



VOLUME 02 ISSUE 02 (2023)

AMERICAN JOURNAL OF
**MEDICAL SCIENCE
AND INNOVATION**
(AJMSI)



PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

Morbid Obesity Associated with Non-Alcoholic Fatty Liver Disease and Complicated by Severe Non-Cirrhotic Portal Hypertension: A Case Report from Rural Kenya

Vonwicks C. Onyango^{1*}, Kenneth H. Makokha², Samuel M. Gachie³, Boniface Mutiso³Nicholas M. Mutuma³, Paul M. Kamau³

Article Information

Received: July 17, 2023**Accepted:** August 09, 2023**Published:** August 14, 2023

Keywords

Obesity, Non-Alcoholic Fatty Liver Disease, NAFLD, Portal Hypertension, Non-Cirrhotic Portal Hypertension, Kenya

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease and is closely linked with obesity and metabolic syndrome. Portal hypertension in NAFLD typically occurs in the cirrhotic phase of the disease and may present with esophageal varices, splenomegaly with splenic sequestration syndrome, ascites, and features of liver failure. However, recent experimental and clinical data show the occurrence of portal hypertension in NAFLD in the absence of fibrosis or cirrhosis. We present such a clinical case from rural Kenya in this study with the literature review that proposes novel mechanisms for such non-cirrhotic portal hypertension in NAFLD.

INTRODUCTION

The World Health Organization defines obesity as an excessive or abnormal accumulation of body fat that presents a risk to health. A body mass index (BMI) of 25-29.9 kg/m² defines overweight individuals, while a BMI of ≥ 30 is obesity. A BMI of ≥ 40 kg/m² (or ≥ 35 kg/m² in association with comorbidities) defines severe obesity, also called morbid obesity (Apovian, 2016). By 2015, it was estimated that >600 million adults worldwide had obesity, with the number of obese people having more than doubled since the 1980s in >70 countries. The prevalence was higher for females than males at all socioeconomic and age-group levels (Afshin *et al.*, 2017). In this study, a high BMI accounted for >4 million deaths globally, with 60% attributed to obesity, especially cardiovascular diseases. Obesity is associated with significant multisystemic dysfunction, including cardiovascular, metabolic, hepatobiliary, musculoskeletal, psychosocial, and neurological diseases, etc. Obesity (especially in the setting of metabolic syndrome) is a major risk factor for non-alcoholic fatty liver disease (NAFLD), in which patients have hepatic steatosis with or without inflammation and fibrosis and in the absence of a secondary cause of the steatosis (Younossi *et al.*, 2011). NAFLD is the most common liver disease, with a global prevalence of 25% (Araújo *et al.*, 2018). This prevalence was replicated in a Kenyan study by Mburu *et al.*, in which the prevalence of NAFLD was 26.2% among overweight and obese children in Nairobi (Mburu *et al.*, 2023). However, most cases of NAFLD are diagnosed in the 4th to 5th decades of life (Cotter & Rinella, 2020). NAFLD encompasses a disease spectrum that includes steatosis

with or without inflammation (non-alcoholic liver, i.e., NAFL), non-alcoholic steatohepatitis (NASH), which includes hepatic necroinflammation and fibrosis, and eventual liver cirrhosis. Patients with cirrhotic NAFLD should be screened for hepatocellular carcinoma and esophageal varices (Powell *et al.*, 2021).

Case Presentation

Presenting Illness and Physical Examination

A 62-year-old married mother of three from Naivasha, Kenya, a retired teacher, was referred to us for upper gastrointestinal endoscopy in the evaluation of a 2-week preceding history of symptomatic microcytic hypochromic anemia with a hemoglobin of 8.4g/dl and a mean corpuscular hemoglobin (MCV) of 69 fl. Notably, she was morbidly obese with previous multiple comorbidities and complications including: obstructive sleep apnea syndrome, hypertension (well controlled on medications), previous mesenteric ischemia in 2013 needing exploratory laparotomy with gangrenous bowel excision and primary anastomosis, proximal deep venous thrombosis of the right leg in 2014 which was treated with 6 months of warfarin anticoagulation, left sided Bell's palsy in 2016 treated with prednisone and acyclovir but having residual ipsilateral hemifacial weakness, bilateral lower limb varicose veins for which she was using bilateral external compression stockings, and severe bilateral knee osteoarthritis worse on the right knee for which she had undergone a total knee replacement in 2017. Six months earlier, she had an ultrasound diagnosis of fatty liver disease with no complications during a routine medical evaluation at her local hospital. She was a lifetime non-

¹ Department of Medicine, St. Joseph Rift Valley Hospital, Gilgil, Nakuru County, Kenya

² Department of Endoscopy, St. Joseph Rift Valley Hospital, Gilgil, Nakuru County, Kenya

³ St. Joseph Rift Valley Hospital, Gilgil, Nakuru County, Kenya

* Corresponding author's e-mail: drvonczelo@gmail.com

smoker and non-ethanol user.

Her physical examination was remarkable for moderate conjunctival pallor, bilateral palmar erythema, and no obvious spider naevi, she was morbidly obese with a body mass index of 44.98 kg/m² (weight of 121 kilograms, height of 1.64 meters), she had a blood pressure of 114/69 mmHg, she was dyspneic at rest with a respiratory rate of 24 breaths per minute with a baseline oxygen saturation of 84% in room air; and a random blood sugar of 184mg/dl. Her abdomen was of markedly increased girth with multiple striae distensae and caput medusae, non-tender to palpation with bilateral flank dullness, and an obviously palpable splenomegaly about 6cm below the left costal margin in the mid-clavicular line. A digital rectal exam showed grade 2 hemorrhoids with melena stools. She had grade 2 bipedal pitting edema, distended external jugular veins with elevated jugular venous pressure to about 8 cm, a diffuse apex beat with loud P2, normal and regular S1 and S2 heart sounds, and a grade 4/6 tricuspid regurgitation murmur. She had bi-basal lung crackles and a neurological examination remarkable for left hemifacial paresis (from prior Bell's palsy) with no features of hepatic encephalopathy.

Diagnostic Work Up

Her important work-up findings included a complete blood count showing anemia with a hemoglobin of 8 g/dl with an MCV of 70 fl, leucopenia with total a white blood cells of $3.1 \times 10^3/\text{uL}$, and thrombocytopenia with platelets of $90 \times 10^3/\text{uL}$ (the leucopenia and thrombocytopenia due to splenic sequestration from the portal hypertension). She had an elevated glycated hemoglobin (HbA1c) of 7.1% (insulin resistance), a normal creatinine of 0.9 mg/dl, normal aspartate transferase, bilirubin, and prothrombin time (INR). She had negative HIV and hepatitis B and C screening tests. An abdominal ultrasound showed a normal-sized liver with normal wall margins but with marked fatty infiltration and no other lesions, an enlarged spleen measuring 16.18cm with several prominent collateral

veins, and moderate ascites (in keeping with portal hypertension). Upper gastrointestinal endoscopy showed grade 3 esophageal varices with hyperemic gastric fundus but no obvious ulcers or active bleeding (see Figure 1 Series of the esophageal varices on endoscopy). A chest x-ray showed cardiomegaly with pulmonary edema and prominent pulmonary vessels. An electrocardiogram showed a normal sinus rhythm, right axis deviation, and p-pulmonale (right atrial enlargement); an interval echocardiogram showed a normal left ventricular ejection fraction of 70% with concentric left ventricular hypertrophy, both atria and right ventricular outflow tract markedly enlarged, moderate-to-severe tricuspid regurgitation with an estimated right ventricular systolic pressure elevated at 55 mmHg (features of pulmonary hypertension), and no obvious intracardiac thrombi.

Management and Follow-Up

The patient was clinically diagnosed with morbid obesity associated with non-alcoholic fatty liver disease (NAFLD) and complicated with features of non-cirrhotic portal hypertension (splenomegaly with splenic sequestration, ascites, esophageal varices, and hemorrhoids). This was against a background of other multiple target organ damages. She underwent a multidisciplinary team review, with specific management including: endoscopic esophageal variceal banding with initial 6-to-12-week surveillance endoscopies and repeat banding when needed as per our institutional protocol. She has since undergone three banding events (See Figure 2 series taken post endoscopic esophageal variceal banding). She was also put on propranolol to prevent re-bleeding of the esophageal varices, omeprazole and metoclopramide for the gastritis, hematinic drugs for the anemia, the heart failure (which was predominantly due to cor pulmonale) was managed with furosemide, spironolactone, losartan, and sildenafil (the latter to

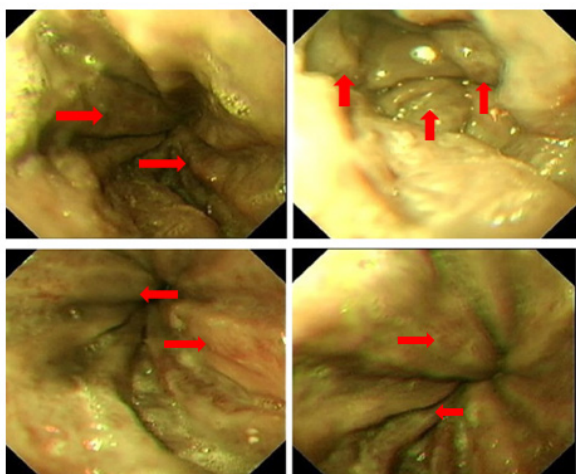


Figure 1: Grade 2-3 esophageal varices (red arrows) for the patient seen on endoscopy. There was no active bleeding observed during endoscopy.

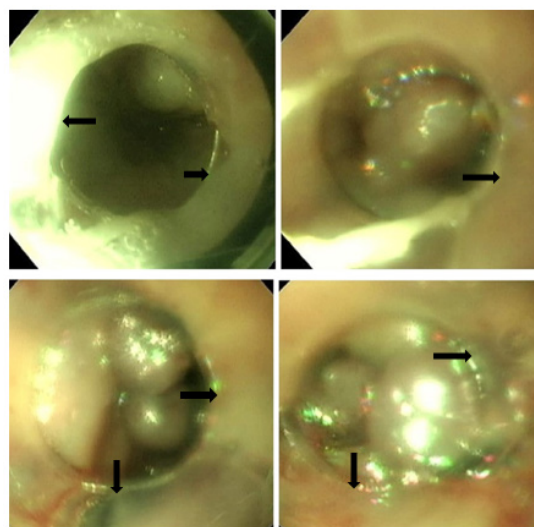


Figure 2: Esophageal variceal banding done for the patient on the initial, and subsequent serial follow-up endoscopy. Notice the bands in place (black arrows).

reduce pulmonary hypertension). Nocturnal continuous positive airway pressure (CPAP) for the obstructive sleep apnea syndrome was recommended following a formal polysomnogram, but the patient could not afford it and currently uses nocturnal nasal-prong oxygen delivered by an oxygen concentrator. She is also receiving multiple supportive therapies within a multidisciplinary team. She was enrolled in the nutritional program to help with diet and weight management and has been active to date (she has since lost 12 kg). She developed a second episode of unprovoked proximal deep venous thrombosis on the left leg 3 months later, which was treated with rivaroxaban for 6 months, and was subsequently put on life-long warfarin (the cheaper option) with careful monitoring of the INR and surveillance for bleeding disorders. The leucopenia and thrombocytopenia have persisted during follow-up, but the anemia has since resolved.

DISCUSSION

Portal hypertension develops when there is increased pressure in the portal venous system and is associated with increasing portal collateral blood flow (porto-systemic anastomosis). This leads to ascites, esophageal varices, caput medusae, hemorrhoids, liver failure manifestations (including hepatic encephalopathy, coagulopathy, etc.), and hepatorenal syndrome (Simonetto *et al.*, 2019). The two most common causes of portal hypertension globally are cirrhosis and non-cirrhotic periportal fibrosis from hepatic schistosomiasis, or portal vein thrombosis (Mauro & Gadano, 2020). Our patient has splenomegaly with features of splenic sequestration (thrombocytopenia and leucopenia, both of which have persisted in her follow-up tests), esophageal varices needing repeat bandings, ascites, caput medusae, and hemorrhoids. The etiology of the anemia is multifactorial, with the most prevalent cause being iron deficiency anemia from multiple etiologies, including portal hypertensive gastropathy.

Portal hypertension in NAFLD usually occurs in the cirrhotic phase of the disease. It is unusual to find manifestations of portal hypertension in NAFLD without associated liver cirrhosis. However, recent clinical and experimental data shows the occurrence of portal hypertension in the absence of significant fibrosis or cirrhosis. There is growing evidence that portal venous pressure may begin to rise early in the NAFLD pathogenetic process when fibrosis is either absent or insignificant. In an observational study of 100 patients with NAFLD associated with clinically significant portal hypertension (encephalopathy, esophageal varices, ascites, and splenomegaly) undergoing staging liver biopsy, 88 of them had cirrhosis. However, in 12 of the patients (12% of cases), fibrosis was mild or absent (Mendes *et al.*, 2012). These patients had a greater degree of hepatic steatosis compared to those without portal hypertension. Our patient has not had any features of liver cirrhosis in multiple follow-up ultrasound scans of the liver over the last 2 years. There was a marginal increase in fatty infiltration of the liver initially, but this has plateaued

and remained static since the onset of her weight loss journey. Admittedly, the utility of ultrasonography in general medical diagnosis is limited by user-dependent variabilities.

One of the proposed mechanisms for this non-cirrhotic portal hypertension in NAFLD is a combination of impaired hepatic sinusoidal hemostasis and hepatocellular ballooning leading to increasing intrahepatic vascular resistance and thus portal hypertension before the development of cirrhosis. Both of these processes are initiated by progressive lipid accumulation in the hepatocytes (steatosis), which causes a mechanical barrier to sinusoidal flow and eventual hepatotoxicity from the lipidosis-induced hepatocyte ballooning (Baffy, 2018). Other proposed intrahepatic factors include steatosis-induced endothelial cell dysfunction and splanchnic vasodilatation, both of which increase intrahepatic vascular resistance early in NAFLD. Insulin resistance is associated with NAFLD non-cirrhotic portal hypertension through increased hepatocyte burden of adipose tissue lipolysis with resultant hepatotoxicity, endothelial dysfunction, and increased portal pressures (Nababan & Lesmana, 2022). Our patient also has insulin resistance, with a HbA1c of 7.1%.

The first-line therapy for NAFLD is lifestyle changes, especially diet and physical exercise, to reduce body weight to a more normal BMI. Non-selective beta blockers, e.g., propranolol and carvedilol, help to reduce portal and splanchnic pressures, thus reducing the incidence of primary and repeat variceal bleeding. Other medications include statins, renin-angiotensin-aldosterone system (RAAS) blockade, and sodium-glucose transport protein 2 (SGLT2) inhibitors given in a judicious and rational manner (Nababan & Lesmana, 2022). Our patient is already on most of these strategies, which have been individualized based on her practical realities.

CONCLUSION

The occurrence of portal hypertension in NAFLD is usually encountered during the cirrhotic phase of the disease. However, novel pathophysiological mechanisms have recently been proposed to explain the experimental and clinical observations of non-cirrhotic portal hypertension in NAFLD, as presented in this case report. Admittedly, more advanced non-invasive (e.g., transient elastography, computerized tomography, magnetic resonance imaging scans, etc.) and invasive diagnostic tests and procedures (e.g., liver biopsy) need to be carried out to further evaluate and characterize the hepato-portal dysfunction in our patient, preferably in a specialized center. These ideal interventions are unfortunately limited by financial and other constraints that define the reality of rural medicine.

REFERENCES

- Afshin, A., Forouzanfar, M. H., Reitsma, M. B., Sur, P., Estep, K., Lee, A., Marczak, L., Mokdad, A. H., Moradi-Lakeh, M., Naghavi, M., Salama, J. S., Vos, T., Abate, K. H., Abbafati, C., Ahmed, M. B., Al-Aly,

- Z., Alkerwi, A., Al-Raddadi, R., Amare, A. T., . . . Murray, C. J. L. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*, 377(1), 13-27. <https://doi.org/10.1056/NEJMoa1614362>
- Apovian, C. M. (2016). Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care*, 22(7 Suppl), s176-185.
- Araújo, A. R., Rosso, N., Bedogni, G., Tiribelli, C., & Bellentani, S. (2018). Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future. *Liver Int*, 38 Suppl 1, 47-51. <https://doi.org/10.1111/liv.13643>
- Baffy, G. (2018). Origins of Portal Hypertension in Nonalcoholic Fatty Liver Disease. *Dig Dis Sci*, 63(3), 563-576. <https://doi.org/10.1007/s10620-017-4903-5>
- Cotter, T. G., & Rinella, M. (2020). Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. *Gastroenterology*, 158(7), 1851-1864. <https://doi.org/10.1053/j.gastro.2020.01.052>
- Mauro, E., & Gadano, A. (2020). What's new in portal hypertension? *Liver Int*, 40 Suppl 1, 122-127. <https://doi.org/10.1111/liv.14366>
- Mburu, A. N., Laving, A., Macharia, W. M., & Sande, J. (2023). Prevalence of non-alcoholic fatty liver disease in overweight and obese children seeking ambulatory healthcare in Nairobi, Kenya. *BMJ Open Gastroenterol*, 10(1). <https://doi.org/10.1136/bmjgast-2022-001044>
- Mendes, F. D., Suzuki, A., Sanderson, S. O., Lindor, K. D., & Angulo, P. (2012). Prevalence and indicators of portal hypertension in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*, 10(9), 1028-1033. <https://doi.org/10.1016/j.cgh.2012.05.008>
- Nababan, S. H. H., & Lesmana, C. R. A. (2022). Portal Hypertension in Nonalcoholic Fatty Liver Disease: From Pathogenesis to Clinical Practice. *J Clin Transl Hepatol*, 10(5), 979-985. <https://doi.org/10.14218/jcth.2021.00593>
- Powell, E. E., Wong, V. W., & Rinella, M. (2021). Non-alcoholic fatty liver disease. *Lancet*, 397(10290), 2212-2224. [https://doi.org/10.1016/s0140-6736\(20\)32511-3](https://doi.org/10.1016/s0140-6736(20)32511-3)
- Simonetto, D. A., Liu, M., & Kamath, P. S. (2019). Portal Hypertension and Related Complications: Diagnosis and Management. *Mayo Clin Proc*, 94(4), 714-726. <https://doi.org/10.1016/j.mayocp.2018.12.020>
- Younossi, Z. M., Stepanova, M., Afendy, M., Fang, Y., Younossi, Y., Mir, H., & Srishord, M. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol*, 9(6), 524-530.e521; quiz e560. <https://doi.org/10.1016/j.cgh.2011.03.020>