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Dehydroepiandrosterone in Nonalcoholic Fatty Liver Disease

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease (CLD) in many developed countries and results in a serious public health problem worldwide. NAFLD includes a wide spectrum of liver diseases, ranging from simple fatty liver, which is usually a benign and nonprogressive condition, to nonalcoholic steatohepatitis (NASH) which may progress to liver cirrhosis (LC), hepatic failure and hepatocellular carcinoma (HCC) in the absence of significant alcohol consumption (Ludwig et al., 1980, Matteoni et al. 1999). About a third of people with NAFLD will develop NASH, and about 20% of people with NASH will go on to liver fibrosis and cirrhosis, with its accompanying risk of liver failure and even HCC (Yasui et al. 2011). In Japan, current best estimates make the prevalence of NAFLD approximately 20% and of NASH 2% to 3% in the general population. Pathophysiology of primary NASH still hasn't been completely clarified. According to the "two-hits" model of NASH pathogenesis proposed by Day and James (Day & James. 1999), excessive triglyceride accumulation is the most likely first step. The second step may relate to an increase in oxidative stress (Sumida et al. 2011a), which, in turn, triggers liver cell necrosis and activation of hepatic stellate cells, both leading to fibrosis and ultimately to the development of LC. Although the number of NASH cases in women is known to be higher than in men over 50 years of age, the mechanisms remain unknown (Hashimoto & Tokushige, 2011). According to our study produced by Japan Study Group of NAFLD (JSG-NAFLD) including nine hepatology centers in Japan (Sumida et al., 2011b), NASH patients with significant or advanced fibrosis (Brunt stage 2-4) was more prevalent in females than in males (Fig.1). Although plausible mechanisms have been proposed, including estrogen deficiency after menopause, iron accumulation generating hydroxylradicals via Fenton reaction (Sumida et al., 2009), and so on, precise mechanisms have not been clarified. Although several factors have been associated with more advanced NAFLD, the biological basis of the histological diversity of severity of NAFLD [i.e., why some patients develop simple fatty liver and others develop NASH with advanced fibrosis] remains unknown. More advanced NAFLD is characterized by insulin resistance, oxidative stress, and advanced fibrosis.

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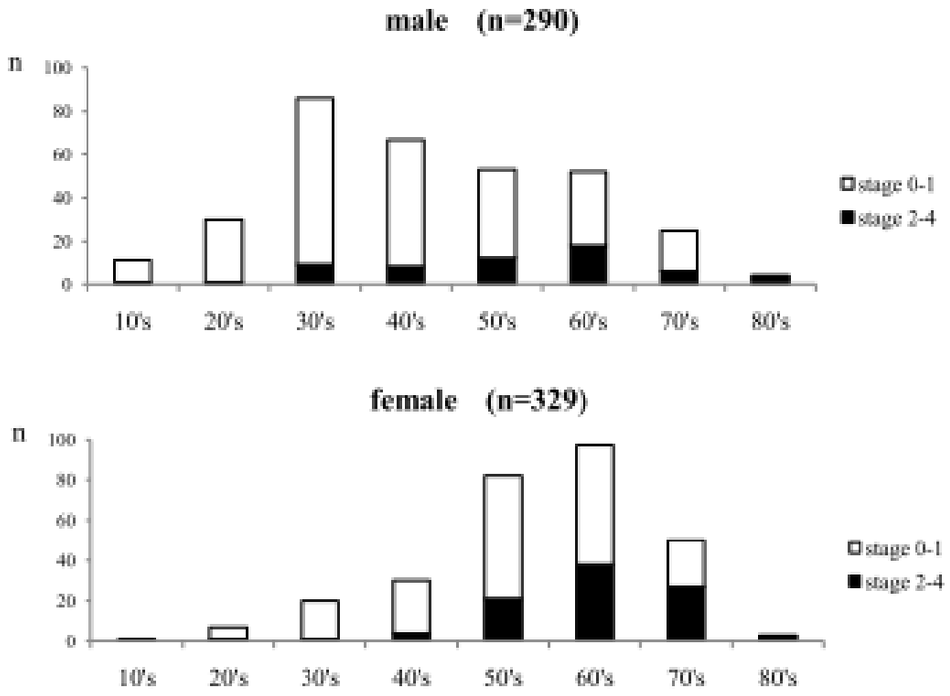

Fig. 1. The distribution of age and gender in patients with biopsy-proven NAFLD (n=619) according to fibrosis stage (stage 0-2 or stage 3-4) in Japan Study Group of NAFLD (JSG-NAFLD), including nine hepatology centers throughout Japan.

Endocrine hormones control cell metabolism and the distribution of body fat and, therefore, may contribute to the development of NAFLD/ NASH. Dehydroepiandrosterone (DHEA), and its interchangeable sulfated form, DHEA sulfate (DHEA-S), is the most abundant circulating steroid hormone and is produced primarily by the zona reticularis of the adrenal cortex in response to adrenocorticotropic hormone. DHEA has been known to have a variety of functions, including anti-oxidative stress, decreasing insulin resistance, anti-atherosclerosis, and anti-osteoporosis (Baulieu et al. 2000). DHEA-S concentration is independently and inversely related to death from any cause and death from cardiovascular disease in men over age 50. It has been postulated that DHEA and DHEA-S may be discriminators of life expectancy and aging (Phillips et al. 2010). In this chapter, we describe here the role of DHEA or DHEA-S in the pathogenesis or treatment of NAFLD.

2. NAFLD and dehydroepiandrosterone

2.1 What is dehydroepiandrosterone?

DHEA, and its interchangeable sulfated form, DHEA-S (Fig 2.), are the most abundant circulating steroid hormone in healthy individuals. They are produced from cholesterol by the zona reticularis of the adrenal cortex. DHEA is produced from cholesterol through two cytochrome P450 enzymes. Cholesterol is converted to pregnenolone by the enzyme P450 scc (side chain cleavage); then another enzyme, CYP17A1, converts pregnenolone to 17α-Hydroxypregnenolone and then to DHEA. (Fig 3) (Arlt, 2004). DHEA is made primarily in the adrenal glands (which also produce about 150 other hormones) and released into the blood. In different organs it is converted into a variety of more commonly known steroid

hormones, including androstenedione, testosterone, and estrogen. DHEA and DHEA-S levels peak at approximately age 25 years and decrease progressively thereafter, falling to 5% of peak levels by the ninth decade. DHEA is a potential mediator of ROS synthesis (Bednarek-Tupikowska et al., 2000) and has also been reported to augment insulin sensitivity (Lasco et al., 2001, Jakubowicz et al., 1995, Kawano, 2000, Dhatariya et al., 2005) and peroxisome proliferator activation. (Poynter & Daynes, 1998, Peters et al., 1996), a transcription factor that regulates lipid metabolism, and procollagen type I, collagen precursor that has been associated with hepatic fibrosis of NASH. Both cross-sectional and longitudinal data have clearly indicated that serum concentrations of DHES-S decrease with age. Advocates of DHEA recommend it to prevent the effects of aging.

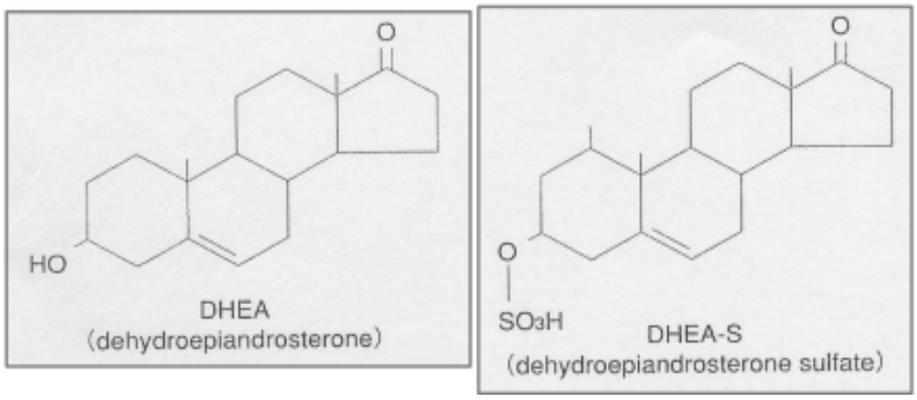

Fig. 2. DHEA and DHEA-S

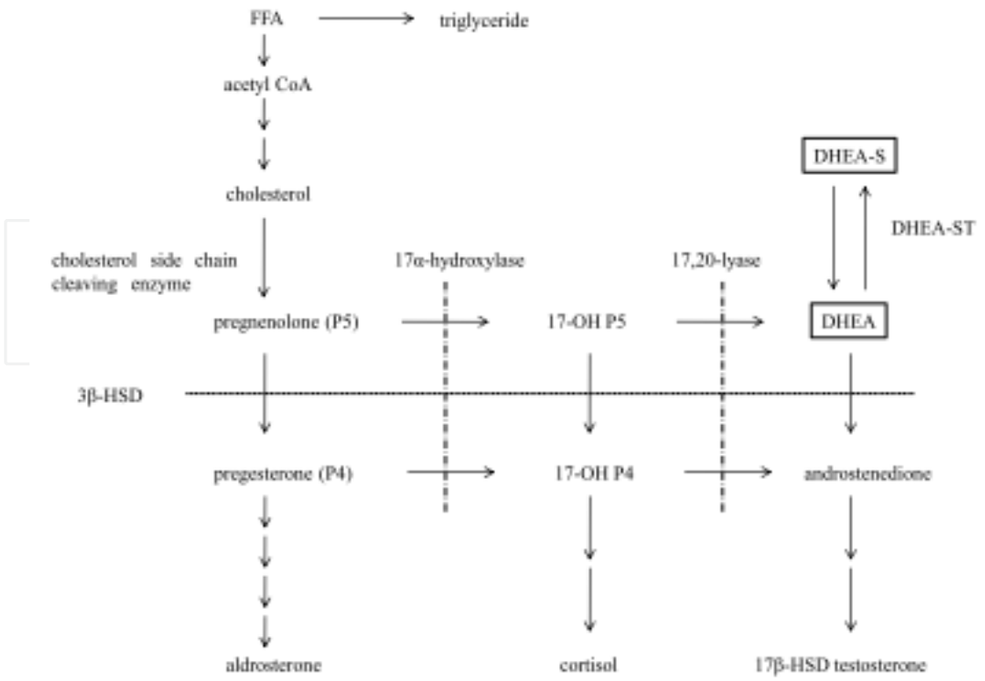

Fig. 3. Synthesis pathway of DHEA and DHEA-S

2.2 The significance of serum DHEA-S levels

Whereas DHEA levels naturally reach their peak in the early morning hours, DHEAS levels show no diurnal variation. From a practical point of view, measurement of DHEAS is preferable to DHEA, as levels are more stable. The Baltimore Longitudinal Study of Aging (BLSA) is a multidisciplinary observational study of the physiological and psychological aspects of human aging and diseases and conditions that increase with age. In BLSA, men who had higher DHEAS levels had significantly greater longevity than men with lower levels. (Roth et al., 2002) In Japan, a 27-year study in a community-based cohort (Tanushimaru study) indicated that DHEAS level may be a predictor of longevity in men, independent of age, blood pressure, and plasma glucose (Enomoto et al, 2008). Low serum levels of DHEA(-S) predict death from all causes, cardiovascular disease, and ischemic heart disease in elderly Swedish men. (Ohlsson et al., 2010) On the basis of these results, serum DHEA level is known to be an indicator of longevity at least in men and is often determined in anti-aging checkups (Nishizaki et al., 2009) . Elevated levels of DHEA are found in patients with Cushing syndrome or congenital adrenal hyperplasia, while DHEA levels are reported to be low in some people with anorexia, end-stage kidney disease, type 2 diabetes, AIDS, adrenal insufficiency, and in the critically ill. Some studies suggested that low serum DHEA-S levels were associated with the metabolic syndrome (Muller et al., 2005, Chen et al., 2010). In contrast, several studies found that DHEA levels are not different between subjects with metabolic syndrome and without. (Fukui et al., 2007, Haring et al., 2009, Akishita et al., 2010) It is suggested that age per se is an important correlate of the associations between DHEA-S and metabolic variables. In this way, the previous studies regarding the association between endogenous DHEA-S level and metabolic syndrome are inconsistent. Previous studies have shown that diabetic patients with high serum levels of insulin have lower serum levels of DHEA and DHEA-S. (Yamaguchi et al., 1998). A negative correlation between DHEA and hyperinsulinemia has been repeatedly demonstrated. (Kauffman et al., 2006, Saygili et al., 2005, Vasarhelyi et al., 2003). Fukui and colleagues reported that low levels of DHEA are associated with atherosclerosis and deterioration of urinary albumin excretion in male patients with type 2 diabetes (Fukui et al., 2004, 2005, 2006). Similarly, Serum DHEA-S level seem to be associated with atherosclerosis in diabetic postmenopausal women independent of age, body stature, diabetic status, and other atherosclerotic risk factors (Kanazawa et al., 2008).

2.3 DHEA-S levels in NAFLD

Recently, Charlton *et al*. observed that levels of DHEA are significantly lower in patients with histologically advanced NASH, as compared with patients with mild NASH or simple fatty liver. (Charlton M, 2009). DHEA levels exert a good sensitivity and specificity in discriminating patients with more advanced histological disease, as shown by the receiver operating characteristic (ROC) analysis. To validate their results, we also determined circulating DHEA levels in Japanese patients with 133 biopsy-proven NAFLD. Of 133 patients, 90 patients were diagnosed as NASH: 73 patients had stage 0–2, and 17 had stage 3 or 4. In addition, 399 sex- and age-matched healthy people participating in health checkups who had normal levels of alanine aminotransferase (ALT) levels (≤ 30 IU/L) were also enrolled as the control group. Body mass index (BMI), aspartate aminotransferase (AST), ALT, γGT, triglyceride, and HOMA-IR were significantly higher in NAFLD patients than those in the control group, whereas serum DHEA-S levels were similar between both groups. Consistent with our result, in patients with polycystic ovary syndrome (PCOS), DHEA-S levels were

similar between those with NAFLD and without. (Kauffman et al., 2010). According to a cross-sectional population-based study derived from data of 1912 men, however, the highest risk of hepatic steatosis was found in subjects with the highest serum DHEA-S levels (Völzke H et al., 2010). DHEA and DHEAS levels of post menopausal women with fatty liver were greater than those of post menopausal women with normal histology. (Saruç et al., 2003) These results are contrast to our study. Discrepancies between these studies and ours might be explained by differences in the selection of subjects, sex, size of the study populations and ethnicity.

Only in our NAFLD patients, NASH patients had lower levels of serum DHEA-S levels compared to non-NASH patients (Fig 4). Serum DHEA levels were negative correlated with age in males and females (Fig 5). A " dose effect " of lower DHEA-S and advanced fibrosis was observed, with a mean DHEA-S of 170.4±129.2, 137.6±110.5, 96.2±79.3, 61.2±46.3, and

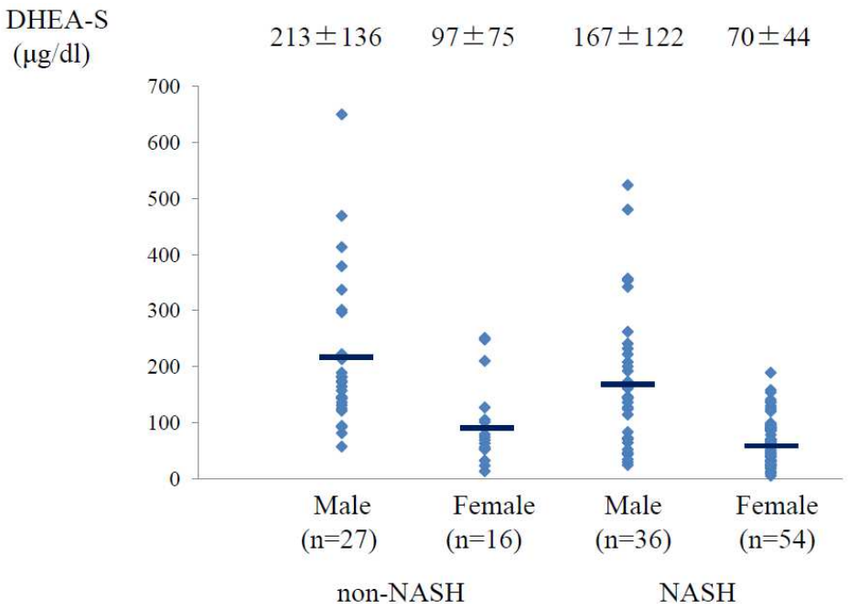

Fig. 4. Serum DHEA levels in biopsy-proven NAFLD.

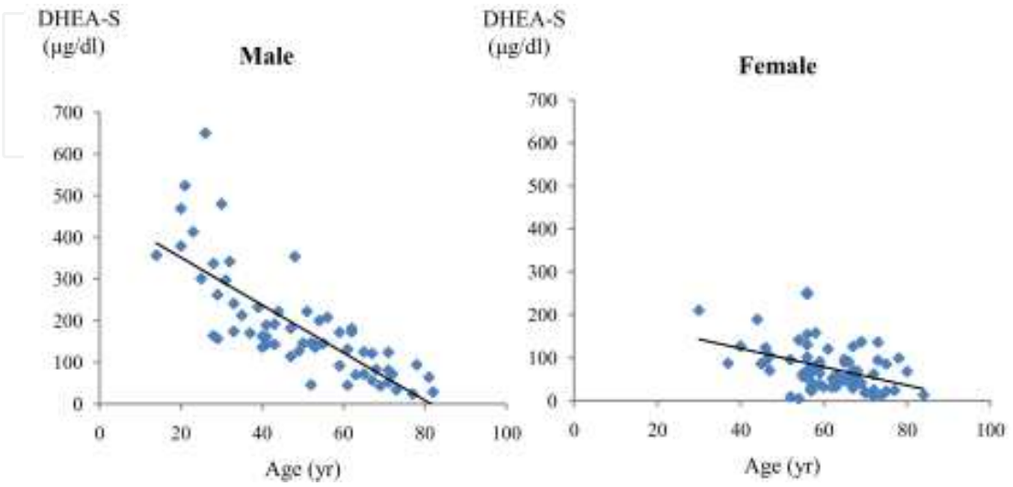

Fig. 5. The relationship between serum DHEA-S levels and age in NAFLD patients

30.0±32.0, for fibrosis stages 0, 1, 2, 3 and 4, respectively. The area under the ROC curve for DHEA in separating patients with and without advanced fibrosis was 0.788. The sensitivity of a DHEA-S-value of 66 mg/dL or less for the presence of more advanced NAFLD was 76.5% and specificity was 73.3% (85/116) (Fig 6)(Sumida et al., 2010a). Our data suggest that patients with DHEA-S levels greater than 66 μg/dL are highly unlikely to have advanced NAFLD (4/89 patients, sensitivity 76% and specificity 73%). Multivariate logistic regression analyses found that serum level of DHEA-S below 66μg/ml was selected as an independent predictor for advanced fibrosis even after adjusting for age, gender and insulin resistance (Table 1). We intended to support the concept that the association between low levels of DHEA and worsening histology is independent of age, sex and insulin resistance. Decreased levels of DHEA can have important roles in the progression hepatic fibrosis in NAFLD. It is expected that determinant of serum DHEA become a predictor of hepatic fibrosis in NAFLD. A 53-year female who had been pointed out her fatty liver without any medications was referred to our hospital because of thrombocytopenia (platelet count $4.6\times10^4/\mu l$). Her BMI was $31.6 kg/m^2$ and she had mildly elevated transaminase activities (AST 61IU/l, ALT 59IU/l) and prolonged prothrombin time (66%). Laparoscopic findings revealed nodular liver and her liver histology showed NASH (Brunt grade 3, stage 4) (Fig 7). Her DHEA-S levels was the lowest (5μg/dl) among our NAFLD patients.

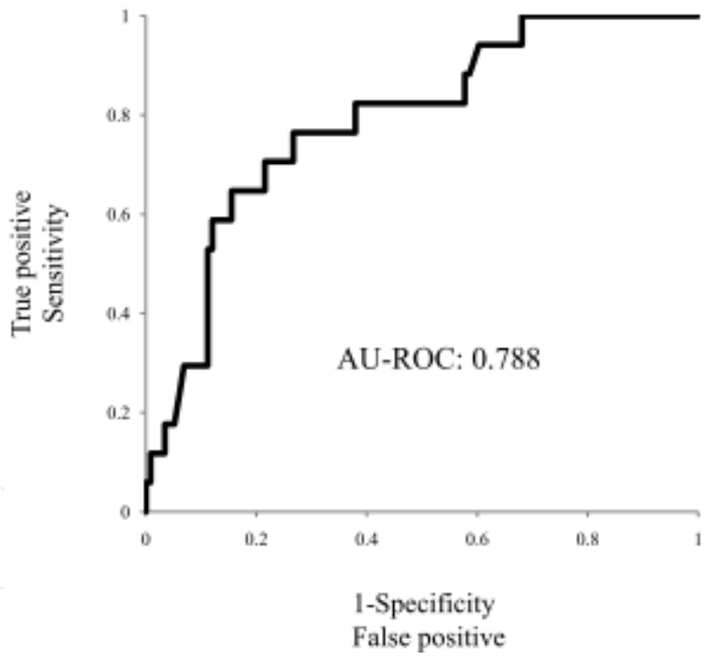

Fig. 6. ROC analysis for predicting severe fibrosis (stage 3-4).

Free fatty acids (FFAs), which lead to oxidative stress in NASH, are the major source of DHEA (Fig 3). The inability to produce appropriate amounts of DHEA in response to FFAs may translate into a more rapid and worsening progression toward NASH (Manco et al., 2008). Serum DHEA-S levels depend on adrenal DHEA production and its hepatic metabolism mediated by DHEA sulfotransferase (DHEA-ST) which catalyzes sulfonation of DHEA to form DHEA-S. It is hypothesized that a low level of DHEA-S was due to a defect in sulfurylation in patients with hepatic cirrhosis, since DHEA-ST is synthesized in the liver

Variables	Odds ratio	95% confidence interval	*P-value*
DHEA-S ≦66 μg/dl	4.9549	1.1691-20.9996	0.0229
age≧65 yr	2.8962	0.7843-10.6948	0.1106
sex (female)	1.9494	0.3765-10.0935	0.4264
HOMA-IR≧5	2.3671	0.6276-8.9273	0.2033
BMI ≧28 kg/m^2	1.0446	0.2619-4.1658	0.9508
Diabetes	1.6007	0.3904-6.5023	0.5107
Dyslipidemia	0.2500	0.0682-0.9162	0.0364
Hypertension	0.4184	0.1022-1.7126	0.2256

HOMA-IR, homeostasis assessment model for insulin resistance; BMI, body mass index

Table 1. Logistic regression models of the association of NAFLD (advanced versus mild) with dehydroepiandrosterone sulfate (DHEA-S) levels and other clinical variables

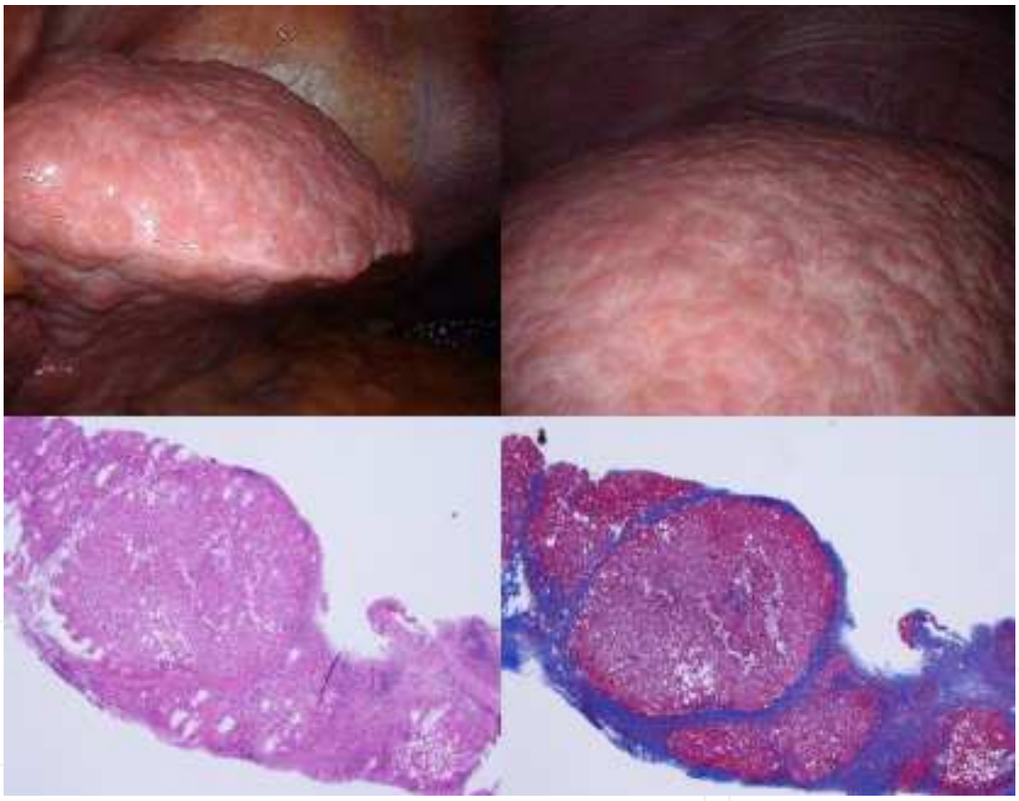

Fig. 7. Laparoscopic findings and liver histology of a case of NASH-LC who was referred to Center for Digestive and Liver Diseases, Nara City Hospital. A: laparoscopy (lt lobe), B: laparoscopy (rt lobe), C: microscopy (HE stain), D: microscopy (Masson-trichrome stain).

(Franz et al., 1979). It was also important to consider whether low levels of DHEA-S might occur as a result of CLD in general versus a specific phenomenon of histologically more advanced NAFLD.

Nakajima T et al revealed that telomere shortening, a marker of senescence, could be associated with hepatic steatosis, insulin resistance, oxidative stress in the liver, and impaired regenerative response in NAFLD patients (Nakajima et al., 2006). The hepatic

expression of senescence marker protein-30 (SMP30), which was identified as an antioxidant and anti-apoptotic protein, decreased in the proportion of the hepatic fibrosis in NAFLD patients (Park et al., 2010). These results suggest that the association of aging with NASH pathogenesis is noteworthy.

2.4 DHEA as a candidate for the treatment of NASH

There is no specific established treatment for NASH. Management of NASH consists of lifestyle modification including a healthy diet and physical exercise. DHEA has been widely touted as an anti-aging supplement. For years DHEA was promoted as a miracle weight loss drug, based upon some rodent studies that indicated DHEA was effective in controlling obesity in rats and mice. Other rodent studies found similar promising results for DHEA in preventing cancer, arteriosclerosis and diabetes. A randomized, double-blind, placebo-controlled trial showed that DHEA replacement therapy significantly decreases not only in visceral fat area and subcutaneous fat area, but also in insulin resistance. (Villareal & Holloszy, 2004). In contrast, DHEA replacement has no detectable effect on body composition, physical performance, insulin action, or quality of life (Nair et al., 2006). Therapeutic benefits of hormone supplementation for the treatment of aging, insulin resistance and cardiovascular disease remain obscure and controversial. DHEA can cause higher than normal levels of androgens and estrogens in the body, and theoretically may increase the risk of prostate, breast, ovarian, and other hormone-sensitive cancers. A protective effect of DHEA was reported in an orotic acid-induced animal model of fatty liver disease (Goto et al., 1998). Since the clinical usefulness of DHEA for NAFLD patients has never been investigated, there is a great need for prospective, randomized, multicenter and well-designed trials.

3. Conclusion

Recent studies have demonstrated that more advanced NAFLD, as indicated by the presence of NASH with advanced fibrosis stage, is strongly associated with low circulating DHEA-S. Although NASH patients with severe fibrosis are frequently observed in aged-female patients, the precise mechanisms of this phenomenon remain to be resolved. Lower levels of serum DHEA in females compared to in males may contribute to the fibrosis progression of NASH. There are thus several potential mechanisms for DHEA deficiency to promote histological progression in NAFLD. DHEA deficiency presents an appealing new therapeutic target for the treatment and prevention of NASH. Since the association of NAFLD with endocrine diseases such as hypothyroidism (Liangpunsakul & Chalasani, 2003), adult growth hormone deficiency (Takahashi et al. 2007), and PCOS (Baranova et al. 2011) has recently been suggested, the pathogenesis of NASH should be explored in the view of anti-aging medicine or endocrinology (Loria et al.,2010).

4. Acknowledgment

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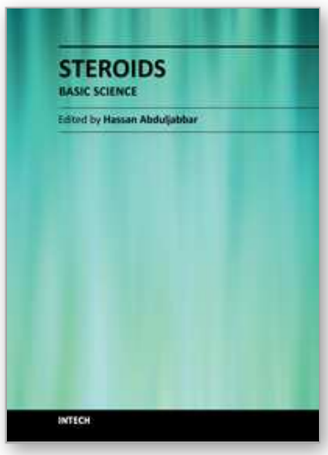

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This book explains the basic science of steroids and is targeted towards professionals engaged in health services. It should be noted that medical science evolves rapidly and some information like the understanding of steroids and their therapeutic use may change with new concepts quickly. Steroids are either naturally occurring or synthetic fat-soluble organic compounds. They are found in plants, animals, and fungi. They mediate a very diverse set of biological responses. The most widespread steroid in the body is cholesterol, an essential component of cell membranes, and the starting point for the synthesis of other steroids. Since the science of steroids has an enormous scope, we decided to put the clinical aspects of steroids in a different book titled "Steroids-Clinical Aspects". The two books complete each other. We hope that the reader will gain valuable information from both books and enrich their knowledge about this fascinating topic.

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