Gender-specific liver aging and magnetic resonance imaging

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Abstract: The number of imaging studies performed on elderly individuals will increase in the next several decades. It is important to understand normal age-related changes in the structural and functional imaging appearance of the liver. This article highlights a number of liver aging aspects which are particularly relevant to magnetic resonance imaging (MRI). Physiology of aging liver is associated with a reduction in size, in perfusion, and in function. Pulsed echo-Doppler showed substantial reduction of portal flow in elderly subjects, particularly those after the age of 75 years old. An MRI biomarker diffusion derived vessel density (DDVD) demonstrated that liver microperfusion volume in healthy females starts to decrease even before menopause age. Liver fat content and iron content increase with aging, and the change is more substantial in women after menopause. Adult men have higher liver fat and iron contents than women from the start and change less during aging. Nonalcoholic fatty liver disease (NAFLD) is very common among assumed healthy subjects. There is a male predominance of NAFLD from the paediatric population up to fifth decade of life in adults. After the age of 60 years, women overtake their male counterparts in prevalence of NAFLD. Higher liver fat leads to decreased apparent diffusion coefficient (ADC) and intravoxel incoherent motion (IVIM)-D_{slow} measures. Higher liver iron content shortens T2* measure, lower ADC and IVIM-D_{slow} measures, increases imaging noises and decreases liver visibility. Young women have high liver T1rho value and then decrease substantially, while liver T1rho in men remains relatively unchanged with aging. In positron emission tomography (PET) studies, aging is associated with an increase of both liver fluorine-18-fluorodeoxyglucose maximum standard uptake and mean standard uptake values.

Keywords: Magnetic resonance imaging (MRI); liver; vessel density; aging; diffusion; fat; iron; positron emission tomography (PET); fluorodeoxyglucose (FDG)

The number of imaging studies performed on elderly individuals will increase in the next several decades. It is important to understand normal age-related changes in the structural and functional imaging appearance of the liver. Healthy aging of organs is a well-studied topic and covered in many imaging literatures. Aging of some organs such as brain, spine, hip/knee joints etc. can be well noted on imaging (1-3). For example, intervertebral disc nucleus pulposus appears high signal in young subjects, while typically appear grey/low signal in older subjects. A grey/low signal disc nucleus pulposus would suggest degeneration if seen among young subjects, but considered part of normal aging in elderly subjects (3). Quantitative T2 and T1rho relaxation times of the disc nucleus pulposus show apparent reduction with healthy aging (4). However, the aging of liver has got less attention among radiology

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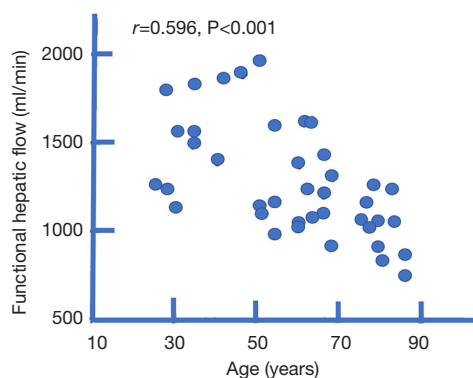
Figure 1 The relationship between aging and functional hepatic flow measured by the hepatic clearance of D-sorbitol. The reduction in hepatic blood flow is particularly evidential after the age of 75 years. Adapted from reference (16).

community. This article highlights a number of liver aging aspects which are particularly relevant to MRI.

Physiology of liver aging: reduction in size, in perfusion, and in function

Physiology of liver aging has been well studied. Macroscopically the liver undergoes 'brown atrophy' with old age. The brown appearance is secondary to the accumulation of pigmented waste products within hepatocytes. Hepatocytes in elderly subjects contain denser body compartments, such as secondary lysosomes and lipofuscin, than do hepatocytes in younger subjects (5). Lipofuscin accumulation is associated with chronic oxidative stress and a failure to degrade damaged and denatured proteins (6). At the cellular level, hepatocytes grow in size but decrease in numbers with age (7). Mitochondria of hepatocytes increase in size but decrease in overall number with age (8).

Post-mortem studies suggest that there is an age-related fall in liver weight, which has been well confirmed by *in-vivo* imaging studies (9-11). It is estimated that, compared with those under 40 years of age, individuals above the age of 65 years have 25–35% lower liver volume (12).

Old age can be associated with a reduction in hepatic blood flow of about 35–40%. This has been documented using a variety of technical methods (13-16). Zoli *et al.* (16) studied hepatic blood flow in 40 normal subjects in four age groups (<45, 45–60, 61–75 and >75 years). Each group consisted of 10 subjects (five men and five women). Total hepatic flow was measured by pulsed echo-Doppler, as the

sum of portal and hepatic artery blood flow. Functional hepatic flow was measured by the hepatic clearance of D-sorbitol. Both total hepatic flow and functional hepatic flow significantly decreased with age, particularly in subjects over 75 years (*Figure 1*). Zoli *et al.* noted that portal vein size did not change with age, varying from 1.16 to 1.03 cm, while echo-Doppler measured portal blood velocity and flow decreased from the age of 45 years onwards. Hepatic artery velocity and flow did not change significantly in various age groups, although a mild increase (possibly compensatory) was observed between 45 and 75 years. The hepatic artery flow constituted 17% of total hepatic flow in younger subjects; after the age of 45 years, it rose to about 25%, the proportion then remaining stable. In the oldest group (>75 years) total hepatic flow decreased by 30%.

Fiel *et al.* (14) reported an increasing arteriolar wall thickness and a decrease in luminal diameter of liver arterioles with aging (*Figure 2*). The thickening of the sinusoidal endothelial lining with collagen and fall in endothelial cell fenestrations can impair blood flow through liver sinusoids and hepatic perfusion, and reduce oxygen-dependent hepatocyte function (17).

Using an magnetic resonance imaging (MRI) biomarker DDVD (diffusion derived vessel density) (18,19), we demonstrated liver microperfusion volume in healthy females starts to decrease even before menopause age (*Figure 3*) (20). In suggesting that DDVD reduction started during the middle age at least for females, our *in-vivo* imaging results concur with the histological study of Fiel *et al.* (14). DDVD data also show young women have higher liver microperfusion volume than young men (20).

The liver has a pivotal role in the regulation of the metabolism of carbohydrates, proteins and lipids. While most of the routine clinical tests of liver function do not change significantly with aging, the synthesis of proteins, lipid and glucose decreases with age. The index of routine clinical liver function tests to correlate with age is bilirubin (21). Bile flow and bile salt formation are reduced by about 50% in elderly subjects (12). There is a significant negative correlation between plasma albumin concentration and age (22). Dong *et al.* (23) reported age was associated with modest decreases in albumin and γ-glutamyl transpeptidase concentrations, and increases in bilirubin concentration, after adjustments for sex, alcohol use, and components of the metabolic syndrome. It has been estimated that serum albumin decreases by 0.54 g/L per decade (24). Aged liver is associated with a reduction of galactose elimination, a reduction in binding of radiolabelled galactosyl-albumin,
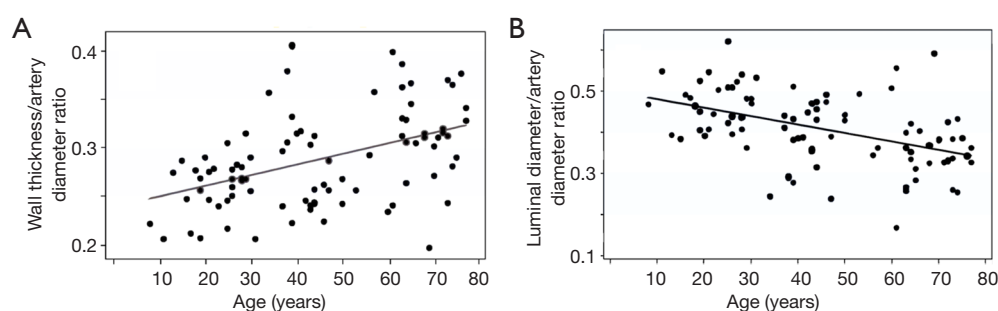
Figure 2 The relationship of increasing ratio of the wall thickness to cross sectional hepatic arteriolar diameter with increasing age (A), and a decreasing ratio of luminal diameter to cross sectional hepatic arteriolar diameter with increasing age (B). Adapted from (14).
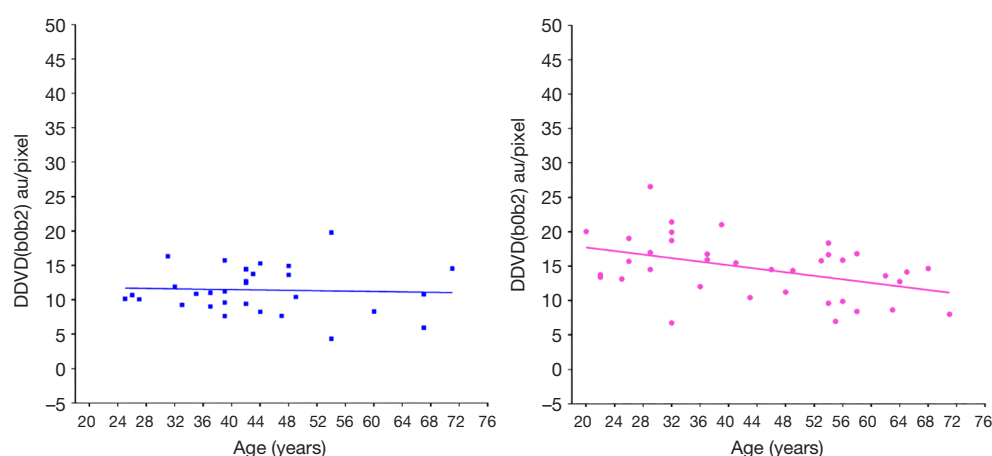
Figure 3 Liver DDVD measurement (y-axis) of healthy volunteers and their ages (x-axis). The results of men (left, n=31) do not show an apparent trend, while the results of women (right, n=37) show a trend of decrease as age increases (P=0.01). Note male subjects do not have sufficient representation for >60 years old group in this study. DDVD(b0b2) refers to signal difference between b=0 $vs.$ b=2 s/mm^2 images. DDVD, diffusion derived vessel density. Reproduced with permission from (20).

and reduction of urea synthesis (10,25,26).

Among elderly subjects, there is a more limited liver function reserve. Complex liver functions are less responsive to challenges, leading to a higher disease susceptibility. A change in drug clearance with aging is an important factor for the high prevalence of adverse drug reactions among the elderly. In a survey of more than 1,200 elderly patients admitted to an acute care hospital, Hurwitz (27) found that the incidence of adverse drug reactions more than tripled beyond the age of 70 years. Well-known changes in the clearance of drugs that undergo hepatic metabolism are attributed to age-associated alterations in hepatic enzyme activity and to reduced liver size and hepatic blood flow. It is recommended that, for the elderly, drugs which are metabolized and excreted by the liver should be used at a starting dose which is 30–40% smaller than the average dose used in middle-aged adults (15).

Increase of liver fat content with aging

Efficient fat metabolism is paramount to the maintenance of systemic nutritional homeostasis. The ability of mammals to store and draw on fat reserves has been a driving force throughout evolution in an environment with intermittent nutrient availability. In a typical adult, lipids comprise 80% of energy reserves. With the improved nutrition in modern society, overstore of fat in liver has been an issue. In general populations, liver fat content increases with age.

Ulbrich *et al.* (28) studied 80 healthy Swiss volunteers aged between 20 and 62 years (10 men/10 women per
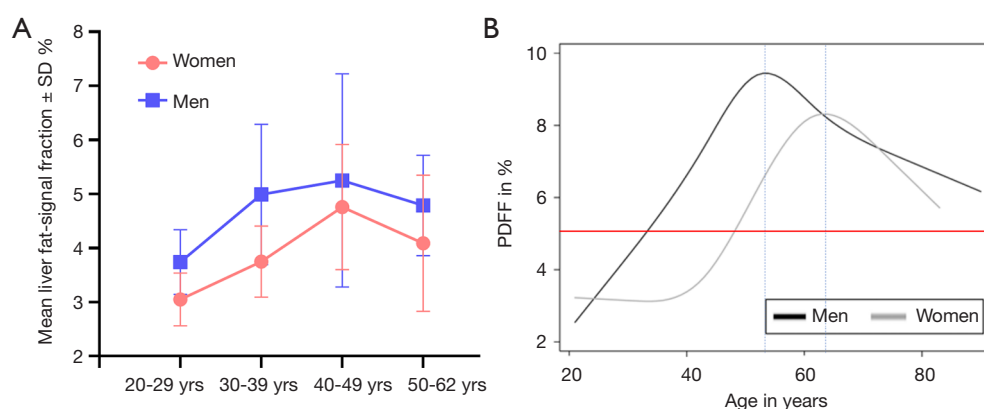
Figure 4 Gender-specific relationships between age and liver fat content. (A) Gender-specific relationships between age and liver signal fraction among 40 Swiss men and 40 Swiss women. Adapted from (28). (B) Gender-specific relationships between age and liver fat content (PDFF) among 1,225 German men and 1,336 German women. Adapted from (29).
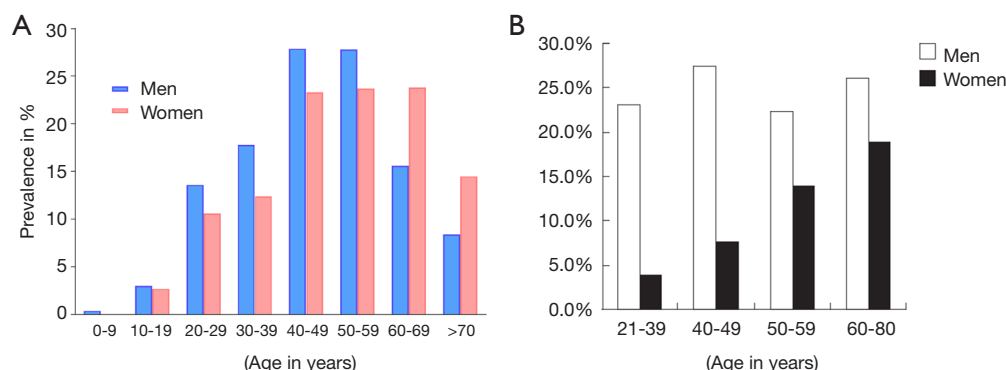
Figure 5 Age- and gender-specific prevalence of ultrasonography estimated nonalcoholic fatty liver disease (NAFLD). (A) Prevalence of NAFLD among 1,271 Japanese men and 1,303 Japanese women. Adapted from (33). (B) Prevalence of NAFLD among 1,829 Japanese women and 2,572 Japanese men. Adapted from (32).

decade) with normal body-mass index. It was reported that fat signal fraction (FSF) ranged from 2.77% to 10.06% (mean 4.69%±1.38%) for men, and ranged from 1.80% to 7.56% (mean 3.91%±1.10%) for women. Liver fat content was higher in men than in women and peaked in the fifth decade for both men and women (*Figure 4A*). Kühn *et al*. (29) quantified liver proton density fat fraction (PDFF) in a population-based study of 2,561 participants (1,336 women; median age, 52 years; 25th and 75th quartiles, 42 and 62 years), and reported the median PDFF was 3.9% (range, 0.6–41.5%). In men, liver-fat content increased continuously between age 20 and 50 years; in women, liver fat content increased began 20 years later, extending from 40 to 65 years (*Figure 4B*). In the Dallas Heart Study where

hepatic fat content was assessed in 2,287 participants using MR spectroscopy, Szczepaniak *et al*. (30) reported a median liver fat content of 4.7% (25% and 75% quantiles, 2.7% and 8.6%).

Nonalcoholic fatty liver disease (NAFLD) is common worldwide. The mildest form of NAFLD is simple steatosis, characterised by intrahepatic fat (triglyceride) accumulation alone (≥5% of liver weight). Currently, the diagnosis of NAFLD is based on detection of hepatic steatosis by liver biopsy or imaging, exclusion of other liver diseases, particularly alcohol and hepatitis B/C. In nonalcoholic steatohepatitis (NASH), hepatic necroinflammatory changes are present and a characteristic perisinusoidal pattern of liver fibrosis is common. Up to

25% of NAFLD patients have NASH. The true prevalence of NASH, the most clinically relevant subset of patients with NAFLD, is difficult to establish because this is a histologic diagnosis.

NAFLD is common among assumed healthy population. Epidemiological studies suggest male predominance of NAFLD from the paediatric population up to fifth decade of life in adults. After the age of 60 years, females overtake their male counterparts in prevalence of NAFLD, with an age and gender distribution resembling that of cardiovascular disease (31-33) (*Figure 5*). In the US, an estimated one-third of the population has NAFLD and approximately 2–5% have NASH (34). A study in predominantly middle-aged American employees or outpatients (without known liver disease) found that the prevalence of steatosis by ultrasonography was 47%; in this study, NASH was confirmed histologically in 12% of the total cohort or 30% of the ultrasound positive subgroup (35). One ultrasonographic study of 26,527 Chinese subjects (age: 47.41±10.13 years, range: 20 to 70 years) receiving medical health check-ups shows NAFLD prevalence was 31% in men and 16% in women (36). NAFLD prevalence is rapidly increasing in China (37).

Liver fat content also has implications in routine imaging. Meier *et al.* reported the CT attenuation of adult liver decrease significantly with increasing age (11). It has been well known that liver steatosis induces MR diffusion measure reduction (38-42). Liver fat increases the size of hepatocytes, and the increased size of liver cells is associated with a smaller extracellular space and this may lead to a restriction of molecular motion of water molecules. Echo planar image acquisition commonly uses spatial-spectral pulses for fat suppression (i.e., water-only excitation). Water excitation pulses have a spectral bandwidth centered on the water peak (located at 4.7 ppm), while the NMR spectrum of triglycerides in liver fat has several peaks (between 4.2 and 5.3 ppm) close to the water peak (43). Water excitation pulses, even in the absence of B_0 inhomogeneities will excite about 9% of the triglyceride proton magnetization (44). Thus, lipid signal peaks near water are often incompletely suppressed by the fat suppression techniques; and the measured diffusivity may incorporate the diffusion constant of lipid, which is much slower than water, with higher *b*-values leading to even lower observed diffusion coefficient (43,44).

Increase of liver iron content with aging

In healthy subjects there are iron storage depots located for the most part in the liver, spleen, and bone marrow. Iron is stored in the liver as iron (III) oxyhydroxide particles in the form of ferritin and hemosiderin. Hemosiderin is a degradation product of ferritin particles that is insoluble and is more likely to aggregate. States of negative iron balance occur when the body requirements for iron exceed the amounts being absorbed from the gastrointestinal tract. This may be the result of physiological events such as growth spurts, menstruation and pregnancy, or of any pathological state that causes blood loss. In healthy subjects without diet iron deficiency, liver iron concentration rises sharply in men toward the end of the adolescent growth spurt in the late teens and reached maximum before 40 years old. After 40 years old, liver iron level remains constant or slightly increases until approximately the age of 70 years, after which it may declines (45-48). In women, liver iron concentration remains relatively low until after the fourth decade of life, after which they exhibit a steep rise. The relative low mean value among women in the 21- to 40-year-old group is associated with a high iron demand of menstruation during the childbearing age. Maximum levels observed in women after menopause are approximately two thirds of those for men of comparable age (45-51).

Liver iron can particularly affect T2* imaging and diffusion weighted imaging (DWI). R2* (1/T2*) is commonly used to evaluate hepatic iron concentration (38,52,53), with higher iron concentration shortens T2* (and increases R2*). Schwenzer *et al.* (54) assessed 1.5 Telsa T2* relaxation time of liver in a cohort of 129 healthy German subjects (85 women, 44 men; age range: 20 to 70 years, mean age, 47.9±11.4 years), and reported a mean liver tissue T2* value of 28.1 ±7.1 ms (range, 13.6–45.9 ms), which corresponds to a mean R2* of 35.6 s^{-1}. There was a significantly higher hepatic T2* values for women (14.7–45.9 ms) than for men (13.6–43.1 ms, P<0.01). 'Iron overload' was observed in approximately 7% of participants. A statistically significant correlation of T2* decrease over age was seen (for men, Pearson *r*=–0.30, P<0.05; for women, *r*=–0.46, P<0.0001).

In a study of 2,561 German participants (1,336 women; median age: 52 years), Kühn *et al.* (29) quantified liver iron content with R2* at 1.5 Telsa, and study participants were stratified as follows: none iron overload (R2*, ≤41.0 s^{-1}), mild iron overload (R2*, >41 s^{-1}), moderate iron overload (R2*, >62.5 s^{-1}), high iron overload (R2*: >70.1 s^{-1}). Median R2* was 34.4 s^{-1} (range, 14.0–311.8 s^{-1}). It was shown that men had 20.9% higher 'liver iron' content compared with women. 'Iron overload' was observed in 17.4% of

participants, with male participants of 27.2% and female participants of 9.0%. The severity distribution was mild: 14.7%, moderate: 0.8%, and high content: 2.0%. A combination of hepatic steatosis and 'liver iron' overload was observed in 9.3% of the study participants. Liver iron content was mainly associated with mean serum corpuscular haemoglobin in men and in women. In women, age was also associated with liver iron.

However, it should be noted that the measured liver R2* value is confounded by the presence of hepatic steatosis. In a study of patients with NAFLD/NASH, Bashir et al. (55) reported that liver PDFF was positively correlated with R2* at both 1.5T and at 3T. They suggested that for patient population with NAFLD/NASH, R2* is not a reliable technique for quantifying liver iron when high level liver iron deposition is relatively rare. It is suggested that intrahepatocellular triglyceride droplets can cause susceptibility effects. Although individual iron particles have much greater susceptibility effects than individual similarly sized fat droplets, the amount of iron encountered in the NAFLD/NASH population tends to have a narrow range from none to mild, while the range of fat content is broad. In cases with high liver fat content, liver fat has a greater impact on measured R2* values than liver iron.

With DWI, iron deposition can create both macroscopic sub-voxel magnetic field inhomogeneities that leads to errors in ADC (apparent diffusion coefficient) estimation. Sener (56) reported magnetic field inhomogeneities can lead to a reduction of ADC measure in the brain. Higher liver iron content is also associated with lower liver ADC measure. Chandarana et al. (57) studied this effect in phantom and in liver using a 1.5 Tesla magnet. In phantoms, there was a decrease in ADC (b-values: 0/50/500 s/mm^2) and T2* with increasing iron concentration. Patients with hepatic siderosis had significantly lower signal-to-noise ratio and ADC (b-values: 50/500 s/mm^2) compared with patients without siderosis. There was a significant correlation between liver T2* and ADC (r=0.83). Signal-to-noise ratio at b=50 and 500 s/mm^2 and ADC had a significant negative correlation with pathologic iron grade (r=−0.67 to 0.77). Bülow et al. (58) studied the relationship between ADC (b-values: 50/400/800 s/mm^2) and liver iron content in subjects without liver fibrosis and without steatosis (total 33 cases, among them 11 cases had an increased liver iron content) and demonstrated a moderate negative correlation between ADC values and iron load.

With a study in 34 men and 52 women, Metens et al. (59) reported that normal liver parenchyma visibility on DWI and ADC measure (b-values: 150, 600, 1,000 s/mm^2) are influenced by age and iron content. Normal DWI liver visibility negatively correlates with normal range iron content markers. Liver visibility was better in young women but degrades with age in both genders. The liver average ADC was negatively correlated with age, and the values were higher in women (0.785±147×10^{-3} mm^2/s) than in men (0.742±103×10^{-3} mm^2/s; P=0.027). Liver T2* (at 3 Tesla) in men (19.3±4.2 ms, range 13.8–28.6 ms) was statistically significantly lower than that in women (22.7±4.6 ms, range: 13.2–31.0 ms; P=0.016). In women, liver T2* decreased statistically significantly with age. Metens et al. (59) noted an underestimation of the parenchymal ADC in patients with low liver visibility together with an increased uncertainty of the ADC value. Therefore, while the signal of the normal liver parenchyma is often used as a reference to establish the DWI signal of the hepatic lesions, the normal liver signal intensity can vary according to the age and gender iron content dependence.

Recently, we performed a study with 30 men and 36 women and demonstrated a trend of IVIM (intravoxel incoherent motion)-D$_{slow}$ decreasing related to healthy aging (*Figure 6*) (20). IVIM-D$_{slow}$ is broadly similar to ADC measure without very low b-values.

The liver iron change with aging is also expected to be relevant in liver susceptibility imaging (quantitative susceptibility mapping) (60,61).

Decrease of liver T1rho measure in women with aging

T1rho (T1ρ) relaxation time describes spin-lattice relaxation in the rotation frame at the presence of an external radiofrequency pulse in the transverse plane. It has been demonstrated that T1rho elongation is a sensitive biomarker for collagen deposition and thus a sensitive biomarker for liver fibrosis (62-64). To translate liver T1rho MRI into clinical practice, it is important to know the physiological liver T1rho measure in healthy subjects. We conducted a healthy volunteer study in 62 women (mean age: 38.9 years; range: 18–75 years) and 34 men (mean age: 44.7 years; range: 24–80 years). Female liver T1rho value ranged between 35.07 and 51.97 ms and showed an age-dependent decrease, with younger women having a higher measurement (65). The male liver T1rho value ranged between 34.94 and 43.39 ms, with no evidential age dependence (*Figure 7*).

The underlying cause for such liver T1rho dynamics and
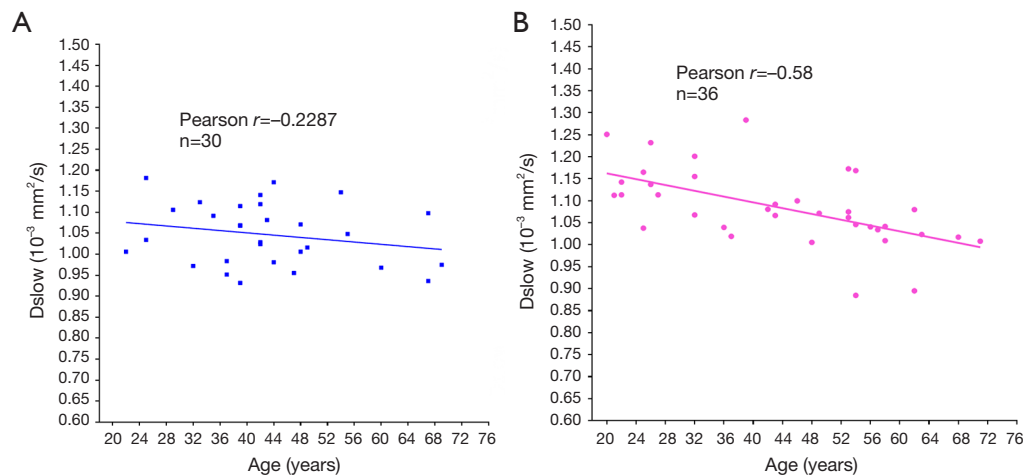
Figure 6 The relationship between age and liver IVIM-D_{slow} in healthy men (A) and women (B). Aging is associated with a general reduction of D_{slow}, which is more apparent in women than in men. Overall young men have lower D_{slow} measure than young women, which could be due to that, compared with young women, young men generally have higher liver iron content, higher liver fat content, and lower blood perfusion volume. IVIM, intravoxel incoherent motion. Reproduced with permission from (20).
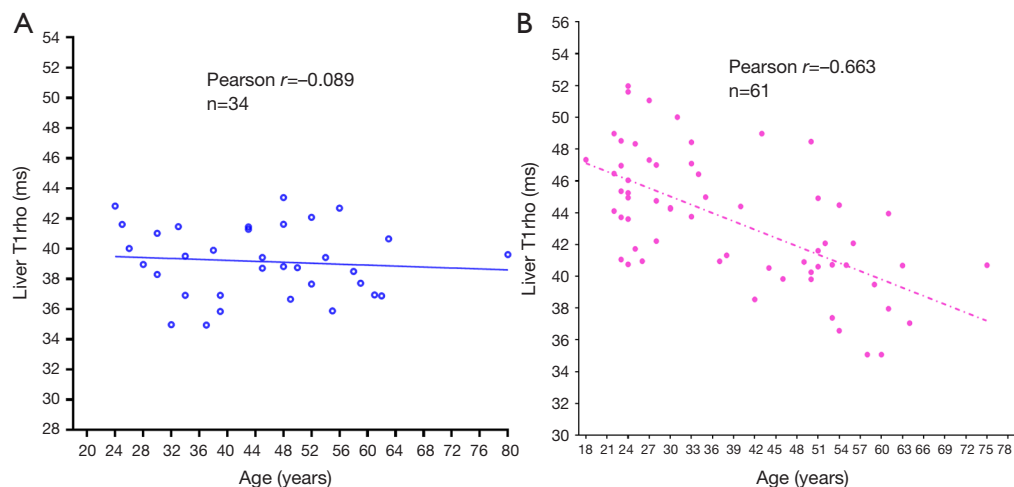
Figure 7 The relationship between liver T1rho and age in healthy men (A) and women (B). A very substantial age-related reduction of liver T1rho measure is noted in women, but not apparent in men. Reproduced with permission from (65).

male female difference remains unknown. Compared with other MRI techniques such as T2* and diffusion imaging, T1rho may be relatively insensitive to physiological liver iron deposition (66). For subjects without apparent liver steatosis (i.e., <5% fat content) and when fat suppression technique is applied, the contributed from liver fat to T1rho shortening is expected to be limited relative to the physiological variation of liver T1rho. Our previous analysis suggests that 10% additional liver fat contribute to

1.55 ms liver T1rho shortening (67). Also, for both women and men, no association was seen between body mass index and liver T1rho (65). Therefore, we do not expect the liver T1rho dynamics is largely affected by liver iron and fat contents. One may think there would be age- and gender-associated collagen content variation in healthy aging liver. Till now, studies on this topic remain limited, and most studies were conducted on animal models. Mild fibrosis is a hallmark of the aging of various organs, including the
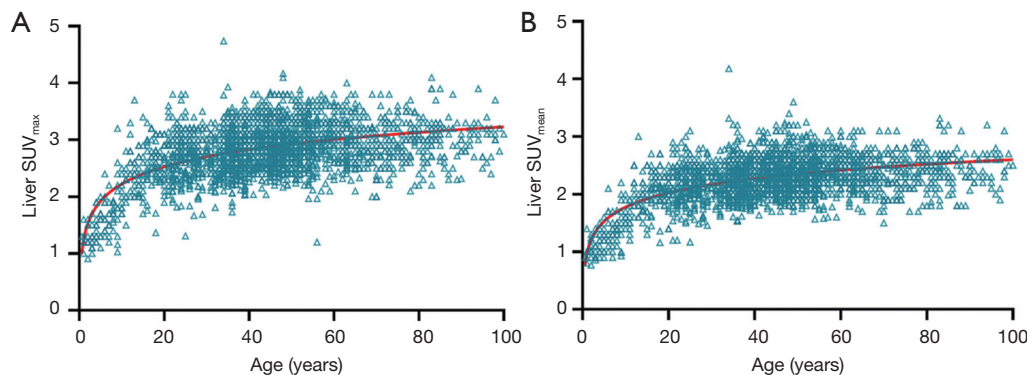
Figure 8 Age-related changes of standardized uptake values (SUV) in the liver, with data of 2,526 subjects (1,436 men and 1,090 women). (A) liver maximum SUV; (B) liver mean SUV. Reproduced with permission from (72).

liver, which reflects increased deposition of the extracellular matrix. Grasedyck *et al*. (68) reported 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. In an aging rat model, Gagliano *et al*. (69) reported that interstitial collagen accumulated significantly in the oldest animals, mainly in the periportal area. An increase of collagen content in aging livers does not explain the reduction of liver T1rho.

Increase of liver fluorodeoxyglucose (FDG) uptake with aging

Since aged livers are associated with less blood perfusion and decreased hepatocyte number, one would expect aged livers have less fluorine-18-FDG uptake. However, it has been well documented that aging is associated with an increase of both liver maximum standard uptake value (SUVmax) and liver mean standard uptake value (SUVmean) on FDG positron emission tomography (PET) imaging (11,70-72). Cao *et al*. (72) studied a total of 2,526 subjects underwent FDG PET/CT examinations, and reported that liver SUVmax and SUVmean rise rapidly until the age of 20 and then show a slow upward trend without reaching a plateau (*Figure 8*). Meier *et al*. (11) noted that, the metabolic activity of the liver increases significantly with age in adults, and the overall metabolic volumetric product, a measure that takes into account an organ's volume and metabolism by multiplying the hepatic volume by the hepatic mean SUV, trend slightly upward with age. While aging is associated with an increase of liver FDG uptake, Lin

et al. (70) reported that there is no statistically significant relationship between sex, hepatitis B virus and hepatitis C virus infection status, and SUVmax or SUVmean of the liver.

The causes for this significant increase in liver metabolism in aging liver have not been fully elucidated (72). It may reflect cumulative inflammatory changes secondary to increasing duration of exposure to processing of toxins by liver (71).

PET/MRI scanners have been introduced in clinical use. In PET imaging, liver FDG uptake is commonly used as the reference standard for diagnosis, therapy assessment, and quality control. Radiologists should be familiar with this age-related increased liver FDG uptake in elderly population. This high physiological background FDG uptake may reduce diagnostic sensitivity and accuracy for detecting malignant lesions and result in false negative findings in the liver on PET imaging.

In conclusion, aging livers are associated with a reduction in organ volume and blood perfusion (in total and in per volume tissue), an increase in fat and iron deposition, and an increase in FDG uptake. With liver aging, quantitative MR metrics show lower DDVD, shortened T2*, lower ADC, lower IVIM-D$_{slow}$, and in women lower T1rho. These changes are generally more apparent in women due to women's physiological cycle of menstruation, pregnancy, and later menopause. These aspects should be considered during interpreting daily clinical images as well as in designing research. On the other hand, the aging process can vary greatly from person to person. Furthermore, subclinical diseases in apparently normal persons, smoking habits, nutritional differences and other factors will provide

'noises' and contribute to the wide variability in aging process.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-21-227). The author serves as the Editor-In-Chief of *Quantitative Imaging in Medicine and Surgery*. The author has no conflicts of interest to declare.

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