Review Article

Science of Nonalcoholic Fatty Liver Disease in Anti-Aging Medicine 2011

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease caused primarily by obesity, and its incidence among Japanese adults is rapidly rising at 10-40%. Most NAFLD presents as simple steatosis, but some are nonalcoholic steatohepatitis (NASH) progressing to hepatic cirrhosis or hepatocellular carcinoma. NAFLD is diagnosed by the following three features; (1) alcohol non-consumers (“non-drinkers”), (2) steatosis, and (3) exclusion of liver disease caused by other factors, with non-drinkers including light consumers of alcohol in amounts not engendering alcoholic liver disease. Dietary treatment is the basis of therapy, but evidence concerning exercise therapy has accumulated recently, and its mechanisms have been explained.

Dehydroepiandrosterone (DHEA) is an androgenic intermediate metabolite produced by the adrenals and known as an Anti-Aging hormone with an improving effect on insulin resistance, an antioxidant effect, and an antifibrotic effect. Serum dehydroepiandrosterone sulfate (DHEA-s) has been shown to present low levels in advanced stages of NAFLD and diminished DHEA may contribute to progression of NAFLD. Growth hormone (GH) plays a crucial role not only in childhood growth but also in adult metabolic regulation, and adult GH deficiency (GHD) leads to increased visceral fat, dyslipidemia, and decreased QOL. Complicating NAFLD/NASH is a frequent occurrence in adult GHD and is improved by GH replacement therapy. On this basis, aging is an important risk factor for progression of NASH, which suggests a need for discussion of NASH and NAFLD from the perspective of Anti-Aging Medicine.

KEY WORDS: oxidative stress, insulin resistance, exercise, dehydroepiandrosterone, growth hormone

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease caused primarily by obesity 1-3). In developed countries, overeating and lack of exercise are rapidly increasing the obese population, and this development has made NAFLD the most frequently occurring liver disease, control of which is urgent. Though most NAFLD presents as simple steatosis, 10-20% is nonalcoholic steatohepatitis (NASH) progressing to hepatic cirrhosis or hepatocellular carcinoma. Aging is an extremely important risk factor for pathologic progression, and the disease is certainly one in the purview of this academic symposium. The keynote address of the symposium held to share the most recent information on NAFLD was followed by a presentation of recent findings concerning mechanisms of exercise therapy inhibiting steatosis, the relation between the Anti-Aging hormone dehydroepiandrosterone (DHEA) and progression of NAFLD, and the role of growth hormone (GH) in NAFLD pathology and treatment. Our paper summarizes this information.

2. What is NAFLD/NASH

1) Overview of NAFLD/NASH

Excess fat in the liver is stored in the hepatic cytoplasm as fat globules and presents as steatosis. The causes of steatosis include increased uptake of fatty acids by the liver, accelerated synthesis or decreased burning of fatty acids, and impaired synthesis or decreased release of fatty acids from the liver. Pathologically, steatosis is defined as observation of fat globules in 5-10% of the hepatocytes progressing to hepatic cirrhosis. Clinically, fatty liver disease is classified as alcoholic and nonalcoholic (NAFLD). Causes of NAFLD include obesity, diabetes, dyslipidemia, drug agents (e.g., steroid, tetracycline), lipid metabolism disorder, endocrine disease (e.g., Cushing syndrome, GH deficiency), poisoning (e.g., white phosphorus), and advanced malnutrition, but the majority...
NAFLD is the hepatic pathology of metabolic syndrome but incidence of cardiovascular events and liver-related death cirrhosis is 10-25% in 5 years, and 5-year survival is 70-95%. Fatty liver disease is rare. In NASH, progression to hepatic coma, esophageal varices, and ascites.

Cirrhosis presents symptoms of liver failure such as jaundice, coagulability, and albumin levels decrease. Decompensated other markers of hepatic fibrosis rise, and in cirrhosis, platelets, fibrosis progresses to bridging fibrosis, hyaluronic acid and with gradual progression, leads to hepatic cirrhosis. When levels. Hepatic fibrosis represents an index of severity which, the diseases occur not infrequently in cases with normal ALT and biochemistry assays are characterized by elevated

3) NAFLD/NASH pathology

In more than 90% of cases, NAFLD or NASH complicates lifestyle-related diseases such as obesity, diabetes, dyslipidemia, hypertension. Subjective symptoms are often not recognized until progression to hepatic cirrhosis, and the opportunities for diagnosis include regular health examinations. Hematology and biochemistry assays are characterized by elevated transaminases, ALT foremost, but note should be taken that the diseases occur not infrequently in cases with normal ALT levels. Hepatic fibrosis represents an index of severity which, with gradual progression, leads to hepatic cirrhosis. When fibrosis progresses to bridging fibrosis, hyaluronic acid and other markers of hepatic fibrosis rise, and in cirrhosis, platelets, coagulability, and albumin levels decrease. Decompensated cirrhosis presents symptoms of liver failure such as jaundice, hepatic coma, esophageal varices, and ascites.

With regard to prognosis, liver-related mortality in simple fatty liver disease is rare. In NASH, progression to hepatic cirrhosis is 10-25% in 5 years, and 5-year survival is 70-95%. The most frequent cause of death is cardiovascular event, followed by malignant tumor and liver-related death, and the incidence of cardiovascular events and liver-related death is significantly higher than that in the general population. NAFLD is the hepatic pathology of metabolic syndrome but also aggravates insulin resistance in the liver and represents a cause of metabolic syndrome. The interaction of both diseases also engenders a vicious circle. Elevation of oxidative LDL, plaque formation on carotid duplex ultrasound, and other such findings are also observed frequently in NAFLD and are noted risk factors for cardiovascular events and diabetes. NAFLD must also be understood as a systemic disease, not merely a liver disease. In NASH-related cirrhosis 1), the 5-year rate of hepatocarcinoma is approximately 10%, 5-year survival is approximately 70-80%, and liver-related death is the most frequent cause of death, at 70-80%.

4) NAFLD/NASH diagnosis

NAFLD is diagnosed by (1) no-alcohol consumption status (“non-drinker”), (2) diagnosis of fatty liver through liver tissue or diagnostic imaging (US, CT, MRI), and (3) exclusion of liver disease due to other causes 1-3). Non-drinkers include individuals consuming alcohol to an extent not causing alcoholic liver dysfunction (ethanol conversion of 20 g/day or lower, Japanese sake conversion of 180 ml/day or lower). Given the lack of blood biochemistry markers to diagnose fatty liver, and its not infrequent occurrence among cases presenting normal AST and ALT, histological diagnosis or diagnostic imaging is essential. The need for exclusion of liver disease due to other causes stems from the fact that other liver diseases also cause fatty liver. NAFLD also complicates viral liver disease or autoimmune hepatitis and aggravates these conditions.

The diagnostic criteria for NASH are NAFLD accompanied by presentation of steatohepatitis in the hepatic pathology observed. Severity in the pathologic diagnosis of NASH is diagnosed by activity (grade: hepatocyte swelling, fat deposition, inflammatory cellular infiltration) and fibrosis (stage) 4,5,12).

Liver biopsy for pathologic diagnosis is an invasive test, but at present, there are no established hematology assay markers or diagnostic imaging methods for diagnosis of NASH. Indices under study include the apoptosis marker CK-18; TNF-α, IL-6 and other inflammatory cytokines; adiponectin, a beneficial adipocytokine; oxidative stress-induced thioredoxin; oxidative LDL; and high-sensitivity CRP 13). A number of scoring systems combining multiple parameters have also been reported, and the NAIFC score, created in Japan, provides high diagnostic accuracy for NASH 14). Systems such as NAFLD fibrosis score 15) relating to severity of fibrosis have also been devised and are useful for assessing severity 16).

Problems in NASH diagnosis include the lack of hematodiagnostics markers and consequent reliance on exclusionary diagnosis, and the need for liver biopsy in diagnosis. From the standpoint of numbers as well, liver biopsy for diagnosis of NASH in all cases of NAFLD is impractical. Cases of diagnosed NAFLD also indicated for additional liver biopsy are (1) cases of NASH where stringent treatment is deemed necessary, and (2) cases requiring differential diagnosis of autoimmune hepatitis and other such liver disease. Cases of NASH requiring stringent treatment are cases of NAFLD in which improvement of lifestyle habits is not possible and AST or ALT elevation continues, and those among the elderly, highly obese, diabetics, and individuals with a pattern of decreased liver function.

5) NAFLD/NASH treatment

Treatment strategies devised for NAFLD are tailored to its cause. The pathology progresses through a “first hit” of fatty liver compounded by some type of “second hit.” In this respect,
The treatment first addresses fatty liver by treating obesity or lifestyle habits primarily through diet and exercise therapy; treatment also addresses the second hit (Fig. 1) [1-3,17-20].

Though the most important basic treatment is weight control through diet and exercise therapy, weight loss fails in nearly half of all cases, and this modality of treatment is not simple. In cases where obesity simply cannot be improved, drug treatment and surgical treatment are the final treatment alternatives for relief from the hardships of obesity treatment [20].

For diabetes, drugs improving insulin resistance are the first choice. Such drugs include thiazolidine derivatives (pioglitazone) and biguanide drugs (metformin). Pioglitazone is a drug agent which acts as a peroxisome proliferator-activated receptor γ (PPARγ) and is also reported to improve insulin resistance, accelerate burning of fatty acids by hepatic mitochondria, reduce inflammation, and increase adiponectin production. There are also many reports and a high evidence level for the agent in diabetes-complicated and non-complicated NAFLD [21]. However, aggravation of pathology by discontinuation from the drug makes the time frame of discontinuation a problem. Adverse effects also include weight gain and fluid retention (edema, heart failure). Risk of bladder cancer is another emergent problem.

Metformin regulates blood sugar by inhibiting gluconeogenesis in the liver and increasing sugar uptake by the liver. Efficacy in NAFLD is also reported. Therapeutics for dyslipidemia (e.g., statins, bezafibrate, probucol, EPA), antihypertensives, hepatic fibrosis inhibitors, and drugs with an insulin resistance-improving effect or antioxidant effect (angiotensin II receptor blockers (ARB), calcium blockers) are also administered. Drugs administered to counter the second hit include antioxidants (vitamin E, vitamin C), and ursodeoxycholic acid (urso) used as a liver protectant. These are safe, widely administered drugs with virtually no adverse effects. Vitamin E in particular has drawn attention for a recent report of better efficacy in a comparison of therapeutic effect versus pioglitazone [22].

End-stage cirrhosis caused by NAFLD is a transplant-indicated disease. Recurrence of NAFLD after transplant is reported in approximately 30% of cases, but post-transplant survival is equivalent to that in other non-viral liver disease.

3. Exercise-derived prevention and improvement of fatty liver

Accumulation of intrahepatic fat is caused by an increased blood-borne influx of glucose and fatty acids, the basic substance of neutral fats, and lack of exercise and regular consumption of a diet high in fats and sugars thus contribute greatly to the formation of fatty liver. Additionally, when accumulation of visceral fat has led to a state of insulin resistance, levels of glucose and fatty acids in the blood are constantly elevated, and the inflow of these basic substances is increased; at the same time, the fat metabolism capability of the liver itself weakens, promoting fatty liver. In reality, most metabolic syndrome patients are also known to have concurrent fatty liver [23]. Exercise has a one-time effect of raising energy consumption during exercise as well as fitness effects including reduction of body fat and improvement of insulin resistance; exercise thus represents a plan contributing to prevention and improvement of fatty liver. Recent research has slowly and steadily increased evidence for the effect of exercise on fatty liver and the understanding of its mechanism.

1) Evidence for inhibition of fatty liver by exercise

By increasing the use of sugars and fats, the basic structures of energy, exercise is well known to move the energy balance of the body into deficit and thereby reduce levels of body fat and lipids in the blood. Because exercise dramatically increases energy metabolism particularly in skeletal muscle, to date there have been many studies concerning sugar metabolism and fat metabolism in skeletal muscle. Although there are not many research studies concerning liver function and exercise, it has been suggested that exercise improves liver function because exercise reduces levels of neutral fats, cholesterol, and free fatty acids in the blood and likewise inhibits elevation of aspartate aminotransferase and alanine aminotransferase, indices reflecting liver dysfunction [24,25]. On the other hand, it is quite recent that research efforts to find out the effects of exercise on intrahepatic fat started, and some reports from crosscutting research showed that individuals with exercise habits have little accumulation of intrahepatic fat. Perseghin et al. [26] used MRI to evaluate intrahepatic fat and reported that a significant negative correlation existed between...
levels of routine physical activity and levels of intrahepatic fat, among both NAFLD patients and healthy individuals. In other words, their results suggested that increased energy consumption through increased physical activity inhibited not only fatty tissue, but also accumulation of intrahepatic fat. Krasnoff et al.\textsuperscript{27} also showed that maximum oxygen intake levels were low among patients with a high NAFLD activity score, another finding indicating that performance of exercise greatly preserves cardiopulmonary function and suggesting a link to inhibition of fatty liver and consequent progression to NAFLD. Interventional research completed by St. George et al.\textsuperscript{28} also showed that 3 months of exercise therapy improved indices of liver function in NAFLD patients, and that exercise contributed to improvement of NAFLD or prevention of its progression.

Aerobic exercise has long been regarded as fundamental for preventing disease, given its effects of energy consumption during exercise, reduction of body fat, and substantial efficacy in lowering blood sugar and fats in the blood. Because accumulation of visceral fat and concomitant insulin resistance contribute to progression of fatty liver, aerobic exercise is here again regarded as a fundamental form of exercise for prevention and improvement of these developments.

In contrast, Zelber-Sagi et al.\textsuperscript{29} reported that NAFLD patients performing at least some form of exercise once or more per week had significantly lower accumulation of intrahepatic fat and neutral fats in blood, but in this instance, their research produced the highly interesting finding that effects were greater among individuals performing resistance exercise than those performing aerobic exercise. Likewise, Hallswort et al.\textsuperscript{30} completed interventional research involving an 8-week resistance exercise program which found significant reductions of intrahepatic fat. More recently, a crosscutting study of subjects comprising 813 NAFLD patients found no significant improvement in NASH or hepatic fibrosis from exercise in individuals with habits of low-to-moderate intensity exercise, but a significant effect in individuals with habits of high-intensity exercise, leading the authors to state that exercise plans should place greater emphasis on exercise intensity than exercise quantity.

These results show that even resistance exercise or comparatively high-intensity, short-duration exercise can inhibit fatty liver or progression to NAFLD, i.e., this effect is not limited to walking, jogging, or other aerobic exercise alone. The results also suggest that such exercise is more effective than aerobic exercise performed for longer periods at low intensity.

2) Mechanism of exercise-derived inhibitory effect on fatty liver

While immunological studies have shown that exercise inhibits accumulation of fat in the liver, many aspects of the mechanism are unclear. As mentioned previously, an excess influx of fatty acids and glucose to the liver accelerates synthesis of neutral fats, and it is easy to imagine that the considerable energy consumption of exercise inhibits fatty liver. At the same time, research in animal models of hepatic dysfunction stressed by overeating or by a choline-devoid, methionine-deficient diet have shown decreased fatty acid oxidation capability and substantially increased synthesis capability in the liver, indicating that accumulation of fat within the liver depends on the lipid metabolism capability of the liver itself\textsuperscript{32,33}. In other words, accumulation of neutral fats within the liver is accelerated not simply by an excess blood-borne influx of their basic substances; the phenomenon occurs when the capability for oxidative decomposition of fatty acids in the liver decreases, and the capability for fatty acid synthesis is newly enhanced.

We used KK/Ta mice with fatty liver induced by a high-sucrose diet to investigate the effects of exercise on fatty liver and hepatic lipid metabolism-related enzymes. KK/Ta mice fed a high-sucrose diet for 12 weeks showed a marked increase in hepatic neutral fat content versus Balb/c mice (normal control mice). However, this accumulation of fat was inhibited significantly by the stress of 30 minutes of treadmill exercise 3 times per week (Fig. 2). At such time, fatty acid oxidation-related enzymes in mitochondria, i.e., carnitine palmitoyl transferase II, acyl-CoA dehydrogenase, and trifunctional enzyme were significantly elevated in the exercise group, while

![Fig. 2. Neutral fat content in the liver (A) and histological profile (B) mean ± standard error, *: p<0.05.](image-url)
the level of fatty acid synthase, a fatty acid synthesis enzyme, was substantially lower (Table 1). In other words, these results suggested that exercise inhibited fatty liver by improving the lipid metabolism of the liver itself.

Rector et al.34 reported that stress from 16 weeks of spontaneous running exercise increased fatty acid oxidation capability in hepatic mitochondria in obese rats, which supports our results. Expression of these lipid metabolism-related enzymes is inhibited primarily by transcription factors such as sterol regulatory element-binding protein and PPARα 35,36). Activity of the transcription factors is regulated by substances such as glucose, insulin, free fatty acids, adipokines in the blood 37,38), and exercise-derived improvement of visceral fats and glucose tolerance is deemed related to inhibition of the blood-borne influx of these substances.

High-sucrose and high-fructose diets (fructose being a constituent sugar of sucrose) induce fatty liver more readily than high-glucose diets, starch diets, or high-fat diets 39,40). One cause of this phenomenon is thought to be a higher hepatic glycogen storage rate of sucrose and fructose 41), which accelerates synthesis of fatty acids from sugars saturating the liver. The possible linkage may be that fatty liver is inhibited by exercise-induced sugar consumption, accelerated release of hepatic glycogen into the blood, and inhibition of fatty acid synthesis from dietary sugars. In reality, in a study we completed, exercise inhibited fatty liver markedly, but improvement in glucose tolerance, blood insulin concentrations, and epididymal fat weight was less substantial. St. George et al.38 also reported that exercise-induced improvement in NAFLD was observed independently of quantitative body fat reduction. These findings together suggest that exercise-derived inhibition of fatty liver is also influenced strongly by factors other than visceral fat loss and improvement of insulin resistance.

Additionally, we also observed that expression of heat shock protein 47 (HSP47), a collagen-binding protein, in the liver was lower in an exercise group 42). Because HSP47 functions as a molecular chaperone in the processes of procollagen biosynthesis and secretion in the liver, it is regarded as an index of hepatic fibrosis 43). Consequently, the fact that exercise inhibits fatty liver also suggests a possible linkage to prevention of NASH progression, and these questions require further study.

### Table 1 Time for modulation

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Balb/c</th>
<th>Rest group</th>
<th>Exercise group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>100 ± 3</td>
<td>57.5 ± 4.3</td>
<td>75.8 ± 5.1</td>
</tr>
<tr>
<td>CPT II</td>
<td>100 ± 8</td>
<td>74.4 ± 7.5</td>
<td>135.0 ± 6.7</td>
</tr>
<tr>
<td>Trifunctional enzyme</td>
<td>100 ± 5</td>
<td>45.3 ± 1.9</td>
<td>59.3 ± 3.9</td>
</tr>
<tr>
<td>ACC</td>
<td>100 ± 8</td>
<td>126.3 ± 7.5</td>
<td>126.2 ± 6.2</td>
</tr>
<tr>
<td>ACL</td>
<td>100 ± 6</td>
<td>84.0 ± 3.6</td>
<td>103.0 ± 7.4</td>
</tr>
<tr>
<td>FAS</td>
<td>100 ± 11</td>
<td>124.5 ± 10.7</td>
<td>77.6 ± 4.1</td>
</tr>
</tbody>
</table>

Mean ± standard error

ACD, acyl-coenzyme A dehydrogenase; CPT II, carnitine palmitoyl transferase II; ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; FAS, fatty acid synthase.

*p < 0.05 vs Balb/c. **p < 0.05 vs KK/Ta rest group.

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### 4. Significance of dehydroepiandrosterone (DHEA) in NAFLD

#### 1) What is DHEA

DHEA is an androgenic intermediate metabolite produced and secreted primarily by the adrenals and gonads. It is also present in the body in sulfated form as DHEA-sulfate (DHEA-s), and these forms are mutually convertible. DHEA-s is the steroidal hormone present at highest concentration in the body. Changes in its levels typically track those of DHEA, do not change on an intraday basis, and can be measured stably. DHEA-s begins to increase in both males and females at approximately age 6-7 years, reaches a peak at puberty, continues at high levels until approximately age 13-25 years, and then decreases linearly with age 44). The effect of DHEA as an androgen is approximately 5% weaker than that of testosterone but is known to produce various effects including improvement of insulin resistance 45-49), antioxidation 49), PPARα activation 50,51), inhibition of procollagen type 1 synthesis, inhibition of arteriosclerosis, and inhibition of osteoporosis.

#### 2) Significance of serum DHEA-s measurement

A study of male residents of Baltimore found that high levels of DHEA served as an index of longevity in parallel with low body temperature and hypoinsulinemia. In Japan, a 27-year longitudinal study among residents of Taneshimaru, Fukuoka Prefecture found that survival rates among males were significantly higher in a high DHEA-s group, independent of blood pressure or blood sugar levels 52). Based on these data, DHEA-s is known as an index of longevity at least among males and is measured as an Anti-Aging index 53). However, caution is advised in that abnormal elevation is observed in Cushing syndrome, congenital adrenocortical hyperplasia, and other such diseases; low levels are observed in anorexia nervosa, chronic stress, and aggravation of diabetes; and improvement of these illnesses returns levels to normal. Elevation of DHEA-s levels is also reported to inhibit insulin resistance and metabolic syndrome 54), but elevation of DHEA-s is also conversely reported to pose a risk of metabolic syndrome, and a consensus does not exist 55). Fukui et al. reported that decreased levels of DHEA among males with type II diabetes were associated with arteriosclerosis and onset of kidney disease 56,57).

#### 3) DHEA in NAFLD

Charlton et al. measured serum DHEA-s levels in NAFLD and reported that DHEA-s showed lower values in cases progressing to NASH fibrosis 58). We also performed Anti-Aging screening among 133 Japanese individuals diagnosed with NAFLD by liver biopsy and measured serum DHEA-s levels in 399 healthy age- and sex-matched individuals with normal ALT (30 IU/L or lower) who went through Anti-Aging screening 59). The composition of NAFLD cases included 90 with NASH (Brunt stage 0-2 / 3-4: 73/17) and 43 non-NASH. In the NAFLD group alone showed lower values in NASH versus non-NASH cases and decreasing levels of DHEA-s with progression of fibrosis reflected by Brunt stage.
specifically, Stage 0: 170.4±129.2, Stage 1: 137.6±110.5, Stage 2: 96.2±79.3, Stage 3: 61.2±46.3, Stage 4: 30.0±32.0 mg/dL (mean ± SD, Fig. 3). Determination of factors contributory at stage 3 or higher by multivariate analysis showed that age, sex, and HOMA-IR were independent factors, and serum DHEA-s < 66 μg/mL was also a significant independent factor. The area under the receiver operating characteristics (ROC) curve and differentiation of Stage 3 and higher progression was good, at 0.79, and with serum DHEA-s of 66 μg/mL taken as a cutoff value, sensitivity was 77% and specificity was 73% ![Fig. 3](DHEA-S decreases in conjunction with progressive fibrosis in NAFLD 59). These findings suggest an association between reduced DHEA-s and progression of NASH fibrosis and indicate that measurement of DHEA-s may be useful for discriminating cases of fibrotic progression.

### 4) Potential of DHEA as a therapeutic agent

A report in the JAMA concerning the anti-obesity effect of DHEA stated that a decrease in visceral and subcutaneous fat and improvement of insulin resistance were obtained among a DHEA-supplemented group in a double-blind, comparative study 62); however, a negative report followed 63), and the usefulness of DHEA in lifestyle habit diseases is controversial at present. Improvement of fatty liver by administration of DHEA was reported in a DHEA-supplement group of an animal model 64), and DHEA supplementation may in the future serve as a treatment for NASH.

### 5. A close association between GH/IGF-I system and pathophysiology of NAFLD/NASH

#### 1) Age-dependent decrement in GH secretion and the role of GH and IGF-I in the development of NASH.

Secretion of growth hormone (GH) from the pituitary declines with age, and serum IGF-I also decreases. Though decreased muscular strength, decreased bone mass, and increased visceral fat are generally observed with increasing age, at least a part of these phenomena are considered to be related to the physiological decline in GH secretion. From this perspective, GH has been administered experimentally for Anti-Aging objectives, but at present, there is no clear evidence demonstrating usefulness. However, considering that the incidence of NAFLD increases with age, there is a substantial plausibility that the age-attendant decline in GH secretion bears on the risk for onset of NAFLD in the general population.

Adult growth hormone deficiency (GHD) is a state of impaired GH secretion caused by functional or organic abnormalities. Causes of adult GHD include tumors of the hypothalamic and pituitary regions, inflammation, granuloma, leukemia, head trauma, and aftereffects of radiotherapy. Epidemiologically, the annual rate of new onset of GHD is estimated as approximately 1800 individuals among 7000 patients examined each year for panhypopituitarism, in which GHD often occurs, but many additional latent cases are thought to exist.

Fatigability, decreased stamina and concentration, and other diminishments of QOL are observed as subjective symptoms of adult GHD, as are the physical symptoms of increased body fat (visceral fat), decreased bone mass, and decreased muscular strength. Increases in visceral fat in particular cause metabolic abnormalities, insulin resistance, and other conditions which are similar to those of metabolic
syndrome; cardiovascular changes are frequent; and the survival prognosis is poor \(^65\). NAFLD may also be associated with such increases in visceral fat. Supplementary treatment of adult GHD with GH was approved in Japan in April 2006. Supplementary GH treatment improves QOL and abnormal body composition (i.e., decreases in fat, particularly visceral fat, and increases in non-fat body weight). Though evidence as to whether survival prognosis is improved remains inadequate, one report states that rates of death, malignant tumor, and myocardial infarction were improved in a GH treatment group, suggesting that survival prognosis may also be improved \(^66\).

2) Adult GHD with complicating NASH

Adult GHD presents pathologies highly resembling those of metabolic syndrome, with reported observations including frequent liver dysfunction, and small-scale retrospective research suggests that the incidence of NAFLD may be high \(^67,68\). We reported our experience of a case demonstrating dramatic improvement by GH treatment of adult GHD complicated by NASH \(^69\). In this case of a 31-year-old male, panhypopituitarism was attributed to pituitary stalk transection. In the pediatric phase, the patient received both cortisol and thyroxine and was also treated for short stature by GH supplementation, but at age 18 years, GH supplement therapy was discontinued. Thereafter, liver dysfunction and dyslipidemia worsened successively, and a detailed workup was performed. Visceral obesity and insulin resistance were observed, liver biopsy was performed for suspected severe NAFLD on abdominal ultrasound investigation, and NASH was diagnosed. When the patient was treated for adult GHD by GH supplementation, AST, ALT, and γ-GTP returned to normal rapidly (Fig. 4), and decreased high-sensitivity CRP concentration and decreased oxidative stress markers were observed. Ultimately, 6 months of GH treatment produced dramatic histological improvement (Fig. 5).

3) Incidence, therapeutic effect, prognosis of NAFLD/NASH in adult GHD

When we analyzed 69 cases of panhypopituitarism with concomitant GH deficit from cases in our studies to elaborate the incidence of complicating NAFLD/NASH in adult GHD, we found a marked increase in this incidence. Cases in this group treated with GH supplementation demonstrated significant improvement of liver function, and cases who underwent liver biopsy before and after treatment demonstrated significant histological improvement of NASH (manuscript submitted). These results suggest that the GH-IGF-I system plays an important physiological role in the liver.

The prognosis of NASH in panhypopituitarism including adult GHD is reportedly poor \(^70\). In 21 panhypopituitarism patients who underwent liver biopsy, 10 had NASH, burnout NASH, or hepatic cirrhosis. When these cases were observed prospectively for 66 months, 2 of 6 deaths were found to be liver-related death, and an additional 2 cases were indicated for liver transplant due to liver failure \(^70\). In a separate report, 133 of 1411 adult GHD cases in a no-GH therapy group developed malignant tumors in 5-year longitudinal observation (9%, relative risk versus control population: 1.83), and these included 7 cases of hepatocellular carcinoma (HCC). In contrast, the incidence of malignant tumor was significantly reduced in a GH therapy group, and no cases of HCC were observed \(^69\). This reduction in HCC may be attributable to a result in which progression from NASH to hepatic cirrhosis and then HCC was prevented.

Fig. 4. A case of NASH markedly improved by GH supplementation therapy \(^69\)
4) Mechanism of onset for NAFLD/NASH in adult GHD and therapeutic applications

Adult GHD presents elevation of inflammatory markers \(^{71,72}\) and increased oxidative stress \(^{73,74}\) associated with increased visceral fat. GH supplementation improves these abnormalities. GH secretion is also inhibited among obese patients, and serum GH concentration is reportedly decreased generally in NAFLD \(^{75}\), and these results suggest that decreased GH secretion itself may play a causal role in obesity and onset of NAFLD/NASH. We analyzed a GH-deficient rat representing a model of adult GHD to investigate this pathology and found that NASH occurred as in humans, and that administration of GH/IGF-I reduced oxidative stress and improved both mitochondrial morphology and liver tissue. Administration of GH/IGF-I to a NASH model mouse to investigate general therapeutic application in NASH also demonstrated an improvement of histology. Though the general treatment of NASH through weight loss and improvement of lifestyle habits achieves some effect, as do other treatments such as antioxidant agents and insulin resistance-improving agents, treatments are nonetheless still inadequate for improving long-term outcomes. Further exploration of the relationship between adult GHD and NAFLD/NASH may achieve linkages between general understanding of the onset mechanism for NASH and therapeutic applications.

6. Conclusion

In Japan, where the era of gluttony has arrived, NAFLD has become the most prevalent liver disease. In the span of several years, NAFLD/NASH is predicted to become the most important disease causing hepatic cirrhosis and hepatocellular carcinoma. Age-related decreases in DHEA and GH have been suggested as contributory to pathologic progression of NAFLD, and future therapeutic application of these substances is possible; further investigation of the pathology of NASH is needed from perspectives of endocrinology and Anti-Aging Medicine \(^{76}\). Though there is no disagreement regarding the usefulness of exercise therapy as treatment, additional scientific validation is needed to determine the optimal exercise parameters for preventing fatty liver. Reports of telomere shortening \(^{77}\) and decreased expression of senescence marker protein-30 in cases progressing to NASH \(^{78}\) are highly interesting in the context of associations between aging and pathologic progression of NASH; these observations portend an understanding of the pathology informed by aging, and the development of relevant modes of treatment.

Conflict of interest statement:

The authors declare no financial or other conflicts of interest in the writing of this paper.
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