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Review article

Liver Training: Yes or No?

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Abstract

The objective of this article was to review the function of the liver and its change with aging and discuss whether liver training is necessary. The liver has three major roles: the first being metabolic function as a chemical processing factory, including metabolism, detoxification and synthesis; the second being exocrine function, such as bile secretion; and the third being endocrine function, which mainly consists of the secretion of insulin-like growth factor-I (IGF-I). The liver is the largest organ in the human body with a very high functional reserve. The liver's age-related functional decline is smaller than its potential function. There is no training method to improve the liver's exocrine and endocrine functions. Morphological changes, such as fibrosis in the course of progression from chronic hepatitis to cirrhosis, lead to decreased liver functional reserve and eventually to a fatal consequence. Liver training by exercise "supports the liver" by: 1) stimulating growth hormone secretion from the pituitary gland to promote IGF-I production from the liver, 2) improving metabolism of nitrogen-containing compounds and improving hyperammonemia under a condition of reduced liver functional reserve by maintaining or increasing skeletal bone mass, and 3) improving non-alcoholic fatty liver disease (NAFLD), rather than "training the liver". Training the liver by drinking alcohol is synonymous to inducing enzymes of the microsomal ethanol-oxidizing system (MEOS) in the liver, which not only results in an increased alcohol intake, enhanced glycation stress due to an increased production of advanced glycation end products (AGEs) and an additional burden on the liver, but it also increases the risk of esophageal cancer. Excessive alcohol consumption does nothing good; it only causes harm. From these facts, it can be concluded that there is no need to "train the liver" by drinking.

KEY WORDS: Ethanol, acetaldehyde, microsomal ethanol-oxidizing system (MEOS), insulin-like growth factor-I (IGF-I), advanced glycation end products (AGEs)

Introduction

If one is asked to name the roles of the liver, then its function as a chemical processing factory, including metabolism, detoxification and synthesis, and exocrine function, such as bile secretion, will be named as the two major functions. However, the organ also has endocrine function; it is the third function. In my report, this third function[1)] is emphasized. After encountering a patient with insulin-like growth factor-II (IGF-II) producing hepatocellular carcinoma accompanied by paraneoplastic syndrome[2)], We have paid more attention to the liver as an endocrine organ that produces IGF-I. Many of the pituitary hormones stimulate other target organs to promote the secretion of second messenger hormones, including the thyroid hormone stimulated by thyroid-stimulating hormone (TSH), adrenocortical hormones (*e.g.* cortisol) stimulated by adrenocorticotropic hormone (ACTH), and estrogen and testosterone stimulated by gonadotropin-releasing hormone (GnRH). Similarly, growth hormone (GH) stimulates the liver to secrete IGF-I.

The objective of this article is to compile information on age-related changes in these three liver functions in comparison with other organs, and discuss whether we should train the liver to slow its functional decline.

Age-related changes in liver function

First, we would like to give an overview of the age-related changes in liver function. An analysis involving 7,071 healthy volunteers (5,107 males and 1,964 females) and 162 patients (123 males and 39 females) followed for at least 10 years has shown age-related increases in the serum concentrations of aspartate transaminase (AST), alanine transaminase (ALD), γ-glutamyl transpeptidase (γ-GTP) and cholinesterase and age-related decreases in serum albumin concentration and

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platelet count [3]. Major factors contributing to these age-related changes include metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and alcohol consumption among middle-aged people, and malnutrition among the elderly [3-6]. Decreased serum albumin and abnormal indocyanine green (ICG) test results are more commonly observed in those aged over 75 years, although no marked change is observed in the ICG retention rate [6].

Next, we would like to compare the age-related changes in liver function with those of other organ functions. In an analysis of 135 elderly patients undergoing coronary bypass surgery, only a minor age effect was seen on liver function, as compared to decreases in respiratory function (*e.g.* gas exchange) and kidney function [7]. Taking these data together, it is implied that there is little need to train the liver to maintain its function, given the minimal age-related decline which is less compared to the decline of other organ functions.

Metabolic function

Regarding the metabolic function of the liver, let us take drug metabolism as an example. Drug disposition is the net result of the absorption, distribution, metabolism and excretion processes. Drugs administered to a human body will be absorbed into the circulation, distributed to various tissues through the blood circulation system, and then rapidly eliminated from the circulation via metabolism in the liver or urinary excretion in the kidney [8]. Drugs that have reached their site of action will exert pharmacological and adverse effects in a dose-dependent manner. In the elderly, age-related functional changes are observed in each of these processes [9,10]. Drugs are primarily metabolized in the liver and kidney. The decline of the detoxification function of the liver is more significantly attributed to chronic hepatitis and cirrhosis rather than age-related changes. Taking the metabolism of propiverine hydrochloride as an example, only a slight increase in the percentage of the unchanged form and a slight decrease in oral clearance were observed in the healthy elderly compared to the healthy young, with relatively similar levels of maximum clearance (Cmax) [11]. In the elderly, drug metabolism is significantly affected by age-related decline in kidney function, with toxicities of renotropic drugs imposing a significant risk to the elderly [12,13]. The liver has a well-developed anti-oxidant system, since metabolism of toxins always results in free radicals released from the toxins. The age-related decrease in the tissue content of coenzyme Q10 (CoQ10), a major antioxidant, is lower in the liver than in the heart, kidney and lung (***Fig. 1***) [14]. Taken together, it can be said that the liver has a high metabolic potential, which is minimally affected by age-related changes.

Exocrine function

With respect to the exocrine function of the liver, there have only been a limited number of reports regarding the age-related changes in bile secretion. When looking at the blood concentration of bile acid, instead of bile secretion, reports show an age-related increase in the bile acid level [15], which, from the drug metabolism point of view, is likely primarily due to the age-related decrease in biliary excretion/clearance [16]. Except for the age-related decreases in gallbladder motility [17] and bile concentration function [18] reported in association with stone formation, there seems to be little age effect on biliary function. In animal studies, no age-related change in total bile acids level was observed, although bile acid composition analysis showed changes in the levels of some bile acids, including tauro-β-muricholic acid, cholic acid and glycocholic acid [19-21]. There is currently no way to directly improve the exocrine function of the liver, other than by supportive therapy with exogenous bile acid supplementation.

Endocrine function

The liver is an endocrine organ that produces IGF-I. The serum IGF-I level decreases with age in both men and women [22,23] (***Fig. 2***). Given the close correlation between IGF-I and GH levels [24], it is believed that the age-related decrease in IGF-I is due to a decrease in pituitary GH secretion. Progression from chronic hepatitis to cirrhosis leads to a marked numerical decrease in active hepatocytes, resulting in reduced liver functional reserve and a sharp decrease in the serum IGF-I level. In patients with portal-hypertensive gastropathy associated with liver cirrhosis, a significantly greater decrease in the serum IGF-I level is observed, as compared to in patients with atrophic gastritis without cirrhosis (***Fig. 3***) [25].

A decreased serum IGF-I level is also observed in patients with NAFLD, suggesting that the decreased GH/IGF-I is

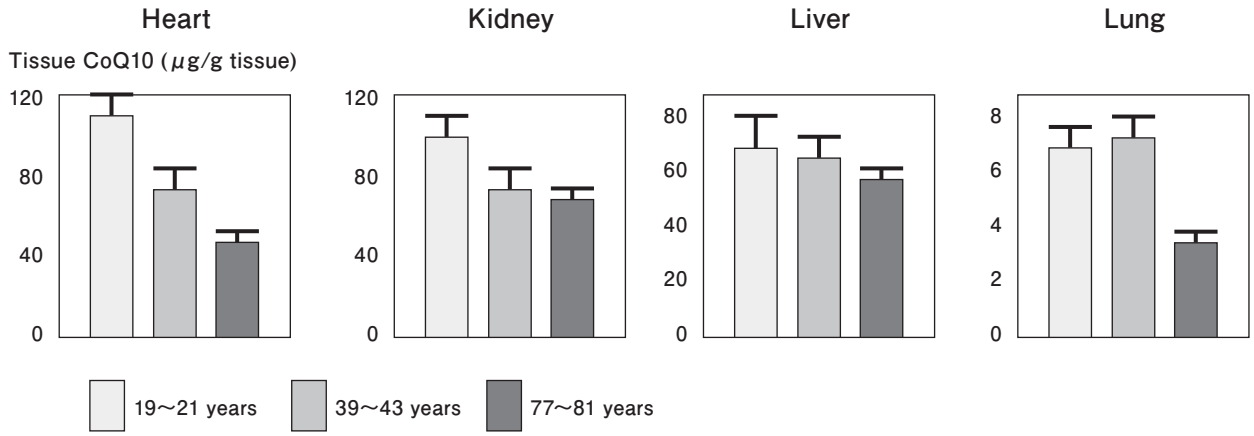

Fig 1. **Age-related changes in the tissue content of CoQ10 in the heart, kidney, liver and lung.**
Results are presented as mean ± standard deviation. Adapted from reference 14). CoQ10, coenzyme Q10.

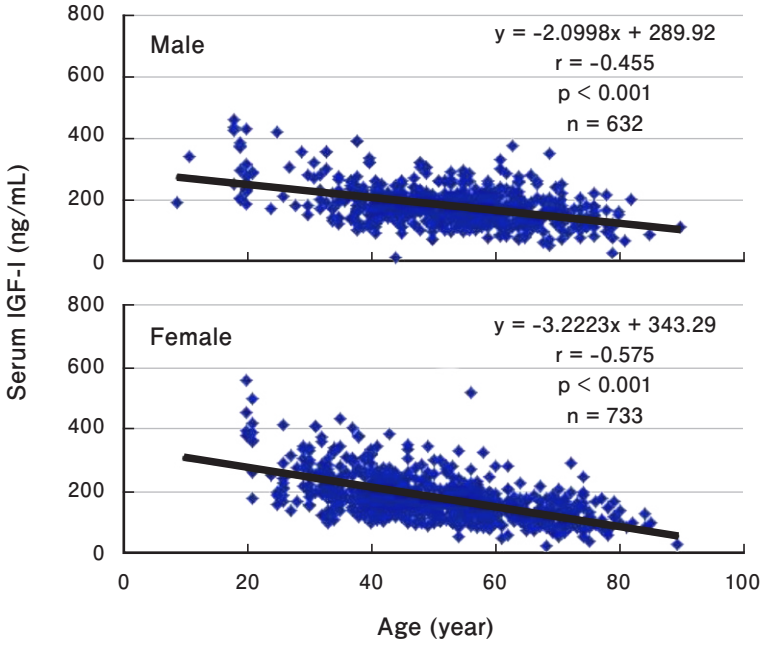

Fig 2. **Change in serum IGF-I level with age**

Adapted from reference 23). IGF-I, insulin-like growth factor-I.

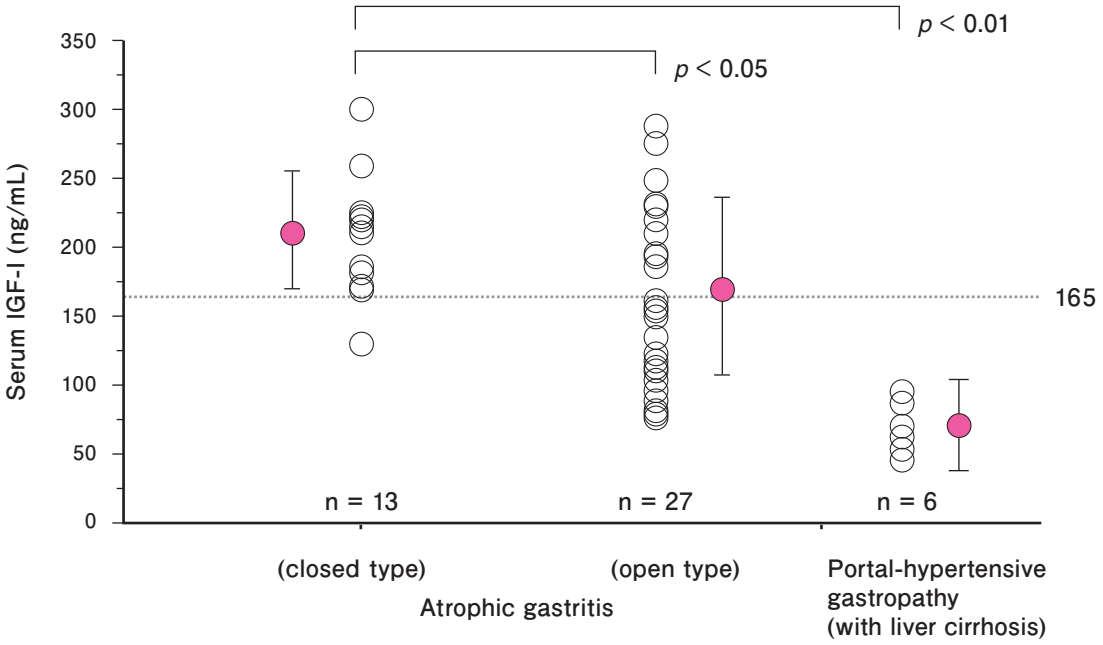

Fig 3. **Serum IGF-I levels in patients with portal-hypertensive gastropathy associated with liver cirrhosis and those with atophic gastritis.**

Results are presented as mean ± standard deviation. Analyzed by Kruskal-Wallis ANOVA. Adapted from reference 25). IGF-I, insulin-like growth factor-I.

attributable to aging and poor lifestyle, among other factors, and can lead to the development of NAFLD [26]. IGF-I can be increased by exercise, better sleep quality and proper intake of protein/amino acids, which should be considered as pituitary stimulating activities, rather than liver training methods. An increased serum IGF-I level achieved by exercise is illustrated in *Fig. 4* [27]. It can be concluded that there is no way to increase IGF-I production through liver training.

Other functions of the liver include its role as an organ of the immune system. The liver contains an abundance of immune cells, including Kupffer cells, and which regulate not only local immunity in the liver, but also immune responses throughout the body. As an organ into which exogenous antigens, such as intestinal bacteria and endotoxins, are consistently flowing through the portal system, the liver is known to induce systemic immune tolerance [28]. Therefore, it is not worthwhile to challenge the liver with intestinal bacterial or endotoxins to enhance its immunological function.

Liver functional reserve

Liver functional reserve markedly declines during the fibrosis stage of progression from chronic liver disease to cirrhosis. This decline leads to various changes, including reductions in detoxification activity, ICG clearance, portal blood flow, albumin synthesis, and the serum IGF-1 level, and an increase in the blood ammonia level. These variables generally show only minor changes with age.

In healthy individuals, the portal blood flow declines immediately after exercise and returns to the baseline level 20-30 minutes after exercise, while this portal hemodynamic recovery is delayed in individuals with decreased liver function [29]. Studies using the ICG test have also shown delayed ICG excretion after an intense exercise load in healthy individuals [30, 31] and after an exercise load in individuals with decreased liver function [32]. In animal studies, an intense exercise load also resulted in decreased portal blood flow, increased serum AST, ALD and creatine phosphokinase (CPK) levels, and decreased hyaluronic acid (HY) uptake as calculated by subtracting serum HY concentration in the hepatic vein from that in the portal vein [31]. These observations indicate that high-intensity exercise, or exercise load in individuals with decreased liver function, reduces portal blood flow and thereby affects the functions of liver parenchymal and sinusoidal cells. Thus,exercise is unlikely to lead to an improved liver functional reserve without proper evaluation of the functional reserve and a strict setting of exercise load.

Can the liver be trained by exercise?

Along with dramatic lifestyle changes, the prevalence of lifestyle-related diseases, such as type 2 diabetes, dyslipidemia, metabolic syndrome and obesity, is increasing in Japan. The upstream of metabolic syndrome is visceral fat accumulation, which, together with metabolic disorder, worsens arteriosclerosis. NAFLD is a phenotype of metabolic syndrome in the liver and known as a precursor of nonalcoholic steatohepatitis (NASH). It is also associated with high glycation stress and suggested to have a role in systemic carcinogenesis. NAFLD responds well to exercise as well as diet therapy. Exercise therapy for NAFLD patients is intended to rescue the liver by improving its glycolipid metabolism, rather than training the liver.

Growing attention is being paid to the complementary relationship between skeletal muscles and the liver. The liver produces muscle hypertrophying factors to promote skeletal muscle formation. In the case of liver failure, glycogen and amino acids are supplied from skeletal muscles to compensate for energy imbalance in the liver. Moreover, the decreased

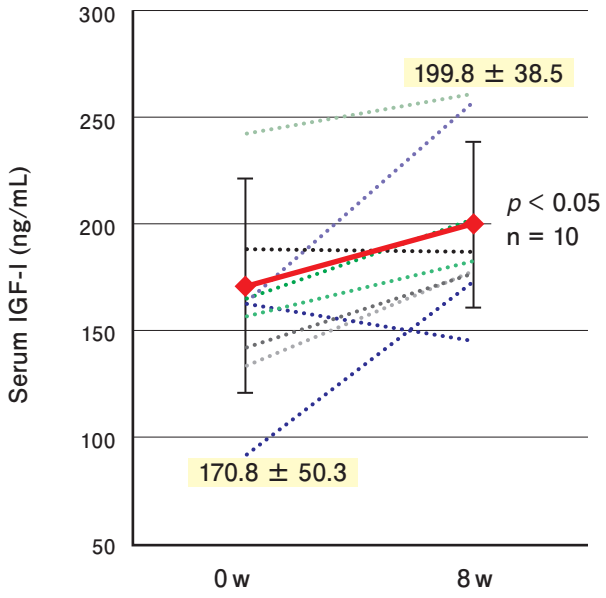

Fig 4. **Increased serum IGF-I levels achieved by exercise**

Women with no prior exercise experience (mean age 40.3 ± 1.9 years) participated in a 40-minute exercise program performed 3 times a week for 8 weeks at a fitness club. Results are presented as mean ± standard deviation. Pre- and post-exercise data were compared by the paired t-test. Adapted from reference 27). IGF-I, insulin-like growth factor-I.

liver production of muscle hypertrophying factors results in increased catabolism of skeletal muscles, leading to sarcopenia (skeletal muscle atrophy) [33]. Patients with sarcopenia have a significantly lower post-transplant survival rate compared to those without sacropenia, with low skeletal muscle mass identified as an independent prognostic factor for post-liver transplant outcomes [34]. Kidney disorder and skeletal muscle atrophy are identified as risk factors for hyperammonemia associated with the use of antineoplastic agents, such as mFOLFOX6 [35]. These conditions are associated with reduced kidney excretion and reduced metabolism/degradation of urea nitrogen in skeletal muscles, thus leading to hyperammonemia. Skeletal muscles have been shown to partially metabolize ammonia even in patients with liver cirrhosis, suggesting an important role of skeletal muscles, especially in patients with decompensated liver cirrhosis [36]. Preventing the progression of sarcopenia by exercise therapy or nutritional intervention may lead to an improved prognosis of patients with liver disease [33,34], although these therapies are performed with the intention to protect the liver by maintaining and increasing skeletal muscle mass, rather than by "training the liver".

What do you train by drinking?

It is not a wise choice to "train the liver" by drinking. The first reason for this is the high carcinogenic risk associated with alcohol consumption. Alcohol taken into the body is metabolized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), which have been associated with genetic polymorphisms and enzymatic deficiency. Low ADH1B activity and ALDH2 deficiency are known to dramatically increase the risk of esophageal cancer related to alcohol consumption. Acetaldehyde (AA), a substance known to cause high glycation stress, exhibits mutagenicity at a concentration of 50-100 μM or higher. After drinking, the salivery AA concentration reaches up to 100 μM, while the blood AA concentration reaches 20 μM in ALDH2 deficient individuals and 2-5 μM in ALDH2 active individuals, but it can reach 50 μM after excessive alcohol consumption even in ALDH2 active individuals [37-39]. Thus, people whose face turns red after drinking are easily identified as those at risk. However, people with low ADH1B activity tend to misjudge themselves as being tolerant to alcohol, as their face does not turn red clearly, resulting in increased alcohol intake, and ethanol metabolism occurs slowly. This type of people are at the highest risk of cancer, as they are exposed to ethanol and AA for longer period of time after excessive alcohol consumption, and the addition of smoking habit will increase their cancer risk ratio to more than 300.

The microsomal ethanol-oxidizing system (MEOS) is among the ethanol metabolism pathways that is most effectively "trained" by drinking [40-44]. An increased alcohol intake will lead to the induction of hepatic microsomal MEOS and subsequent increase in the proportion of MEOS-medicated ethanol metabolism (about 20% of total), resulting in an increased reduced/oxidized ratio of nicotinamide adenine dinucleotide ($NADH/NAD^+$) and increased AA production [43,44]. The MEOS consists mainly of cytochrome P-450. In particular, cytochrome P-450 2E1 is a strong free radical generator and thus is more likely to cause cellular damage through lipid peroxidation than other P-450 cytochromes. Cytochrome P-450 is also a typical drug metabolism pathway that is subject to competitive inhibition with ethanol after drinking, resulting in prolonged drug half-life and enhanced drug potency, or enzyme induction in the absence of ethanol, resulting in a shortened drug half-life and weakened drug potency. These mechanisms complicate drug therapy and thus require extra attention [44].

The second reason is that habitual drinking increases the risk of hypertension. There is a dose-response relationship between drinking and hypertension, and the risk is independent of the type of alcoholic beverage consumed or physical constitution, *e.g.* with or without ADH/ALDH gene polymorphisms [45]. An analysis of 238 individuals (90 males and 148 females) who received a thorough medical checkup at the National Center for Global Health and Medicine in Japan, also identified excessive alcohol consumption, in addition to menopause and a high total cholesterol level, as a risk factor for increased bone aging (decreased bone mineral density) among women [46].

The third reason is that alcoholic beverages promote glycation [47] and thereby increase glycation stress. As a glycation intermediate, AA is involved in the production of advanced glycation endproducts (AGEs) [48].

AGEs derived from glyceraldehyde (GLA) are known to have a particularly high toxicity and are thus referred to as toxic AGEs (TAGE) [49,50]. AA-derived AGEs are also likely to be of high toxicity, but their reaction pathways have not been well characterized in humans. When reacted with rat serum albumin (RSA) and bovine serum albumin (BSA), AA emitted a spectrum of fluorescence similar to those of AGEs derived from other glycation intermediates, such as glyoxsal (GO), methylglyoxal (MGO) and GLA. AA-albumin reaction products have been shown to be neurotoxic, found in the autopsied brain of alcoholics [48] and toxic to cultured hepatocytes [50]. ***Figure 5*** shows a comparison of the fluorescence spectra of solutions of glucose, GLA and AA reacted with human serum albumin (HSA) [51]. The maximum emission wavelength is 460 nm in all curves, indicating that these reaction products contain an abundance of fluorescent AGEs. AA-derived AGEs may thus be involved in the pathogenesis of cerebropathy [48] and hepatopathy [50].

We would like to present our data on the relationship between drinking and glycation stress. An analysis of fluorescence intensity from skin AGEs in Japanese people has shown age-related increases in fluorescence intensity and individual variability [52]. Although the observed individual variability is the result of cumulative lifestyle differences, alcohol consumption, as well as smoking and lack of sleep, were identified as a major aggravating factor for glycation stress [53]. ***Figure 6*** shows a higher fluorescence intensity from skin AGEs in non-drinkers than in drinkers in the 20s age group. This may be because in this young age group, drinking induced a slight increase in the activity of the ethanol/AA metabolism pathway, thus resulting in reduced AGEs production. In the 30s and older age groups, however, the negative impact of drinking is more evident, with metabolism being overwhelmed by AGE production.

The leading causes of death among those in their 20s are accidents and suicides. Accidents include traffic accidents and acute alcohol intoxication. From the anti-aging perspectives, in order to prevent alcohol-related deaths among young people, it may not be a bad idea for them to take a trial sip of beer to find out in advance whether they are tolerant to alcohol. These tragic alcohol-related accidents suffered by alcohol intolerant young people who are unaware of their physical constitution at welcome parties for newcomers must be avoided.

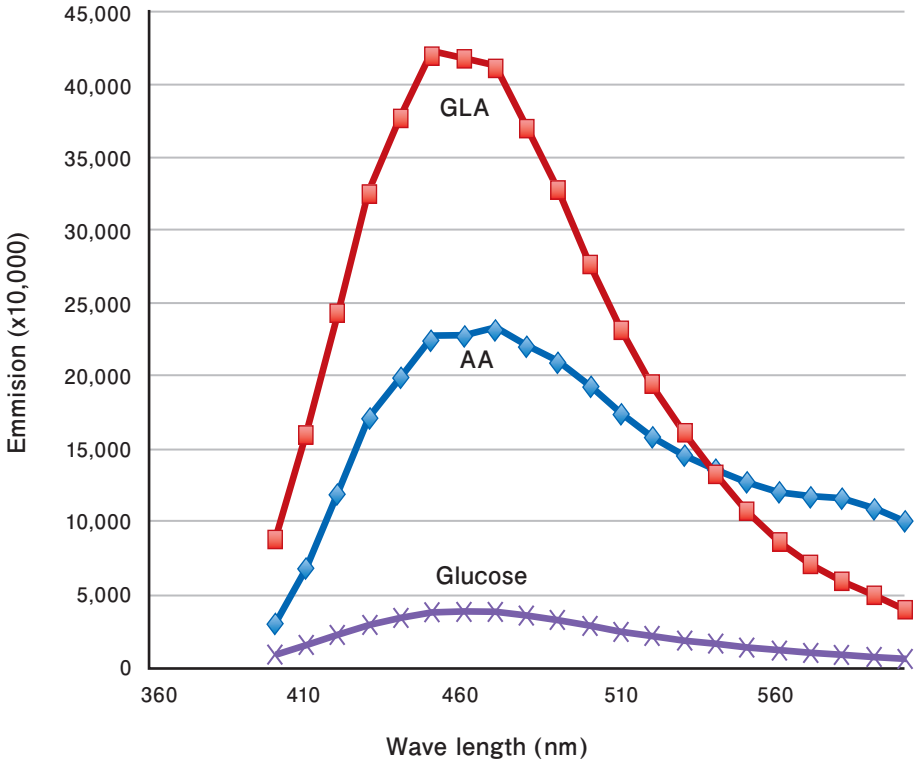

Fig 5. **A comparison of fluorescence spectra for the reaction of albumin with AA, GLA and glucose.**

The concentrations of glucose, GLA and AA are all 500 mmol/mL. HSA concentration is 20 mg/mL. The reaction was done at 37°C for 7 days. Adapted from reference 51). GLA, glyceraldehyde; AA, acetaldehyde; HSA, human serum albumin.

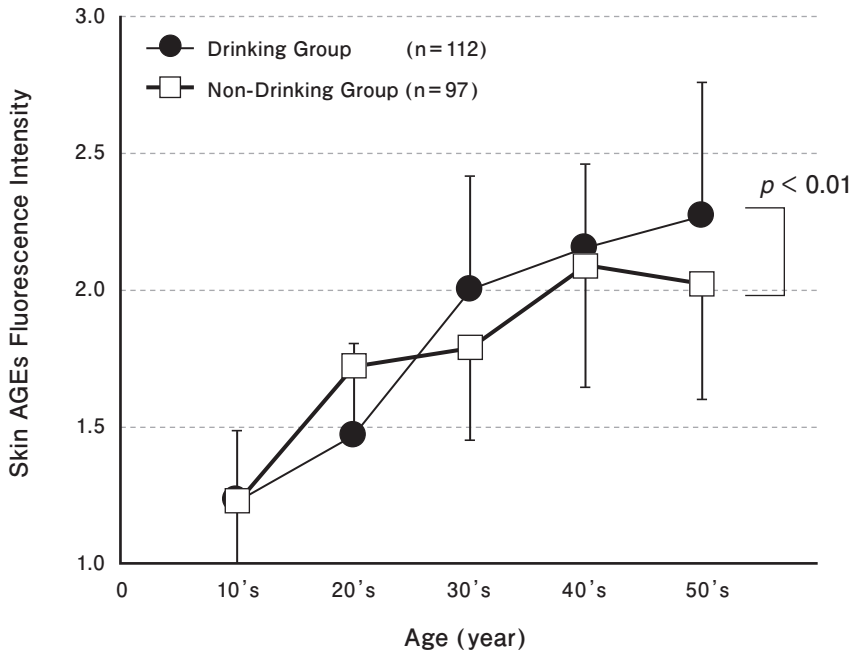

Fig 6. **Age-related changes in skin AGE fluorescence intensity and the effect of drinking**

Fluorescence intensity was measured in the medial aspect of the upper arm using an AGE Reader (DiagnOptics). Results are presented as mean ± standard deviation. An intergroup comparison among people aged 20-59 years old by the Mann-Whitney's U-test. The chart was created using the data from reference 53).

Conclusion

The liver is the largest organ in the human body with a very high potential functional reserve; as low as 20% residual function of the liver is believed to be sufficient to maintain human life. Thus, the liver's age-related functional decline is smaller compared to its potential function, and there seems to be no need to actively train the organ. There is no training method to improve the liver's metabolic, exocrine and endocrine functions. Morphological changes, such as fibrosis in the course of progression from chronic hepatitis to cirrhosis, lead to decreased liver functional reserve and eventually to a fatal consequence. Liver training by exercise supports the roles of the liver by 1) stimulating pituitary GH secretion to promote IGF-I production from the liver, 2) improving metabolism of nitrogen-containing compounds and improving hyperammonemia under the condition of reduced liver functional reserve by maintaining or increasing skeletal bone mass, and 3) improving NAFLD. Excessive alcohol consumption only enhances glycation stress and puts a burden on the liver, and does nothing good for the liver. Therefore, I vote "No" to liver training.

Conflict of Interest Statement

The authors state that performance of this study entailed no issues representing a conflict of interest.

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