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Review Article

Association between Obesity and Hepatocellular Carcinoma along with Nitroglycerin-Mediated Vasodilation Study

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ABSTRACT

It is known that Non-Alcoholic Fatty Liver Disease (NAFLD) causes NAFLD-associated Hepatocellular Carcinoma (HCC) and obesity, Type 2 Diabetes Mellitus (T2DM), and Cardiovascular Disease (CVD) as co-morbidities of NAFLD also promote the development and progression of HCC. Previous study indicated that dysregulated metabolites, low grade inflammation, immunity, and autophagy in the tumor microenvironment play a crucial role of HCC progression in obesity status. In this article, the author reviewed the current knowledge of association between obesity and hepatocellular carcinoma along with nitroglycerin-mediated vasodilation study. In result, with respect to the association between obesity and atherosclerosis, obesity is low grade inflammatory status, suggesting that inflammation and/or oxidative stress as a causal factor may induce decreased Flow-Mediated Dilatation (FMD) and impaired Nitroglycerin-Mediated Vasodilation (NMD). The clinical and experimental studies suggested that steatosis-related lipotoxicity may cause hepatocarcinogenesis. It is putative that adipocytes serve as a critical role in the tumor microenvironment through the dysregulated adipokine secretion, leading to the effect of carcinogenesis, metastasis, and chemoresistance. Obesity-associated hepatocarcinogenesis may be associated with the remodeled adipose tissue, genetic factors, inflammation, oxidative stress, and immunity alteration.

Keywords: Obesity-associated HCC, Atherosclerosis, Altered adipose tissue, Hepatic lipogenesis carcinogenesis, Hepatocarcinogenesis

INTRODUCTION

It is known that NAFLD can cause NAFLD-related HCC and obesity as a co-morbidity of NAFLD also promotes the development and progression of HCC. Previous study indicated that dysregulated metabolites, low grade inflammation, immunity, and autophagy in the tumor microenvironment play a critical role of HCC progression in obesity status [1]. It is known that adipocytes serve as a crucial role in the tumor microenvironment through the dysregulated adipokine secretion, leading to the effect of carcinogenesis, metastasis, and chemoresistance [2]. The report also indicated that obesity-associated hepatocarcinogenesis are associated with the remodeled adipose tissue, altered gut microbiome, genetic factors, Endoplasmic Reticulum (ER) stress, oxidative stress and epigenetic alterations [3]. In this article, the current knowledge and trends of association between obesity and HCC along with nitroglycerin- mediated vasodilation study will be reviewed in detail.

LITERATURE OF REVIEW

Link between obesity and atherosclerosis

Due to the epidemics of obesity and Type 2 diabetes mellitus (T2DM), the prevalence and incidence of NAFLD have emerged [4]. It is known that both visceral adipose tissue and liver fat are considered 2 key drivers of cardiometabolic risk associated with a level of total body fat status [5,6]. Previous studies provided that obesity is associated with endothelial dysfunction assessed by Flow-Mediated Vasodilation (FMD) study, increased Intima-Media

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Thickness (IMT) evaluated by common carotid artery, and increased Pulse Wave Velocity (PWV) that are established CVD surrogate markers [7-12]. The study of an association between obesity and impaired NMD has been reported suggesting that decreased NMD may reflect inflammation and oxidative stress [8,13]. It is suggested that inflammation and/or oxidative stress may result in reduced bioconversion of Glyceryl Trinitrate (GTN) to Nitric Oxide (NO), within smooth muscle cells, leading to impaired NMD. According to Ayer's report, it is possible explanation that inflammation associated with obesity, leads to the overabundance of ROS in the vessel wall, resulting in the reduced bioconversion of GTN to NO [8]. The author previously showed the relationship between waist circumference reflecting abdominal adiposity marker and NMD [14]. Endothelial dysfunction has been considered as an early surrogate marker in CVD and an initial step in atherosclerosis condition. Flow-mediated vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) tests in the brachial artery are significant methods for evaluating vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis [15]. The author has described several studies on the diseases of migraine, CVD, Chronic Kidney Disease (CKD), dyslipidemia, aging liver, hypertension and COVID-19 using FMD and NMD procedure [14,16-32]. Obesity is a low grade inflammatory status, thereby, suggesting that inflammation as a causal factor may induce decreased FMD and impaired NMD.

NAFLD-associated HCC

Due to the increased rates in parallel to obesity and T2DM, Non-Alcoholic Fatty Liver Disease (NAFLD) is the common liver disease worldwide [4]. The risk factors and multifactorial process in NAFLD include obesity, T2DM, hypertension, ethnicity, genetic polymorphism PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13, epigenetic factors, transcriptional factors, post-transcriptional modification, and hepatic lipogenesis carcinogenesis as previously described [30]. The growing incidence has showed that NASH/NAFLD has led to an increase of NASH-related HCC [33]. Regarding cirrhotic NAFLD-related HCC, the study by Grimaudo et al. and a meta-analysis have been identified [34,35]. With respect to non-cirrhotic NAFLD-related HCC, the clinical practice guidelines stated that studies have associated obesity and T2DM with the risk of HCC [36]. Bengtsson et al. reported that patients with non-cirrhotic NAFLD-related HCC were observed in 37% of NAFLD-HCC [37]. Regarding obesity status, it is known that BMI level is associated with carcinogenesis risk [38]. Recent study revealed the novel genetic variants in GPAM and APOE that are associated with liver fat content and liver disease showing a robust association between liver damage and lipid biology [39]. Bianco et al. described a causal association between liver fat and HCC suggesting that Polygenic Risk Score (PRS) improve the accurate diagnosis of HCC in individuals with and without severe fibrosis status [40]. Although several risk factors and complex and multifactorial process are present in the progression of NAFLD-related HCC, the author suggests that comprehensive determination using epidemiological factor and PRS including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 may be attributed to the risk stratification, prognosis, and therapeutic strategy in cirrhosis and non-cirrhosis patients with NAFLD-related HCC as previously mentioned [30].

Hepatic lipogenesis carcinogenesis

It is known that obesity is considered as a risk factor for cancer such as NASH-related HCC derived from steatosis, liver injury, inflammation, and fibrosis [41,42]. Recently, Metabolic-Associated Fatty Liver Disease (MAFLD) has been proposed including the metabolic component of fatty liver [43]. The report suggests that the type rather than the amount of lipids is attributable to the transition from steatosis to NASH [44]. The increased hepatic cholesterol including the effect for the mitochondria has regarded as a crucial role in the initiation of NASH [45]. The evidence for cholesterol as a tumor promoter or tumor-suppressor role has been identified in HCC development [41,46]. Ribas et al. concluded the evidence for tumor promoter role of cholesterol in NASH-related HCC associated with an increased expression of the genes involved in immune checkpoints [41]. Liang et al. provided that dietary cholesterol promotes NASH related HCC through dysregulated metabolism and calcium signaling [47]. The study showed that the novel aberrant gene expression, mutation and core oncogene pathways recognized in cholesterol-associated NASH-related HCCs in animal study were observed in human NASH-related HCC [47]. The recurrently mutated genes included RYR1, MTOR, SDK1, CACNA1H and RYR2. With respect to metabolic-related genes, namely, ALDH18A1, CAD, CHKA, POLD4, PSPH, and SQLE were included in human NASH-related HCCs [47]. Based on the evidence, the clinical and experimental studies provided that steatosis-related lipotoxicity may cause hepatocarcinogenesis as previously described [30].

Association between obesity and HCC

It is known that NAFLD can cause NAFLD-related HCC and obesity as a co-morbidity of NAFLD promotes the development and progression of HCC. Previous study indicated that dysregulated metabolites, low grade inflammation, immunity, and autophagy in the tumor microenvironment play a crucial role of HCC progression in obesity [1]. Both visceral adipose tissue and liver fat are considered 2 key drivers of cardiometabolic risk associated with a level of total body fat status [5,6]. Clinically, obesity is strongly correlated with the prevalence of metabolic disorders including insulin resistance, dyslipidemia, hypertension, and NAFLD, leading to obesity-related carcinogenesis [2]. Adipocyte serves as a crucial role in the tumor microenvironment through the dysregulated adipokine secretion, leading to effect of carcinogenesis, metastasis, and chemoresistance. Excessive and dysfunctional adipose tissue dysregulates adipokine secretion, subsequently leading to obesity-associated HCC [2]. It is thought that obesity alters inflammation and stress respond pathways and causes tissue adiposity and tumorigenesis [3]. Evidence provides a close relationship between obesity and the increased incidence of HCC showing that obesity drives HCC, and obesity-related tumorigenesis develops NAFLD-related HCC [3]. Obesity-associated hepatocarcinogenesis are associated with the

remodeled adipose tissue, altered gut microbiome, genetic factors, Endoplasmic Reticulum (ER) stress, oxidative stress and epigenetic alterations leading to dysregulated adipokine secretion and activated Nrf-1, NF-κB, mTOR, P13K/PTEN/Akt, and JAK/STAT signaling pathways [3]. Regarding the immunologic pathways which subsequently activate oncogenic mechanisms, it has been demonstrated that ROS accompanied by the production of lipid peroxidation increases the release of inflammation and inhibitory cytokines including TNF-α, IL-6, leptin and adiponectin [48]. With respect to immune infiltration of fatty liver, experimental study revealed that immune cells and cytokines serve as a crucial role in the pathogenesis of HCC. Previous report provided that prolonged NASH status induces activated CD8+ T-cell subsequently leading to HCC in experimental study [49]. Additionally, a loss of intrahepatic CD4+ T-cells was induced by NAFLD status [50]. Whereas, B-cells, T-cells, natural killer cells and myeloid cell have been associated with the pathogenesis of NASH-induced HCC [51]. It is known that obesity induces altered immune function and systemic endocrine alterations. Previous study showed that the mechanisms of NAFLD/NASH-associated HCC involve metabolites, oxidative stress, altered immune function, pathological inflammatory responses, and alteration of endocrine or adipokine signaling [52]. Llovet et al. suggested that ER stress, pathological lipophagy, increased ROS genesis, and low NADH or NADPH levels induce the altered oncogenic gene in fatty acid-overloaded hepatocytes leading to the malignant cells [52]. With respect to oxidative stress in obesity, mouse model study demonstrated that high STAT-1 level induced progression to NASH, whereas high STAT-3 level progressed HCC, independently of each other, suggesting that similar inflammatory signals can differentially cause [53]. Regarding the progression from NAFLD to NASH, and fibrosis, it is known that lipotoxicity causes hepatocyte death and activated and proliferated Kupfer cells, as well as recruited immune cells to the liver subsequently leading to NASH. The inflammation and tissue damage lead to wound healing with accumulated extracellular matrix proteins with characteristic fibrosis [54]. Recently, Brahma, et al. described that excessive levels of ROS from the fatty acid influx and chronic inflammation is considered as a causative factor for the initiation and progression of HCC [54]. They provided the evidence for the intracellular sources of obesity-induced ROS and molecular mechanisms for hepatic tumorigenesis, and the role of the dysregulated activity of BCL-2 proteins and Protein Tyrosine Phosphatases (PTPs).

DISCUSSION

Obesity is low grade inflammatory status, suggesting that inflammation and/or oxidative stress as a causal factor may induce decreased FMD and impaired NMD reflecting atherosclerosis status. The clinical and experimental studies suggested that steatosis-related lipotoxicity may cause hepatocarcinogenesis. It is putative that adipocytes serve as a significant role in the tumor microenvironment through the dysregulated adipokine secretion, leading to the effect of carcinogenesis, metastasis, and chemo resistance. Excessive and dysfunctional adipose tissue dysregulates adipokine secretion, subsequently leading to obesity-associated HCC. Obesity-associated hepatocarcinogenesis may be associated with the remodeled adipose tissue, genetic factors, inflammation, oxidative stress, and immunity alterations. Regarding oxidative stress, the study showed that high STAT-1 level induced progression to NASH, meanwhile, high STAT-3 level progressed HCC in mouse model study. It is putative that excessive levels of ROS from the fatty acid influx and chronic inflammation are considered as a causative factor for the initiation and progression of HCC.

CONCLUSION

The inflammation and/or oxidative stress as a causal factor may induce decreased FMD and impaired NMD reflecting atherosclerosis status. The clinical and experimental studies suggested that steatosis-related lipotoxicity may cause hepatocarcinogenesis. It is putative that adipocyte serves as a crucial role in the tumor microenvironment through the secreted adipokines, leading to carcinogenesis, metastasis, and chemoresistance. Obesity-associated hepatocarcinogenesis may be associated with the remodeled adipose tissue, genetic factors, inflammation, oxidative stress, and immunity alterations.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

REFERENCES

1. Zhang C, Liu S, Yang M. Hepatocellular carcinoma and obesity, Type 2 diabetes mellitus, cardiovascular disease: Causing factors, molecular links, and treatment options. Front Endocrinol. 2021; 12:808526.
2. Rajesh Y, Sarkar D. Association of adipose tissue and adipokines with development of obesity-induced liver cancer. Int J Mol Sci. 2021; 22:2163.
3. Rajesh Y, Sarkar D. Molecular mechanisms regulating obesity-associated hepatocellular carcinoma. Cancers. 2020; 12:1290.
4. Younossi ZM. Non-alcoholic fatty liver disease: A global public health perspective. Hepatology. 2019; 70:531-544.
5. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444(7121): 881-887.
6. Despres JP. Body fat distribution and risk of cardiovascular disease: An update. Circulation. 2012; 126:1301-1313.
7. Bigornia SJ, Mott MM, Hess DT, Apovian CM, McDonnell ME, Duess MA, et al. Long-term successful weight loss improves vascular endothelial function in severely obese individuals. Obesity. 2010; 18:754-759.
8. Ayer JG, Harmer JA, David C, Steinbeck KS, Seale JP, Celermajer DS. Severe obesity is associated with impaired arterial smooth muscle function in young adults. Obesity. 2011; 19:54-60.
9. Aday AW, Goldfine AB, Gregory JM, Beckman JA. Impact of acipimox therapy on free fatty acid efflux and endothelial function in the metabolic syndrome: A randomized trial. Obesity. 2019; 27:1812-1819.
10. Man E, Cheung PT, Cheung YF. Associations between arterial structure and function and serum levels of liver enzymes in obese adolescents. J Paediatr Child Health. 2017; 53:691-697.
11. Ostrem JD, Evanoff N, Kelly AS, Dengel DR. Presence of a high-flow-mediated constriction phenomenon prior to flow-mediated

dilation in normal weight, overweight, and obese children and adolescents. J Clin Ultrasound. 2015; 43:495-501.

12. Gokce N, Karki S, Dobyns A, Zizza E, Sroczynski E, Palmisano JN, et al. Association of bariatric surgery with vascular outcomes. JAMA Netw Open. 2021; 4:e2115267.
13. Pena AS, Wiltshire E, Mackenzie K, Gent R, Piotto L, Hirte C, et al. Vascular endothelial and smooth muscle function relates to body mass index and glucose in obese and nonobese children. J Clin Endocrinol Metab. 2006; 91:4467-4471.
14. Fujioka K, Oishi M, Fujioka A, Nakayama T, Okada M. Interrelationship among lipid profiles, arterial stiffness, and nitroglycerin-mediated vasodilation in the community-based setting of the Japanese women. Angiol Open Access. 2019; 7:235.
15. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002; 39:257-265.
16. Fujioka K, Oishi M, Fujioka A, Nakayama T. Increased nitroglycerin-mediated vasodilation in migraineurs without aura in the interictal period. J Med Ultrason. 2018; 45:605-610.
17. Fujioka K. Reply to: Endothelium-dependent and-independent functions in migraineurs. J Med Ultrason. 2019; 46:169-170.
18. Fujioka K, Oishi M, Nakayama T, Fujioka A. Association of brachial artery measures with estimated GFR>60mL/min/1.73m^2 in a cross-sectional study of the community-based women. Angiol Open Access. 2019; 7:2317.
19. Fujioka K. Association between endothelial function and aspartate aminotransferase to platelet ratio index in patients without hepatic-associated disease. Int J Case Rep Clin Image. 2021; 3 (4):169.
20. Fujioka K. Propensity to the vascular smooth muscle cell abnormality in migraine without aura and vasospastic angina along with a genome-wide association studies. J Carcinog Mutagen. 2019; 10:334.
21. Fujioka K, Oishi M, Nakayama T, Fujioka A. Correlation between vascular failure (endothelial dysfunction) and fibrosis markers. Jpn J Med Ultrsonics. 2016; 43:S458.
22. Fujioka K. Effect on microRNA-92a in atherosclerosis along with flow-mediated vasodilation study. J Cancer Oncol. 2020; 4(1): 000153.
23. Fujioka K. A novel biomarker microRNA-92a-3p as a link between cardiovascular disease and chronic kidney disease. J Carcinog Mutagen. 2020; 11(2):1000345.
24. Fujioka K. Association between chronic liver disease and atherosclerosis: An inflammation as common pathway. J Clinical Trials. 2021; 11(1):444.
25. Fujioka K. NAFLD/NASH-related hepatocellular carcinoma: Along with the role of genetics. J Cancer Oncol. 2020; 4(2):000165.
26. Fujioka K. A link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19. CPQ Medicine. 2021; 11(4): 01-08.
27. Fujioka K. Cutaneous manifestation and vasculitis of COVID-19 in dermatology. Acta Sci Med Sci. 2021; 5:16-19.
28. Fujioka K. Clinical manifestation of endotheliitis in COVID-19 along with flow-mediated vasodilation study. J Clin Trials. 2021; 11(4): 1000469.
29. Fujioka K. Current genetic advances in NAFLD/NASH: Related hepatocellular carcinoma along with characteristic clinical manifestations. J Carcinog Mutagen. 2021; 12(17):1000001.
30. Fujioka K. Polygenic risk score in NAFLD/NASH-associated hepatocellular carcinoma along with multifactorial process. J Carcinog Mutagen. 2021; 12(6):1000370.
31. Fujioka K. Link between non-alcoholic fatty liver disease and hypertension: non-alcoholic fatty liver disease as a multisystem disease. Int J Clin Case Rep Rev. 2022; 10:203.
32. Fujioka K. Endothelial dysfunction in COVID-19 along with SARS-CoV-2 Omicron variant. Int J Case Rep Clin Image. 2022; 4(1):174.
33. Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management. World J Hepatol. 2017; 9: 533-543.
34. Grimaudo S, Pipitone RM, Pennisi G, Celsa C, Camma C, Marco VD, et al. Association between PNPLA3 rs738409 C>G variant and liver-related outcomes in patients with nonalcoholic fatty liver disease. Clin Gastronterol Hepatol. 2020; 18:935-944.
35. Vilar-Gomez E, Caizadilla-Bertot L, Wai-Sun Wong V, Castellanos M, de la Fuente RA, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018; 155:443-457.
36. EASU Office. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. Diabetelogia. 2016; 59:1121-1140.
37. Bengtsson B, Stai P, Wahlin S, Bjorstrom N, Hagstrom H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int. 2019; 39:1098-1108.
38. Bhaskaran K, Douglas I, Forbes H, Dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014; 384:755-765.
39. Jamialahmadi O, Mancina RM, Ciociola E, Tavaglione F, Luukkonen PK, Baselli G, et al. Exome-wide association study on alanine aminotransferase identifies sequence variants in the GPAM and APOE associated with fatty liver disease. Gastroenterology. 2021; 160:1634-1646.
40. Bianco C, Jamialahmadi O, Pelusi S, Baselli G, Dongiovanni P, Zanoni I, et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. J Hepatol. 2021; 74:775-782.
41. Ribas V, de la ROSA LC, Robles D, Nunez S, Segales P, Insausti-Urkia N, et al. Dierary and genetic cholesterol loading rather than steatosis promotes liver tumorigenesis and NASH-driven HCC. Cancers. 2021; 13:4091.
42. Former A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391:1301-1314.
43. Eslam M, Sanyal AJ, George J. MAFLD: A consensus–driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020; 158:1999-2014.
44. Alonso C, Fernandez-Ramos D, Varela-Rey M, Martinez-Arranz I, Navasa N, Van Liempd SM, et al. Metabolomic identification of subtypes of nonalcoholic steatohepatitis. Gastroenterology. 2017; 152:1449-1461.
45. Ioannou GN. The role of cholesterol in the pathogenesis of NASH. Trends Endocrinol Metab. 2016; 27:84-95.
46. Carr BI, Giannelli G, Guerra V, Giannini EG, Farinati F, Rapaccini GL, et al. Plasma cholesterol and lipoprotein levels in relation to tumor aggressiveness and survival in HCC patients. Int J Biol Markers. 2018; 33:423-431.
47. Liang JQ, Teoh N, Xu L, Pok S, Li X, Chu ESH, et al. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. Nat Commun. 2018; 9(1):4490.
48. Kutlu O, Kaleli HN, Ozer E. Molecular pathogenesis of nonalcoholic steatohepatitis-(NASH) related hepatocellular carcinoma. Can J Gastroenterol Hepatol. 2018; 8543763.

49. Wolf MJ, Adili A, Piotrowitz K, Abdullah Z, Boege Y, Stemmer K, et al. Metabolic activation of intrahepatic CD8+ T-cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes. Cancer Cell. 2014; 26:549-564.

50. Ma C, Kesarwala AH, Eggert T, Medina-Echeverz J, Kleiner DE, Jin P, et al. NAFLD causes selective CD4+ T lymphocyte loss and promotes hepatocarcinogenesis. Nature. 2016; 531:253-257.

51. Sutti S, Albano E. Adaptive immunity: An emerging player in the progression of NAFLD. Nat Rev Gastroenterol Hepatol. 2020; 17:81-92.

52. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021; 7:6.

53. Grohmann M, Wiede F, Dodd GT, Gurzov EN, Ooi GJ, Butt T, et al. Obesity drives STAT-1-dependent NASH and STAT-3-dependent HCC. Cell. 2018; 175:1289-1306.

54. Brahma MK, Gilglioni EH, Zhou L, Trepo E, Chen P, Gurzov EN. Oxidative stress in obesity-associated hepatocellular carcinoma: sources, signaling and therapeutic challenges. Oncogene. 2021; 40:5155-5167.