

The influence and therapeutic effect of dietary pattern on liver diseases in the United State

Jiayin Liu^{1,*,†}, Chenxin Wang^{2,†} and Yushu Xiao^{3,†}

¹Department of Nutritional Science, School of Public Health, University of Michigan Ann Arbor, 500 S. State Street, Ann Arbor, MI 48109, USA

²School of Food Science and Engineering, Northwest Agriculture & Forestry University, 22 Xinong Rd, Yangling, Shaanxi, 712100, China

³School of Public Health, University of Washington, 305 Raitt Hall, Seattle, WA 98195-3410, 353410, United State

*Corresponding author Email: yushux@uw.edu

† These authors contributed equally.

Abstract. Liver disease includes many types of diseases like cirrhosis and non-alcoholic fatty liver, and liver disease is one of the main causes of death in the United State. In addition to genetic factors, diet can influence the gut microbiota which makes fermentation of non-digestible food possible and then influence the development of specific types of liver diseases like alcoholic liver disease, nonalcoholic liver disease, dysbiosis, liver cirrhosis, and hepatocellular carcinoma. Furthermore, the dietary pattern can also directly determine the development of liver diseases, while the consumption of a high amount of fatty, alcohol, and sugar do harm to liver diseases. Although the dietary habit may cause exacerbation of liver diseases, it can also prevent people suffer from liver diseases or even with a therapeutic effect. This paper summarized the specific effect of diet on gut microbiota which can influence liver diseases and the influence of typical diet on liver diseases, and the paper also concluded diet therapy for liver diseases.

Keywords: Liver diseases, gut microbiota, dietary pattern, therapeutic effect.

1. Introduction

The liver plays an important part inside the human body, its function concludes blood falter, metabolism, synthesis of particles and many other functions related to human's daily life. There are over hundreds of liver diseases have been diagnosed by a human so far, and become the main causes of death for a long time. Meanwhile, the causes of liver diseases are countless, one of the most common reasons is long-term unhealthy living habits include unhealthy dietary patterns like overconsumption of alcohol. Dietary can directly influence liver diseases by subtle influence on metabolism day by day, and dietary can also influence liver diseases through doing effect on gut microbiota. Specifically, high-protein diets provide a suitable environment for potentially pathogenic and excess intake of sweeteners can affect the acid-base balance of the intestinal flora [4, 5]. Among plenty of therapy methods for liver diseases like liver transplantation, interventional surgery and ablation surgery, keeping a healthy diet pattern is one of the safest methods for patients or healthy people to delay the course of the disease or prevent cadre disease. For instance, whole grain can slow the course of disease of nonalcoholic liver disease, and high-fat, high-sucrose and low-fiber do have a negative influence on body metabolism. In this paper, the mechanism of gut microbiota being changed by different diet patterns, and the influence of high-fatty, over-alcoholic and high-sugar consumption diet on liver diseases would be discussed, respectively. In addition, detailed information on therapeutic effect of diet on liver diseases would be provided.

2. Data of liver diseases in United State

The statistics shown in this report are based on data from the Centers for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS). The CDC, provides data,

professional knowledge, information and tools to improve health, prevent diseases, injury and disability. The NCHS is the agency of the Federal Statistical System of the United States, NCHS provides statistics to improve the public health of people in American. The morbidity and mortality of liver diseases have great differences from state to state in United State.

2.1 Classification of liver diseases

Liver is the largest solid organ with over 500 functions in our body. It can filter blood, responsible for the metabolism, synthesis and degradation of protein and so on. However, since the liver's multi-function and its location, there are many liver-related diseases that influence people's health. Some liver diseases are caused by infection, such as hepatitis A, hepatitis B, and hepatitis C. Except for infection-caused diseases, drugs, poisons and over ingestion of alcohol can cause liver diseases, such as fatty liver disease and cirrhosis. Furthermore, liver diseases can also be caused by immune system abnormality, and primary biliary cholangitis, an autoimmune disease, belongs to this kind of liver disease. Genetic factors are also responsible for some liver diseases like alpha-1 antitrypsin deficiency, Wilson's disease. Moreover, there are also many other liver diseases like liver tumor, and each disease has its own symptoms.

2.2 The morbidity and mortality of liver diseases and cirrhosis in United State

The data in Table.1 shows the age-adjusted death rate, the number of deaths per 100,000 total population, of chronic liver disease or cirrhosis by State in the United State. For instance, in California, Florida, and Texas, the number of people dying from liver diseases and death rate, more than 12%, is relatively higher. While people living in different states have different income levels and then influence their dietary habits. The data in Table. 2 shows age-adjusted death rates for chronic liver diseases and cirrhosis, by race, and Hispanic origin in the United State. Asian or Pacific Islander shows the lowest morbidity rate, 3.5%, among all races in the United State without an obvious trend of increasing from 2000 to 2018. A previous study showed that there are differences in liver diseases prevalence by race/ethnicity. For nonalcoholic fatty liver disease, Hispanics have prevalence. Although the exact reason for the difference in morbidity between ethnicity, common studies attribute the difference to genetic, metabolic, also dietary pattern, factors [14, 15]. Furthermore, in Figure.1, data about the number of liver cirrhosis deaths in the U.S. by cirrhosis type shows the increasing trend of alcohol-related cirrhosis, that the data of the percent of alcohol-related cirrhosis among cirrhosis rise from 48.16% in the statistic in 2010-2012 to 50.09% in the statistic in 2015-2017. All the data above shows that except for genetic factors, dietary patterns do influence the morbidity and mortality of liver diseases in the United State.

Table 1. Age-adjusted death rate, the number of deaths per 100,000 total population, of chronic liver disease or cirrhosis by State in the United State

State	2015		2016		2017		2018		2019	
	Death Rate	Death	Death Rate	Death	Death Rate	Death	Death Rate	Death	Death Rate	Death
Alabama	12.5	716	13.2	781	12.7	756	12.6	762	13.6	831
Alaska	15.4	114	16.3	124	15.1	121	15.6	121	14.5	110
Arizona	15	1149	14.9	1178	14.3	1137	14	1162	14.5	1217
Arkansas	12.1	421	11.8	416	11.3	399	12.7	455	12.9	464
California	12.7	5425	12.2	5287	12.1	5325	12.1	5390	12.5	5575
Colorado	12.2	735	12.4	751	14	865	13.2	832	14.9	960
Connecticut	8.4	365	8.6	388	9.1	407	7.6	350	8.9	418
Delaware	9.6	111	7.5	92	8.9	106	8.4	109	9.3	118
Florida	11.7	3084	11.9	3226	11.2	3098	11.8	3345	11.1	3192
Georgia	9	1003	9	1009	9.8	1146	9.9	1171	10	1230
Hawaii	8.1	138	7.1	124	7.5	132	6.9	120	7.2	126
Idaho	12.2	218	9.9	190	10.2	197	12.6	249	12.1	249
Illinois	8.7	1289	9.4	1374	9.3	1407	9.4	1421	9.7	1463

Indiana	11.4	859	11.2	869	11.6	900	12.5	981	12	940
Iowa	9.1	328	9.4	343	9.2	337	8.9	331	9.5	357
Kansas	9.7	313	9.8	316	9.7	317	10.9	360	10.6	349
Kentucky	12.6	657	11.9	647	12.8	682	13.4	717	13.7	750
Louisiana	10.5	553	9.7	519	10	543	9.5	515	9.2	509
Maine	11.1	185	10.6	188	10.4	196	10.7	198	10.1	200
Maryland	6.7	471	6.7	466	6.6	484	6.8	489	7.8	573
Massachusetts	8.2	661	8.8	716	9.2	766	9.3	791	8.8	746
Michigan	10.8	1287	10.2	1242	10.9	1323	10.7	1310	11.8	1437
Minnesota	8.5	542	9.2	595	8.6	568	10.1	668	10.7	696
Mississippi	11.1	382	11.1	383	12.6	437	12	432	13	457
Missouri	9.6	678	9.1	660	9.3	690	9.6	718	10.1	743
Montana	15.7	179	13.6	160	16.1	195	11.9	153	15	180
Nebraska	7.8	165	9.3	200	9.9	211	11.2	231	11.3	241
Nevada	14.5	475	12.3	417	13.3	458	13.9	493	13.4	492
New Hampshire	9.3	161	9.6	162	9.1	162	11.9	213	11	193
New Jersey	7.3	782	7.4	801	7.3	797	8.2	893	7.8	853
New Mexico	24.8	566	24.9	572	26.8	605	25.7	591	26.2	594
New York	6.7	1571	6.9	1614	7.1	1671	6.9	1650	7	1670
North Carolina	10.7	1254	10.3	1253	10.3	1273	10.4	1300	11.3	1443
North Dakota	11.6	86	12.4	98	11	87	13.1	106	15.2	116
Ohio	10.7	1506	10.9	1558	11.2	1603	10.6	1521	11.1	1622
Oklahoma	13.7	597	14.6	640	15	670	15.4	686	15.6	705
Oregon	13.7	667	12.2	606	12.6	642	13.5	699	12.6	658
Pennsylvania	8.9	1438	8.7	1414	8	1336	8.2	1366	8.7	1479
Rhode Island	10.6	139	11.5	149	11.2	148	12.7	167	11	141
South Carolina	12.2	716	12.4	749	13.1	812	12.4	791	12.8	826
South Dakota	16.1	139	16.4	158	17.2	153	19.8	186	17.1	154
Tennessee	12.2	957	12.2	960	12.8	1038	13.5	1098	13.7	1118
Texas	13.8	3844	13.5	3880	13.9	4107	13.9	4154	14.3	4359
Utah	9.3	244	8.5	236	8.8	243	10	287	8.8	261
Vermont	8.6	71	8.9	70	8.8	71	7.1	60	9.1	79
Virginia	9.6	943	9.2	894	9.6	970	9.3	944	10	1037
Washington	12.4	1024	11.1	926	11.4	982	11.3	990	12.3	1089
West Virginia	14.2	338	12.8	311	14	337	14.4	350	16.9	394
Wisconsin	8.5	591	9.8	695	9.5	679	10.2	731	10.3	739
Wyoming	18.9	118	13.2	88	14.2	101	19.1	122	22.4	141

Table 2. Age-adjusted death rates for chronic liver diseases and cirrhosis, by race, and Hispanic origin: United States, in 2000, 2005, 2010,2015 and 2018

Race, Hispanic origin	2000	2005	2010	2015	2018
All person	6.2	5.8	6.2	7.6	7.7
White	9.6	9.2	9.9	11.7	11.9
White, not Hispanic origin or Latino	9.0	8.7	9.4	11.1	11.4
Black or African American	9.4	7.6	6.7	7.4	7.1
Black or African American, not Hispanic origin or Latino	9.6	7.7	6.9	7.6	7.3
American Indian or Alaska Native	24.3	21.6	22.8	26.4	27.7
American Indian or Alaska Native, not Hispanic origin or Latino	27.9	27.4	32.1	39.2	42.4
Asian or Pacific Islander	3.5	3.6	3.2	3.3	3.7
Asian or Pacific Islander, not Hispanic origin or Latino	3.5	3.5	3.2	3.2	3.6
Asian, not Hispanic or Latino	---	---	---	---	---
Native Hawaiian or Other Pacific Islander, not Hispanic or Latino	---	---	---	---	---
Hispanic or Latino	16.5	14.1	13.7	14.9	14.5

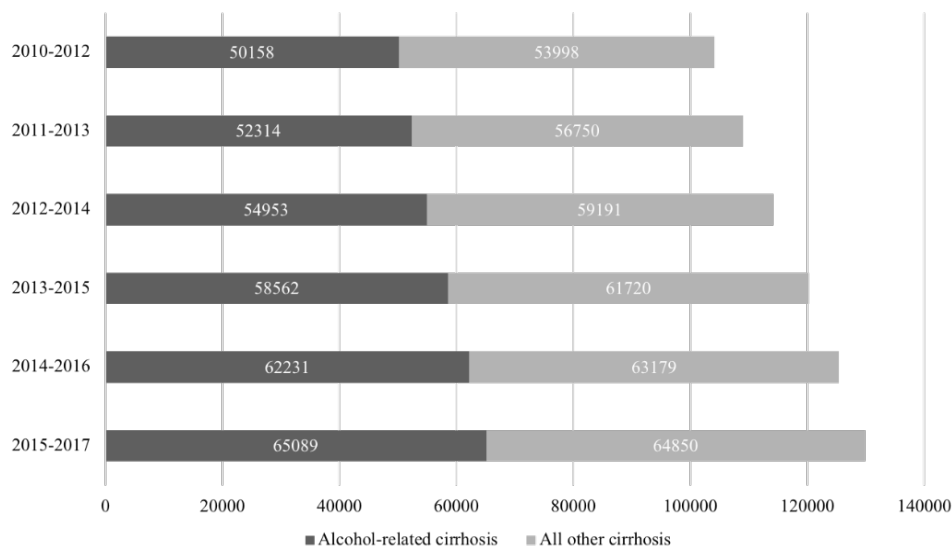


Figure 1. Number of liver cirrhosis deaths in the U.S. from 2000-2017, by cirrhosis type

3. Correlation between different diet patterns and liver diseases, and potentially long-term chronic effect

3.1 Microbiota difference affecting liver diseases caused by diet

3.1.1 Effects of dietary on the gut microbiota

Microbiota refers to the ecological community of microorganisms themselves, while microbiome refers to both the collective genomes of micro-organisms in the environment and themselves. Gut microbiota and its metabolic products relate to gut homeostasis and host health closely. The gut microbiome makes the fermentation of non-digestible substrates possible, and the fermentation process promotes the production of short chain fatty acids in specialist microbes. The major short-chain fatty acids (SCFA) produced are butyrate, SCFAs acetate and propionate, which provide energy for the host. SCFAs may also influence the regulation of the production of lipids to which the interactions with the host are related to the hormones associated with satiety. In addition, SCFAs also relate to the gut environment, such as pH, the balance between nutrient ingestion and microorganisms within the gut. Furthermore, protein, dietary phytochemicals and other bioactive compounds are generated through the intestine.

Dietary patterns can be used to predict the composition of gut microbiota. Sweeteners are used to substitute sugar, and sweeteners may have negative effects on microbiota within the gut. Several pieces of research have shown that sweeteners like aspartame, saccharin can disrupt the microbial diversity and the balance inside the gut.

High-fat diets (HFD) influence the development of dysbiosis due to the more Firmicutes and less Lactobacilli, Bacteroidetes and Bifidobacteria. A study has shown that feeding mice in HFDs for 4 weeks lead to an increase in Bifidobacterium spp., at the same time, the number of C. coccoides group and Bifidobacteria E. rectale decreased. Another study showed that vegans (high in fiber, low in fat and protein) switching their diet pattern into animal-based diet led to the amount of Bacteroides spp. increase considerably and the amount of Firmicutes decrease due to the change in fat content.

High-protein diets (HPD) are beneficial to potentially pathogenic and proinflammatory microbiota, those microbiotas can lead to the increased density of hydrogen sulfide, ammonia and phenols and induce the change of intestinal motility. In addition, the source of protein also influences the gut microbiota and the capacity of secondary metabolites generation. Compared to rats that ingest soy protein, rats that ingest meat protein had more beneficial genus Lactobacillus and less density of SCFAs and related bacteria, such as Bacteroides Fusobacterium.

3.1.2 Effects of Gut Microbiota on Alcoholic Liver Disease

Alcoholic liver disease (ALD) spans a spectrum from steatosis to cirrhosis, fatty liver to alcoholic steatohepatitis. Overdose consumption of alcohol has become the leading cause of a variety of liver diseases, and gut microbiota is recognized as one of the critical points of ALD. Increasing gut permeability is the main feature of ALD due to the alcoholic-related toxic effect directly acting on the epithelial cells in the gastrointestinal tract and also tight-junction protein expressed decrease. This damage of the gastrointestinal barrier leads to a higher possibility of hepatic-related diseases. Moreover, a study that the gut microbiota of alcoholic patients can accumulate the alcohol-induced inflammation in rats supports the opinion that the composition of gut microbiota can influence the susceptibility to ALD.

3.1.3 Effects of Gut Microbiota on Nonalcoholic Liver Disease

Nonalcoholic liver disease (NAFLD), excessive accumulation of triglycerides in liver cells without clear causes like overdose consumption of alcohol, can be divided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Microbiota is important in NAFLD, a study proved the feasibility of gut microbiota to prevent or treat NAFLD by transplanting fecal from mice suffering from NAFLD into healthy mice and causing healthy mice to get NAFLD.

3.1.4 Effects of Gut Microbiota on Dysbiosis and Liver Cirrhosis

Liver cirrhosis refers to the phenomenon that the liver forms irreversible fibrotic scar tissue. Cirrhosis patients usually show intestinal dysbiosis and report observed that the stage of liver injury affinity with the severity of gut dysbiosis. Reviews showed the pathophysiologic situation of gut microbiota, disruption of the intestine, gut-derived LPS in infectious complications and translocation of microorganisms, in liver cirrhosis patients. The previous study of Usami et al. suggested that chronic liver disease can change intestinal flora causing fatty acid metabolism, and then indicated that the “gut-microbiota-liver network” exists in human bodies.

3.1.5 Effects of Gut Microbiota on Hepatocellular Carcinoma

Hepatocellular Carcinoma is the fifth most common cancer and the most common major malignancy in patients with liver cirrhosis and liver diseases. Dietary aflatoxin, excessive alcohol consumption and Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection are the main factors that result in the development of HCC. The mechanism of the development of HCC can be disruption of the gut, dysbiosis, endotoxemia, toll-like receptors and immunomodulation. Research showed that microbial metabolism, Fe transport, and energy-producing systems differ between gut microbiota of HCC patients and healthy people. HCC patients have a higher concentration of gram-negative bacterium within the gut, this may attribute to the increased (Lipopolysaccharide)LPS serum levels, while the accumulation of LPS can cause an overgrowth of the bacteria in the intestinal and change the composition of gut microbiota. The lack of anti-inflammatory bacteria that may exacerbate the development of HCC should be highlighted.

3.2 Directly influence of dietary pattern to liver diseases

3.2.1 Diet pattern with a high intake of fatty foods

For the diet that is specialized in a high intake of fast food, the people who are consuming this kind of diet are consuming a couple of ingredients that no matter speaking from a general public view or a professional view that none of them are healthy. These ingredients include trans-fat, corn syrup, artificial sweetener, coloring agents, etc. Consuming a high intake of fatty foods can simply enlarge the amount of work for the digesting phase, and certainly for the liver. One most common, most known, and most hot spot liver disease currently is fatty liver, and fatty foods can certainly cause fatty liver since the cause of the fatty liver disease is due to an excess amount of calories intake and causes fats to accelerate in the liver subsequently.

3.2.2 Diet pattern with a high amount of alcoholic beverages consumption

Another diet pattern that can heavily affect the health of the liver, and cause liver diseases such as fatty liver and other severe liver diseases subsequently is a diet with a high amount of alcoholic beverages consumption. There is a professional term for such a disease, ALD, and there are three stages for ALD.

The very first stage is an alcoholic fatty liver disease as we have mentioned previously. This is caused by the buildup of the fat from excessive amounts of drinking on the liver, and even a short term, just within a couple of days, can cause such an effect. Although it can be such a fast/quick disease that can happen in such a short period of time, the good news is that this is totally preventable, and the liver condition can possibly return to normal after approximately 2 weeks without alcoholic drinking. However, this very first stage, fatty liver disease, does not have any symptoms. With this being said, it will be harder for the patients to recognize or perceive the disease by themselves. Thus, this alcoholic fatty liver disease can develop into the next stage of ARLD, alcoholic hepatitis. This is caused by the misuse of alcohol for a longer period of time.

Even alcoholic hepatitis has the word hepatitis in the term, it is not infectious hepatitis that people who have such a disease will not infect anyone around them through any methods despite those people who have Hepatitis C and drinking have a higher chance to develop cirrhosis than people who do not even it is just moderate drinking since Hepatitis C is a liver disease that causes cirrhosis already. Nevertheless, people who have this disease are still going through the same level of difficulty that it may be the patient's first time to be aware of the existence of ALD at this alcoholic hepatitis stage. People with alcoholic hepatitis also tend to be malnourished since alcohol has a side effect of suppressing appetite. Even though alcoholic hepatitis is an advanced level of alcoholic fatty liver, it is still curable but not all conditions, only the moderate drinkers can be cured. And this cannot be generalized, other risk factors should also be considered, sex, obesity, genes, race and ethnicity, and the habit of binge drinking.

The last is the final stage, liver cirrhosis. This is an irreversible stage for the liver and can also lead to portal hypertension. It can simply refer to the circumstance that the liver has not been functioning well for a long time, and it has become stiff and swollen, most likely unable to do its job currently. Liver cirrhosis and alcoholic hepatitis share similar symptoms, such as low appetite and vomiting, but a more intense show up such as simply vomiting blood or bleeding in the mouth, confusion, memory loss or even mental fog. Moreover, all these symptoms are caused by years of drinking too much alcohol.

3.2.3 Diet pattern with a high amount of sugar (sweets and add-sugar beverages, etc.)

Besides alcohol, sugar is another evil factor that can cause liver diseases potentially. Too much sugar consumption can also lead to liver diseases that the fat from redundant refined sugar or corn syrup will lead up to fat build-up in the liver to fatty liver disease subsequently. The same cause as alcoholic fatty liver disease. Some research even shows that sugar is no less damaging than alcohol. Most importantly, sugar consumption can be easily overlooked due to the way of consumption. Refined sugar and corn syrup can be consumed in pastries, sugar-sweetened beverages, candy or even dishes in the meal.

Furthermore, the American's cooking method is another factor that can potentially increase the possibility of liver disease, such as deep-frying. Foods that have been deep fried are high in fat, calories, and potentially seasoning. All of these factors, especially fat, can correlate with previous topics that can cause liver diseases. Thus, the cooking method is an irresistible factor for the cause of liver disease.

4. Diet and treatments of chronic liver diseases.

Liver disease has become one of the most important reasons for diseases and death of people in the U.S., the study of liver disease including the differences among races, ethnicities, geographical

reasons, related epidemic diseases and so on. During this period, several new methods came up. There is a significant difference among states and the highest rates of mortality appeared in states in the West and South. Besides, the high prevalence shows relation with low income and fat, which is noted that there is no specific a relation between alcohol consumption and liver disease.

Diet, a complex combination of many nutrients and different compounds people eat working together, is really important in daily life, which is also thought to have a significant correlation with the health state of a person. Different kinds of foods have a variety of influences on the health of the liver. In this part, we will not focus on HBV and HCV because the number of cases is decreasing with the popularization of HBV vaccination and anti-HCV treatment.

Based on the research of Wan-Shui Yang and the group, health can be formed and maintained by proper diet while improper diet is often associated with different kinds of diseases. For example, obesity is associated with the High Fat Diet (HFD) thought to be the most universal cause of liver disease, other kinds of diets like the Mediterranean Diet (MD), however, show potential in treatment. The possible application of diet in the treatments of liver related diseases has attracted attention from researchers. The research of Francesce shows that the clinical picture of pathema of non-alcoholic fatty liver disease (NAFLD) reflects the healthy level of diet and it is an effective way to manage the health of NAFLD patients by improving the quality and quantity of diet. Based on similar results of some observational studies and small, short-term trials, the relief of liver steatosis and metabolic dysfunction were found. Single components were studied too, whole grain can slow the development of NAFLD by benefiting the gut microbiota composition.

There are some habits people should avoid as they may lead to liver disease. First, consuming more than 3 drinks each day and currently smoking more easily causes the death of CLD. Western diet, which is characterized by high-fat, high-sucrose and low-fiber, should be avoided. Because it is closely associated with the development of CLD by influencing the gut microbiota and bile acid metabolism.

Diet quality index (DQI) scores including Healthy eating Index-2010, Alternative Healthy Eating Index-2010, Alternate Mediterranean Diet and Diet Approaches were used in the study of David, which shows that the mortality of CLD has a significant negative relationship with the DQI. So, a healthy level of diet is really important for people stepping away from CLD.

5. Conclusion

In modern society, the relationship between diet and health is increasingly studied and discussed. Different diet patterns and eating habits are used to figure out their effects on the human body, especially the causes and treatments for different diseases like a variety of chronic liver diseases. Based on the data on infection and death rate in the United States, we found different diet patterns function differently in the health of the liver. It is noted that the gut microbiota plays an important role in acting on the liver, influenced by diet. Current treatments for liver diseases focus on the resetting of diet and a new way of acting on the gut microbiota is studied for use in later treatments. Although a variety of approaches have been explored, the radical cure of chronic liver diseases of liver diseases needs to be further studied.

References

- [1] L.L. Miller, W.F. Bale, Synthesis of all plasma protein fractions except gamma globulins by the liver; the use of zone electrophoresis and lysine-epsilon-C14 to define the plasma proteins synthesized by the isolated perfused liver, *J Exp Med* 99(2) (1954) 125-32.
- [2] G.B.D. Disease, I. Injury, C. Prevalence, Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, *Lancet* 388(10053) (2016) 1545-1602.
- [3] B. Saberi, A.S. Dadabhai, Y.Y. Jang, A. Gurakar, E. Mezey, Current Management of Alcoholic Hepatitis and Future Therapies, *J Clin Transl Hepatol* 4(2) (2016) 113-22.

- [4] J.E. Nettleton, R.A. Reimer, J. Shearer, Reshaping the gut microbiota: Impact of low-calorie sweeteners and the link to insulin resistance? *Physiol Behav* 164(Pt B) (2016) 488-493.
- [5] Z. Mokhtari, D.L. Gibson, A. Hekmatdoost, Nonalcoholic Fatty Liver Disease, the Gut Microbiome, and Diet, *Adv Nutr* 8(2) (2017) 240-252.
- [6] W.S. Yang, X.F. Zeng, Z.N. Liu, Q.H. Zhao, Y.T. Tan, J. Gao, H.L. Li, Y.B. Xiang, Diet and liver cancer risk: a narrative review of epidemiological evidence, *Br J Nutr* 124(3) (2020) 330-340.
- [7] S. Zelber-Sagi, F. Salomone, L. Mlynarsky, The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: Evidence and plausible mechanisms, *Liver Int* 37(7) (2017) 936-949.
- [8] L. Yang, Y. Li, S. Wang, X. Bian, X. Jiang, J. Wu, K. Wang, Q. Wang, J. Xia, S. Jiang, A. Zhuge, Y. Yuan, S. Li, L. Li, Western Diet Aggravated Carbon Tetrachloride-Induced Chronic Liver Injury by Disturbing Gut Microbiota and Bile Acid Metabolism, *Mol Nutr Food Res* 65(7) (2021) e2000811.
- [9] G.M. Hirschfield, M.E. Gershwin, The immunobiology and pathophysiology of primary biliary cirrhosis, *Annu Rev Pathol* 8 (2013) 303-30.
- [10] R.A. Stockley, A.M. Turner, alpha-1-Antitrypsin deficiency: clinical variability, assessment, and treatment, *Trends Mol Med* 20(2) (2014) 105-15.
- [11] A. Ala, A.P. Walker, K. Ashkan, J.S. Dooley, M.L. Schilsky, Wilson's disease, *Lancet* 369(9559) (2007) 397-408.
- [12] Age-adjusted death rate, the number of deaths per 100,000 total population, of chronic liver disease or cirrhosis by State in United State, 2021. https://www.cdc.gov/nchs/pressroom/sosmap/liver_disease_mortality/liver_disease.htm.
- [13] Age-adjusted death rates for chronic liver diseases and cirrhosis, by race, and Hispanic origin in United State, 2021. <https://www.cdc.gov/nchs/hus/contents2019.htm#Table-005>.
- [14] K. Bambha, P. Belt, M. Abraham, L.A. Wilson, M. Pabst, L. Ferrell, A. Unalp-Arida, N. Bass, G. Nonalcoholic Steatohepatitis Clinical Research Network Research, Ethnicity and nonalcoholic fatty liver disease, *Hepatology* 55(3) (2012) 769-80.
- [15] R. Lomonaco, C. Ortiz-Lopez, B. Orsak, J. Finch, A. Webb, F. Bril, C. Louden, F. Tio, K. Cusi, Role of ethnicity in overweight and obese patients with nonalcoholic steatohepatitis, *Hepatology* 54(3) (2011) 837-45.
- [16] J. Elflein, Number of liver cirrhosis deaths in the U.S. from 2000-2017, by cirrhosis type, 2019. <https://www.statista.com/statistics/827547/number-liver-cirrhosis-deaths-by-cirrhosis-type/>.
- [17] A.M. Valdes, J. Walter, E. Segal, T.D. Spector, Role of the gut microbiota in nutrition and health, *BMJ* 361 (2018) k2179.
- [18] F. De Vadder, P. Kovatcheva-Datchary, D. Goncalves, J. Vinera, C. Zitoun, A. Duchampt, F. Backhed, G. Mithieux, Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits, *Cell* 156(1-2) (2014) 84-96.
- [19] M.A. Hildebrandt, C. Hoffmann, S.A. Sherrill-Mix, S.A. Keilbaugh, M. Hamady, Y.Y. Chen, R. Knight, R.S. Ahima, F. Bushman, G.D. Wu, High-fat diet determines the composition of the murine gut microbiome independently of obesity, *Gastroenterology* 137(5) (2009) 1716-24 e1-2.
- [20] A.C. Vreugdenhil, C.H. Rousseau, T. Hartung, J.W. Greve, C. van 't Veer, W.A. Buurman, Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons, *J Immunol* 170(3) (2003) 1399-405.
- [21] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, A.V. Ling, A.S. Devlin, Y. Varma, M.A. Fischbach, S.B. Biddinger, R.J. Dutton, P.J. Turnbaugh, Diet rapidly and reproducibly alters the human gut microbiome, *Nature* 505(7484) (2014) 559-63.
- [22] Y. Zhu, X. Lin, H. Li, Y. Li, X. Shi, F. Zhao, X. Xu, C. Li, G. Zhou, Intake of Meat Proteins Substantially Increased the Relative Abundance of Genus *Lactobacillus* in Rat Feces, *PLoS One* 11(4) (2016) e0152678.
- [23] I. Milosevic, A. Vujovic, A. Barac, M. Djelic, M. Korac, A. Radovanovic Spurnic, I. Gmizic, O. Stevanovic, V. Djordjevic, N. Lekic, E. Russo, A. Amedei, Gut-Liver Axis, Gut Microbiota, and Its Modulation in the Management of Liver Diseases: A Review of the Literature, *Int J Mol Sci* 20(2) (2019).
- [24] P.C. Konturek, I.A. Harsch, K. Konturek, M. Schink, T. Konturek, M.F. Neurath, Y. Zopf, Gut(-)Liver Axis: How Do Gut Bacteria Influence the Liver?, *Med Sci (Basel)* 6(3) (2018).

- [25] M. Llopis, A.M. Cassard, L. Wrzosek, L. Bosch, A. Bruneau, G. Ferrere, V. Puchois, J.C. Martin, P. Lepage, T. Le Roy, L. Lefevre, B. Langelier, F. Cailleux, A.M. Gonzalez-Castro, S. Rabot, F. Gaudin, H. Agostini, S. Prevot, D. Berrebi, D. Ciocan, C. Jousse, S. Naveau, P. Gerard, G. Perlemuter, Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease, *Gut* 65(5) (2016) 830-9.
- [26] N. Chalasani, Z. Younossi, J.E. Lavine, M. Charlton, K. Cusi, M. Rinella, S.A. Harrison, E.M. Brunt, A.J. Sanyal, The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases, *Hepatology* 67(1) (2018) 328-357.
- [27] T. Le Roy, M. Llopis, P. Lepage, A. Bruneau, S. Rabot, C. Bevilacqua, P. Martin, C. Philippe, F. Walker, A. Bado, G. Perlemuter, A.M. Cassard-Doulcier, P. Gerard, Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice, *Gut* 62(12) (2013) 1787-94.
- [28] J.S. Bajaj, D.M. Heuman, P.B. Hylemon, A.J. Sanyal, M.B. White, P. Monteith, N.A. Noble, A.B. Unser, K. Daita, A.R. Fisher, M. Sikaroodi, P.M. Gillevet, altered profile of human gut microbiome is associated with cirrhosis and its complications, *J Hepatol* 60(5) (2014) 940-7.
- [29] M. Minemura, Y. Shimizu, Gut microbiota and liver diseases, *World J Gastroenterol* 21(6) (2015) 1691-702.
- [30] M. Usami, M. Miyoshi, H. Yamashita, Gut microbiota and host metabolism in liver cirrhosis, *World J Gastroenterol* 21(41) (2015) 11597-608.
- [31] L. Kulik, H.B. El-Serag, Epidemiology and Management of Hepatocellular Carcinoma, *Gastroenterology* 156(2) (2019) 477-491 e1.
- [32] M.L.Y. Wan, H. El-Nezami, Targeting gut microbiota in hepatocellular carcinoma: probiotics as a novel therapy, *Hepatobiliary Surg Nutr* 7(1) (2018) 11-20.
- [33] H. Lu, Z. Ren, A. Li, H. Zhang, J. Jiang, S. Xu, Q. Luo, K. Zhou, X. Sun, S. Zheng, L. Li, Deep sequencing reveals microbiota dysbiosis of tongue coat in patients with liver carcinoma, *Sci Rep* 6 (2016) 33142.
- [34] M. Basaranoglu, G. Basaranoglu, E. Bugianesi, Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction, *Hepatobiliary Surg Nutr* 4(2) (2015) 109-16.
- [35] K. Yasutake, M. Kohjima, K. Kotoh, M. Nakashima, M. Nakamura, M. Enjoji, Dietary habits and behaviors associated with nonalcoholic fatty liver disease, *World J Gastroenterol* 20(7) (2014) 1756-67.
- [36] A.P. Desai, P. Mohan, A.M. Roubal, R. Bettencourt, R. Loomba, Geographic Variability in Liver Disease-Related Mortality Rates in the United States, *Am J Med* 131(7) (2018) 728-734.
- [37] C.Y. Lian, Z.Z. Zhai, Z.F. Li, L. Wang, High fat diet-triggered non-alcoholic fatty liver disease: A review of proposed mechanisms, *Chem Biol Interact* 330 (2020) 109199.
- [38] F. Sofi, A. Casini, Mediterranean diet and non-alcoholic fatty liver disease: new therapeutic option around the corner? *World J Gastroenterol* 20(23) (2014) 7339-46.
- [39] J.M. Major, J.D. Sargent, B.I. Graubard, H.A. Carlos, A.R. Hollenbeck, S.F. Altekruse, N.D. Freedman, K.A. McGlynn, Local geographic variation in chronic liver disease and hepatocellular carcinoma: contributions of socioeconomic deprivation, alcohol retail outlets, and lifestyle, *Ann Epidemiol* 24(2) (2014) 104-10.
- [40] D. Bogumil, S.Y. Park, L. Le Marchand, C.A. Haiman, L.R. Wilkens, C.J. Boushey, V.W. Setiawan, High-Quality Diets Are Associated with Reduced Risk of Hepatocellular Carcinoma and Chronic Liver Disease: The Multiethnic Cohort, *Hepatol Commun* 3(3) (2019) 437-447.