Protective effects of dietary restriction and physical exercise on intrahepatic fat accumulation

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Abstract This paper discusses the effects of dietary restriction and physical exercise on the maintenance of good health, focusing on intrahepatic fat accumulation, a type of ectopic fat accumulation. Excessive intrahepatic fat accumulation eventually progresses to fatty liver, which may evolve into liver cirrhosis and liver cancer. Physical exercise and dietary restriction are generally accepted as the major non-pharmacological remedies against intrahepatic fat accumulation. However, a combination of diet and physical activity has not necessarily shown expected synergistic or additive effects. In fact, dietary conditions antagonistically blocked the effect of physical activity on fatty liver, and physical inactivity adversely exacerbated the effect of dietary restriction on intrahepatic fat accumulation. These diverse combination effects, as well as etiology-dependent diversity in the activation of cellular signaling pathways leading to fatty liver, suggest the need to optimize remedies for the efficient amelioration and prevention of intrahepatic fat accumulation in a case-dependent manner. As a tentative step to constructing a prescription formula for optimal remedies, the probable advantage of physical exercise over dietary restriction at preventing fat spillover from adipose tissue to liver is noted.

Keywords : fatty liver, physical activity, dietary habits, obesity

Introduction

Lifestyle changes have lead to surplus energy accumulating in the body through conveniences that have decreased daily physical activity and through attractive meals that stimulate overeating. This surplus energy has resulted in a noticeable increase in the obese population. Obesity is a well-documented risk factor for various diseases, and extensive efforts to reduce the obese population have been launched at the administrative level.

Common non-pharmacological remedies for surplus energy are daily physical exercise and dietary restriction. Expending more energy for physical activity through daily physical exercise and reducing energy intake through dietary restriction should restore the balance between energy intake and expenditure. Although this simple balance restoration may reduce body weight, and decrease the obese population, a healthy state is not simply a function of body weight. Previous research, such as that described below, has already established the fact that a healthy reduction in weight cannot be achieved by dietary energy restriction that lacks adequate physical activity, or on the

other hand, by physical exercise that lacks supportive nutritional intake. In a large-scale cohort study conducted in 1989, Blair et al.⁽¹⁾ examined the relationships between obesity, physical activity, and the death rate. They found that obese people who had physically active daily lives had lower death rates than people of standard body weight who did not perform adequate physical exercise. In addition, Lee et al.⁽²⁾ reported the importance of physical activity in reducing the risk of ischemic heart disease, demonstrating that, to control body weight in a healthy manner, it is important not only to control food intake, but also to perform adequate daily physical exercise. Therefore, regardless of body weight, sufficient physical activity is essential for maintaining and promoting good health. Conversely, a cohort of subjects with restricted dietary intake designed to reduce their body weight by around 25% in 6 months with sufficient daily physical exercise, were reported as becoming physically and psychologically worn out⁽³⁾. Note that physical activity cannot overcome the deleterious effects of inappropriate dietary restriction.

These facts not only demonstrate that a healthy state is not a simple function of body weight or the balance between energy expenditure and intake, but also indicate that physical activity and dietary conditions interdepend-

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dently affect health through multiple networked pathways in the body. This review examines this network system, separating a pathophysiologically significant subnetwork that is relevant to intrahepatic fat accumulation.

Intrahepatic fat accumulation

An increase in intrahepatic fat accumulation, a type of ectopic fat accumulation, causes systemic metabolic abnormalities in the body leading to the development of fatty liver, which may evolve into liver cirrhosis and liver cancer⁴⁻⁶. Although fatty liver tends to be comorbid with obesity or being over-weight, a considerable non-obese normal and under-weight population are known to have fatty liver and suffer from abnormalities in liver function and insulin resistance⁷. For example, excessive dietary restriction or malnutrition can lead to fat accumulation in the liver in underweight individuals, as in kwashiorkor, a form of severe protein malnutrition, which is caused by a protein imbalance⁸. Fatty liver also appears in metabolically or genetically susceptible populations with normal body weight^{9,10}. These findings indicate that fatty liver reflects the fact that general health status is not simply a function of body weight. Therefore, it seems appropriate to focus on fatty liver from the perspective of its pathophysiological significance in our search for a healthier lifestyle.

Differential effects of dietary condition and physical activity

As is the case in overweight individuals, dietary restriction and physical exercise are definitely the major non-pharmacological remedies against fatty liver. Several studies have shown that each is effective at reducing liver fat. For instance, Tamura et al.¹¹ showed that only a moderate dietary restriction of 27.9 kcal/day/(kg ideal body weight) significantly reduced liver fat in type 2 diabetes patients in 2 weeks, with only a slight decrease in body weight. Johnson et al.¹² showed that aerobic cycle ergometer sessions at 50-70% maximal oxygen uptake for 30-45 min for 3-4 sessions/week for 4 weeks effectively reduced liver fat without affecting body weight. Halls-worth et al.¹³ showed that mostly resistance exercise at 50-70% one-repetition maximum for 45-60 min, for three sessions/week for 8 weeks was also effective at reducing liver fat without affecting body weight. In animal experiments, a group at Missouri University^{14,15} used Otsuka Long-Evans Tokushima fatty (OLETF) rats to compare the effect of a 30% restriction in diet and the effect of providing a voluntary wheel-running facility. They reported that a 36-week intervention beginning at 4 weeks of age showed that both interventions were comparably effective at attenuating the spontaneous progress of fatty liver in OLETF rats, while exercise had a more favorable effect on promoting the metabolic activity of the liver

and on the concentration of intrahepatic fibroblast growth factor-21, which may be involved in the processes acting against fatty liver.

When two remedies are combined, they can have synergistic, additive, antagonistic, or adverse effects. For example, in the above-mentioned study, Tamura et al.¹¹ examined the effect of walking at 50-60% maximum oxygen uptake on dietary restriction, and found a reduction in intramuscular fat, but no additional effects on liver fat. In this case, dietary restriction seems to antagonistically block the effects of physical exercise on liver fat reduction. Therefore, it is necessary to find an optimum combination of dietary restriction and physical exercise for favorable synergistic interaction.

Physical inactivity and fatty liver (Fig. 1)

Besides the effects of increased physical activity through daily exercise, the effects of extreme physical inactivity and its interaction with dietary condition should be examined more extensively. In 2009, the World Health Organization identified physical inactivity as the fourth leading risk factor for mortality, spurring research on the risks of insufficient physical activity¹⁶.

From this perspective, Zucker fatty (ZF) rats are a suitable model for animal experiments on the effect of physical inactivity. They show low physical activity levels compared with ordinary rats and eventually develop fatty liver¹⁷. Kurosaka et al.¹⁸ found that dietary restriction in ZF rats did not ameliorate the development of fatty liver, but accelerated it. They also found that the same dietary restriction combined with physical exercise prevented intrahepatic fat accumulation and maintained a healthy liver. Although it is not clear whether the interaction with the physical exercise effects reversed or counteracted the effect of dietary restriction in ZF rats, their results clearly indicated that the optimal combination of dietary restriction and physical exercise is crucial for effective amelioration and prevention of fatty liver.

Fatty diet and fatty liver (Fig. 2)

Dietary problems are one of the major factors in the modern lifestyle that may cause an increase in fatty liver. In many cases, excess fat content rather than total energy is the essential problem¹⁹, because even when the total energy intake is very low, excessive fat content has been shown to corrupt energy metabolism.

To distinguish the effect of fatty diet from the effect of excess energy intake, Kurosaka et al.²⁰ compared paired rats that were fed 10%- and 60%-fat diets, each maintaining 20% protein on an energy basis. Although their energy intakes were comparable, the 60%-fat diet resulted in high serum triglyceride (TG) levels with lipid droplet deposition in liver cells. Interestingly, Kurosaka et al.²¹ recently reported that the fat droplet deposition

Fig. 1 Interaction of physical activity and dietary restriction (DR) in the prevention and amelioration of fatty liver. Increased physical activity additively or synergistically enhanced the effects of DR, while physical inactivity adversely reversed the effects of DR to accelerate intrahepatic fat accumulation.

Fig. 2 Interaction of a high-fat diet and physical exercise. The effect of physical exercise on reducing intrahepatic fat accumulation does not occur when the fatty liver is induced by an extremely fatty diet.

in hepatic cells with the 60%-fat diet was hardly curbed when combined with physical exercise. Studies by others of fatty diets of around 60%^{20,22-24)} supported these results, showing insufficient or small effects of physical exercise on the reduction in intrahepatic fat accumulation. In comparison, studies examining fat contents of 30-40% reported substantial inhibitory effects of physical exercise on fatty liver²⁵⁻²⁷⁾. There seems to be a critical fat content for the effectiveness of physical exercise to counteract in-

trahepatic fat accumulation. In Kurosaka et al.²¹⁾, the fatty liver caused by the 60%-fat diet did not necessarily result in a higher TG content in the liver when compared with reported fatty liver models, such as that induced by excessive carbohydrates. Considering this diversity in susceptibility to physical exercise and intrahepatic TG levels, the pathological fatty liver consists of pathophysiologically distinct states that require distinctly different countermeasures.

Mechanisms of intrahepatic fat accumulation

The networked pathways leading to intrahepatic fat accumulation of any etiology ultimately converge on (1) an increase in free fatty acids absorbed by hepatocytes, (2) a decrease in fatty acid β -oxidation, or (3) activation of a *de novo* fatty acid synthetic system²⁸⁾. Aibara et al.²⁹⁾ searched for variation in the pathways involved in various types of fatty liver, such as the fatty livers induced by leptin deficiency (ob/ob), leptin receptor deficiency (db/db), fatty diet, alcohol, and a dietary lack of choline and methionine. They found that proliferator-activated receptor- γ (PPAR- γ) induced fatty liver increased expression of fat-specific protein 27 (FSP27) in all but the alcohol-induced fatty liver. In the alcohol-induced fatty liver, the expression of PPAR- γ did increase the induction of other downstream target proteins, such as adipocyte Protein 2 (aP2) and cluster of differentiation 36 (CD36), but not FSP27. They also found that dietary deficiencies of choline and methionine induced FSP27 expression in a PPAR- γ -dependent manner, but without inducing the enhanced expression of PPAR- γ . These results depict the multiplicity of pathways to a fatty liver, suggesting the need to optimize countermeasures that are formulated according to etiology on a case by case basis.

Most studies of the effects of physical exercise on fatty liver have focused on mitochondrial oxidative capacity. In fatty liver due to a fatty diet, Gonçalves et al.³⁰⁾ found that exercise altered the phospholipid profile of the mitochondrial membranes and improved the respiratory capacity of mitochondria. Borengasser et al.³¹⁾ studied the effects of voluntary exercise on fatty liver in OLETF rats and reported an increase in hepatic complete fatty acid oxidation to CO₂, an increase in carnitine palmitoyl-transferase-1 (CPT-1) activity, and a decrease in hepatic *de novo* lipogenesis proteins with a resultant decrease in intrahepatic fat accumulation. Furthermore, Rector et al.³²⁾ observed that a sudden cessation of daily voluntary exercise in OLETF rats reduced hepatic fatty acid oxidation and mitochondrial enzyme activity and increased the hepatic expression of *de novo* lipogenesis proteins.

Considering these alterations in mitochondrial function in the fatty liver in response to physical exercise, an attractive hypothesis arises, which holds that when the mitochondrial oxidative capacity is decreased in fatty liver, physical exercise readily and efficiently enhances mitochondrial function. This hypothesis should be tested in future experiments.

Relationship between adipose tissue and fatty liver

The vast network through which dietary condition and physical activity interactively prevent intrahepatic fat accumulation remains mostly unexplored. To grasp a key feature of the network, the interaction of hepatic fat with general adipose tissue, including abdominal visceral fat,

may provide an important clue. It is clear that, except in relatively rare but significant cases, hepatic fat tends to link intimately with general adipose tissue. For example, the liver readily accumulates fat from adipose tissue, as observed in mouse models of congenital lipodystrophy³³⁾ and of leptin receptor-b overexpression in adipose tissue³⁴⁾. The endoscopic removal of visceral fat from obese mice fed a fatty diet dramatically ameliorated fatty liver³⁵⁾, indicating that the fat shifted from adipose tissue to liver readily returns to an available reserve capacity in normotrophic adipose tissue.

Slawik et al.³⁶⁾ reported that adipose tissue increases its mass via hypertrophy of the constituent adipocytes rather than an increase in the number of small adipocytes. Since lipolysis activity is markedly higher in hypertrophied adipocytes than in smaller ones³⁷⁾, the reserve capacity for fat accumulation in adipose tissue would generally decrease despite the increase in the mass of adipose tissue, so as to accelerate heterotopic fat accumulation. In ZF rats, we recently showed that when dietary restriction with physical inactivity accelerated intrahepatic fat accumulation, the adipocytes in adipose tissue hypertrophied³⁸⁾. When dietary restriction was combined with physical exercise, fatty liver and adipocyte hypertrophy were both prevented³⁸⁾. Many other studies have also shown that physical exercise inhibits adipocyte enlargement more efficiently than dietary restriction^{39,40)}.

The above consideration suggests that adipocytes should be kept small to leave reserve capacity in adipocytes for fat to accumulate normotrophically, and physical exercise would, therefore, be an essential part of prescriptions for healthy amelioration and the prevention of fatty liver.

Conclusions

This review discussed the preventive and ameliorative effects of two recognized non-pharmacological treatments for fatty liver: dietary restriction and daily physical activity. Depicting a gross view of the vast network of pathways that link dietary condition and physical activity to intrahepatic fat accumulation, the obvious need to prescribe an optimal regimen that considers the detailed cause of each fatty liver is realized. From the current understanding of the interaction between adipose tissue and intrahepatic fat accumulation, physical exercise should be an essential part of the regimen for the healthy prevention and amelioration of fatty liver, and probably part of a program to improve the modern lifestyle.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this article.

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