulation than do other groups, and the maximal responsiveness of older men is lower than other groups), Roberts and associates found no consistent age-related change in the sensitivity and responsiveness of adrenal glands in adults.[68] However, others have found that rat zona glomerulosa (ie, the outer layer of the adrenal cortex) secretes less aldosterone with increasing age.[69,70]

In investigating baseline adrenal gland function in human adults in their fourth decade of life and beyond, researchers likewise have identified a clear inverse association between age and DHEA and DHEA-S levels, with DHEA-S circulating in nonagenarians and centenarians at levels 5 times lower than in younger adults.[71,72] Seals and Esler found that adrenal medullary secretion of catecholamines in response to stress similarly diminishes with increasing age (a finding conflicting with previous research by Mabry and coworkers), although overall decreased clearance of the hormones with age generally offsets the reduced production.[73,74]

In rats, although circulating levels of corticosterone (the principle glucocorticoid in rats) are similar in young and old animals, corticosterone production per adrenal cortical volume, and thus function of each cortical cell, diminishes with age.[65] However, circulating levels of cortisol (produced within the zona fasciculata, the middle layer of the adrenal cortex) and androstenedione (produced within both the zona reticularis, the inner layer of the adrenal cortex, and the zona fasciculata) remain unchanged with age.[75] As such, the age-related decrease in DHEA and DHEA-S production likely is not a result of a functional decline of the entire adrenal cortex, but instead is probably secondary to an age-related decrease in cell count specifically within the zona reticularis. This overall stability of function of the cells within the zona fasciculata reflects either an absolute retention of cellular function or a decrease of function of each cell with a compensatory increase in cell number or size to maintain hormone production. Whatever the underlying cause, the stability of adrenal gland function with age suggested by some researchers is in agreement with our finding of stable adrenal gland metabolic function with age as determined by FDG-PET.

Kidneys

No significant age-associated change in the size or attenuation of either kidney was noted in our study of adults, although the volumes of the kidneys of the included pediatric population did demonstrate significant positive correlations with age. This increase in kidney volume with age supports the findings of Han and Babcock.[76] Dinkel and coworkers found that body weight also correlates significantly with kidney volume in children.[77] However, beginning in young adulthood and middle age and in contrast to the current study's findings, kidney size has been found by other researchers to decrease slowly yet significantly into old age. McLachlan and Wasserman noted a 0.5 cm decrease per decade in kidney length, and Emamian and coworkers attribute such age-associated size decreases primarily to a reduction in parenchyma.[78,79] Gourtsoyiannis and coworkers similarly noting an age-related reduction in renal parenchyma, found a decrease in parenchymal thickness of 10% per decade in

aging adults.[80] Suggesting a "normal" kidney size and without adjusting for such potential changes, Geraghty and coworkers in his study of adults with a median age of nearly 50, measured median left and right kidney volumes to be 201.0 mL and 185.1 mL, respectively.[5] Researchers using US to evaluate adult kidney dimensions have generally noted mean lengths of the left and right kidneys between 10.3 and 11.1 cm, while another study, using conventional renal scintigraphy found a mean kidney length of 11.5 cm.[81-83]

Although the current study did not evaluate age-associated changes in metabolic function of the kidneys (because the renal excretion of FDG currently limits the ability of FDG-PET to quantitate renal parenchymal metabolism), previous studies have used other measures to identify significant age-related alterations in renal function. In newborns, although the kidney is well adapted to reabsorb substances necessary to maintain the body and allow for growth, Spitzer notes that the transport mechanisms of newborn kidneys are less adaptable to changes in dietary proteins and minerals than are those of adult kidneys.[84] However, this adaptability of adult kidneys to changes in body state and diet diminishes as individuals age.[85] Increasing age in adulthood also has been found to be associated with a host of additional renal functional losses. Hollenberg and associates found a decrease in renal perfusion with age in adults.[86] What is more, renal clearance of para-aminohippuric acid decreases whereas the filtered fraction is elevated with age, suggesting an age-related decline in renal functional reserve and overall renal function.[86-88] Drugs like gabapentin have also been shown to be less rapidly excreted by the kidney in older individuals.[89]

A host of mathematical equations (eg, Cockcroft-Gault; Modification of Renal Disease [MDRD]; Jellife; Levey) have been proposed to estimate glomerular filtration rate, creatinine clearance, and other such markers of kidney function, and many of these equations attempt to account for the decrease in kidney function noted with increasing age, among other variables. Fliser and colleagues stress, though, that despite the renal functional decline noted in their study, most elderly subjects still maintained glomerular filtration rates within normal limits.[87] Lin and coworkers, in evaluating actual (ie, using ^{125}I-iothalamate or ^{99m}Tc-diethylenetriaminepentaacetic acid renal clearance studies) and estimated glomerular filtration rates (using a variety of estimation equations) of a population of healthy adults, noted mean and range of estimated glomerular filtration rates of, for example, 97.6 mL/min per 1.73 m^2 and 55.8 to 201.1 mL/min per 1.73 m^2 using the MDRD-1.[90] However, Lin's group and others caution that the MDRD-1 and many other such equations tend to underestimate actual kidney function.[90,91]

Studies have attempted to uncover some of the factors that may contribute to such age-associated changes in the size and function of adult kidneys. Hypertension, hypercholesterolemia, smoking, and atherosclerosis have been found to accelerate these age-related decreases in renal size and function.[92-94] At the cellular level, Melk and coworkers note that the kidneys of older individuals have more glomerulosclerosis, tubular atrophy, interstitial fibrosis, and fibrous intimal thickening in small arteries, whereas Moriguchi and coworkers identified an age-related increase in markers of tubular dysfunction.[95,96] Melk and coworkers contend that such structural and functional changes occur in the setting of increased nonspecific inflammatory response, increased extracellular matrix turnover, and reduced mitochondrial function.[95] Increased fibrosis activation combined with accelerated apoptosis may also contribute to the glomerulosclerosis and interstitial fibrosis noted with increasing age.[97] Goyal also noted an age-associated decrease in the number of tubular and glomerular cells in adults.[98] Changes at a microscopic level also have been noted in aging kidneys that may contribute to the functional changes noted previously. For example, Fardoun and coworkers note that dopamine receptors in the proximal tubules of nephrons become uncoupled from G proteins in aging rats and that this uncoupling and resultant dysfunction likely stems from an accumulation of oxidative stress with age.[99] Also, renal expression of certain proteins associated with lipid synthesis and renal accumulation of cholesterol increases with age, and Jiang and coworkers assert that this accumulation of lipid within the kidney may contribute to some of the functional decline noted in aging adults.[100]

Esophagus

Although the esophagus was not evaluated with CT or PET in this current study of the abdominal organs, others have evaluated structural and functional characteristics of the esophagus. For example, Schmalfuss and colleagues, using CT and MRI, found the normal cervical esophagus to measure fewer than 16 mm in anteroposterior diameter and fewer than 24 mm in lateral diameter, with an average wall thickness of between 3.8 and 4.8 mm.[101] Other researchers have employed a variety of modalities to evaluate esophageal function.

Using manometry, Omari and associates determined that premature neonates (of 33-37 weeks' gestation) have developed and functional motor mechanisms to regulate upper esophageal sphincter resting pressure and relaxation.[102] Comparing the upper esophageal sphincter of preterm and full-term neonates, Jadcherla and coworkers noted peristaltic velocity to be twice as high in full-term neonates as in preterm infants.[103] When comparing the upper esophageal sphincter function of all these neonates to those of middle-aged adults, the researchers found neonates to have a lower resting upper esophageal sphincter pressure, a smaller pressure decrease with relaxation of the sphincter, and greater duration of sphincter relaxation than adults. As such, the amount of time that the upper esophageal sphincter remains open during swallowing appears to decrease between infancy and adulthood.

Among adults, mean resting upper esophageal sphincter pressure is inversely associated with age.[104,105] Then, once the upper esophageal sphincter is contracted, older individuals displayed greater delay in relaxation of the sphincter than did younger subjects.[104] Similarly, the lower esophageal sphincter of older adults functions more poorly than younger

adults, with Ren and colleagues noting less frequent total lower esophageal relaxation after distention with air.[106] Beyond the esophageal sphincters, Ren and colleagues noted that secondary esophageal peristalsis after esophageal distention is evoked with less frequency in older individuals when compared with younger counterparts.[106] Grande and coworkers found peristaltic wave amplitude and velocity decreases with age.[105] Hollis and Castell also found a significant reduction in the amplitude of esophageal peristaltic waves in older individuals, particularly in people older than 80 years; however, these researchers found that the waves are propagated with similar speed and duration in young and old subjects.[107] This finding, they explain, points to a weakening of esophageal smooth muscle, but stability of esophageal nervous system function and esophageal motility, with age. This apparent stability of the esophageal nervous system function is all the more notable given the significant loss of myenteric esophageal neurons with age.[108,109] This loss of esophageal neurons is most substantial in the superior third of the esophagus and reportedly is associated with an increase in size of the remaining neurons.

Stomach

In studying the stomach, researchers commonly used gastric blood flow as a marker of gastric function. Studying gastric mucosal blood flow in adults, Taha and coworkers found no correlation between flow and age in adult nonsteroidal anti-inflammatory drug (NSAID) users.[110] Although Lee's findings agree, in part, with this conclusion of similar gastric blood flow characteristics across age groups, a significant point of distinction separates the 2 studies.[111] Namely, although Lee identified no significant difference between acid-induced changes in gastric blood flow in old and young rats, he demonstrated an inverse correlation between age and both mucosal and serosal basal gastric blood flow in these rats.

In looking at gastric secretory function with age, Goldschmiedt and coworkers noted a positive correlation between age and gastric acid secretion.[112] Feldman and coworkers found no such association between age and gastric acid secretion, although they did identify an inverse correlation between age and pepsin secretion.[112] The role of differences in gastric cell count (eg, increased numbers of parietal cells and decreased numbers of mucous cells with age) is uncertain.[113] Levels of COX-1 mRNA were reduced in stomachs of older rats when compared with levels in younger rats.[114] Because COX-1 is a precursor of mucosal-protective prostaglandins, this reduced level of COX-1 mRNA may help explain others' findings of reduced concentrations of gastric prostaglandins with age, especially in those individuals older than 70 years of age.[115-117]

Gastric emptying also has been used as a marker of stomach function. Studies comparing gastric emptying across age groups often use radiolabeled liquids and solids and have, with some exceptions, generally demonstrated delayed gastric emptying with increasing age.[118,119] O'Donovan and coworkers noted less initial transpyloric flow and slower gastric emptying of liquids in older subjects compared with younger subjects, a finding similar to the slowed gastric emptying of liquids noted in aged rats.[120,121] Moore and coworkers and Kao and coworkers also noted prolonged gastric emptying of liquids with age, although the groups found no age-associated delay in the emptying of solids from the stomach.[122,123] Other studies have shown gastric emptying of both liquids and solids to be statistically significantly slower in older individuals as compared with younger individuals.[124-126]

Of note, Horowitz and coworkers question the clinical significance of this slowed gastric emptying since the absolute difference between the emptying times of many young and old subjects is relatively small.[124] Also, despite the reported delay in gastric emptying, many have found no significant difference in whole-gut transit time between younger and older subjects.[125,126] Although the above discussion demonstrates that studies of gastric function largely rely on measures of gastric emptying to determine gastric function, Linke and coworkers contend that gastric peristalsis is a more sensitive measure of gastric function than is emptying.[127] To the extent that myenteric neuron count may influence such peristalsis, the fact that myenteric neuron count in the stomach of rats remains stable through most of adulthood but decreases in old age may contribute to any changes noted in this marker of gastric function.[128]

The preponderance of the aforementioned research suggests that gastric function should at best remain unchanged with age if it does not in fact decrease. As such, the maximum normal gastroesophageal SUV of 4.0 identified by Salaun and coworkers in a population with a mean age of 57.4 years should hold more-or-less true for adults of any age.[129] At first glance, our findings that show no statistically significant change in gastric metabolic function agree with the assertion that stomach function is stable with age. However, the non-significant positive trend of both mean and maximum stomach SUVs with age suggests either that some level of gastric function thus far unevaluated by researchers may increase with age, or that conditions commonly found in older individuals (eg, gastritis) may contribute to a slightly increased gastric FDG uptake with age.

Small Bowel

In general, past research has found little clinically significant change in small bowel function with age. Because researchers have identified statistically significant differences in small bowel function with age, the lack of clinically significant change in small bowel function likely reflects the reserve capacity of the organ. Some of the statistically significant small bowel functional changes noted with age include the finding by Goodlad and Wright that rat small intestinal absorption per unit length is maximal within the first few weeks of life and then decreases.[130] Other researchers, using urinary lactitol and mannitol recovery ratios, have demonstrated that human intestinal permeability falls starting as early as the first week of life and continues falling throughout childhood.[131,132] Investigation of infants from a developing nation suggested quite the opposite: the intestinal permeability of the small bowel continually increases with age.[133] These con-

trasting findings suggest that environment (ie, diet, infection, etc) may impact certain aspects of small intestinal function.

Age-related changes in small bowel neuron and muscle characteristics also have been widely studied, again with differing results. Small bowel myenteric neuron density displays an inverse association with age. In studying rats, Phillips and Powley noted that small bowel myenteric neuron density decreases linearly with age.[128] A similar age-associated decrease in small bowel myenteric neuron density was noted in children and adults, with the largest diminution noted in the duodenum.[134,135] The propagation velocity of migrating motor complexes also slows, although the amplitude and frequency remain unchanged, with age.[136] Although Anuras and Sutherland found no such age-associated differences in propagation velocity during the migrating motor complex when fasting, they did note an age-associated reduction in contraction frequency after the subjects ingested a meal.[137] Smits and Lefebvre, although noting similar cholinergic longitudinal muscle contraction in response to electrical stimulation in young and aged rat ileum, found longitudinal muscle from the ilea of aged rats to relax somewhat less substantially than that of younger rats.[138] Despite these reported reductions in intestinal function with age, Madsen and Smits and Lefebvre noted no difference in small bowel transit times with age in humans and rats, respectively, whereas Graff and coworkers identified a significant inverse association between age and small bowel transit times.[118,119,121]

The current study agrees with this latter investigation in finding a statistically significant, although not necessarily clinically significant, decrease in small bowel functional activity in adults with age. The decreased intestinal absorption noted with increasing age is also in line with the current study's results that intestinal metabolism diminishes with age. Perhaps some or all of the diminution of metabolic activity noted in the current study may also be secondary to the age-associated decrease in intestinal myenteric neuron density noted by other researchers and the possible impact of that neuron loss on intestinal muscle function. The increase in maximum overall small bowel and colon FDG uptake with age noted in the children included in the current study may suggest that such neuronal losses and secondary muscular dysfunction generally do not begin until adulthood. Indeed, the small bowel and colon of children appear to become more metabolically active with age.

Colon and Rectum

Researchers focusing their efforts further distally in the gastrointestinal tract have identified a variety of changes in colonic and rectal function associated with aging. As in the small bowel, the total number of colonic myenteric neurons decreases with age in rats and in children, particularly during the first 4 years of a child's life.[134,139] Hanani and coworkers, while noting an increase in the surface area of myenteric ganglia with age, found that the proportion of ganglia with cavities and other structural abnormalities increases with age.[140] Gomes and coworkers, commenting on an additional alteration in myenteric ganglia with age, identified a positive association between age and collagen content within myenteric ganglia.[139]

These changes in colonic innervation may impact colonic motility, as may age-related changes in colonic musculature. Infants and young children have more frequent high amplitude propagating contractions than do older children, possibly contributing to young children's increased number of bowel movements relative to older children's bowel habits.[141] Although taenia coli continue to grow into old age and thus could continue to contribute to colonic motility, taenia coli intramuscular collagen levels increase and capillary density relative to muscle volume decreases with age, possibly impacting motility.[142] Smits and Lefebvre noted an overall decrease in rat fecal mass with age, and McDougal and coworkers found colonic transit to slow in older rats compare with younger animals.[121,143] This slowed colonic transit has been found to affect aging humans as well.[118,119] Even so, Graff and coworkers, found no change in male colonic transit times with age, and Loening-Baucke and Anuras found no age-associated change in sigmoidal, rectosigmoidal, and rectal motility.[119,144] What is more, Lopes and coworkers, found that colonic smooth muscle from aged rats in fact contracts more vigorously in response to muscarinic stimulation than does muscle from younger animals.[145]

Additional controversy surrounds changes in the sigmoid colon and rectum with age. Orr and Chen assert that sigmoid function remains essentially intact with age.[146] Although some researchers have agreed, noting no differences between young and elderly with regard to sigmoid, and also rectal, wall elasticity and sensation, others have noted an age-associated decrease in colonic and rectal volume and an increase in the pressure needed to produce the sensation of rectal filling.[144,147,148] The colonic wall as a whole also changes with age, with increasing collagen fibril diameter through maturity and overall wall thickness into the third decade.[149,150] Then, with further aging, human colonic wall demonstrates decreasing collagen fibril diameter, particularly in the left colon, and thus decreasing distal colonic tensile strength from high levels seen in infancy.[147,149,151] The collagen fibrils of the left colon also become more tightly packed and cross-linked with age, reducing the elasticity of the walls.[151,152] This diminished elasticity and expandability, along with a decreased inner colon diameter, contribute to the formation of colonic diverticula in older individuals.[147,152] Taken together, these age-associated changes may contribute to the relatively high prevalence of other gastrointestinal complaints (eg, chronic constipation and fecal incontinence) noted by Talley and coworkers within the elderly population.[153]

Perhaps the relative age-associated increase in collagen content within both colonic myenteric ganglia and taenia coli contributes to the downward trend in metabolic activity of the distal colon and rectum noted in the current study. The upward trend in ascending colon SUV with age may suggest that either an etiology other than collagen replacement is in fact responsible for altering colonic and rectal metabolic activity, or that, with age, collagen deposition is preferentially directed toward the distal colon and rectum and away from

the ascending colon. Also, the impact of diverticulosis on colonic metabolic activity cannot be determined in the current study given the exclusion of subjects with significant diverticulosis from the study.

Conclusion

With the size of the aged population in the United States expected to grow considerably during the next several decades, the number of radiographic and scintigraphic studies to be performed on aged individuals will similarly increase. As such, understanding of the normal age-related changes in structure and function of the abdominal organs is important. In presenting our retrospectively obtained quantitative CT and FDG-PET data and literature review, we sought not only to investigate age-associated changes in normal abdominal organ size, attenuation, and metabolic function to serve as a baseline for future clinical or research investigation but also to demonstrate some basic methodological approaches to perform such quantitative assessments, and to present some points of interest that will hopefully be addressed in future research endeavors. As such, we hope that this article will be useful as a starting point for others involved in research and clinical work related to abdominal organ structure and function.

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