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Diabetes mellitus-induced lower urinary tract symptoms and hepatic steatosis in an older male

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Summary

Diabetes mellitus type 2 (DM-2) is one of the important causes of low-grade chronic inflammation (meta inflammation) seen in almost all tissues in the body. Other possible mechanisms involved in the development of lower urinary tract symptoms (LUTS) with DM-2 are the hypertonicity of the peripheral sympathetic nerves and hyperinsulinemia effects on the autonomous nervous system activity. These further suggests that abnormalities in glucose homeostasis influence the hyperproliferation of the prostate cells resulting in benign prostatic hyperplasia (BPH). Similarly, hepatic steatosis, a form of non-alcoholic fatty liver disease (NAFLD) prevalence among patients with DM-2, is as high as 75%. NAFLD has no symptoms in most diabetic patients. In this study, we present a case of a 64-year-old Black male who had worsening urinary urgency and hesitancy for 4 months, with increasing abdominal girth. Patient was found to have symptoms, diagnostic studies, and physical exam findings indicative of BPH and fatty liver disease. He was treated with hepato-protective medications, tighter control of his blood glucose levels, and blood pressure meds for 13 months. Upon follow-up, most of his symptoms were resolved. Timeline of BPH resolution and decrease in liver size following treatment suggest that DM-2 has a strong correlation with the development of BPH and fatty liver disease in most patients living with diabetes.

Learning points

- Men with type 2 diabetes mellitus (DM-2) tend to have significantly lower serum PSA level, lower testosterone levels, and larger prostate volume compared to non-diabetic male patients.
- Patients with DM-2 have higher prevalence of hepatic steatosis, liver cirrhosis, and end-stage liver failure.
- The role of metformin in reducing hepatic steatosis as stated by several studies is yet to be validated as our patient has been on metformin for 22 years for the management of DM-2 with fatty liver disease.

Background

Non-alcoholic steatohepatitis (NASH) is the last stage or advanced form of non-alcoholic fatty liver disease (NAFLD). NAFLD occurs because of fat accumulation in the liver cells, with subsequent inflammation leading to scarring of the liver and development of liver cirrhosis. NASH often presents with no symptoms or signs in many patients. However, most of the common complaints among patients with symptoms include fatigue and mild right upper quadrant pain. Common risk factors of NASH in addition to DM-2 include hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, polycystic ovary syndrome, sleep apnea, and hypothyroidism (1).

Furthermore, several literature suggest that diabetic patients with high hemoglobin A1c (poorly managed blood glucose level) have higher prevalence of early BPH because high insulin levels can trigger prostate growth (2). This is also because when blood glucose level remains constantly high, the pancreas continues to pump more

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insulin, conversely, such high blood level of insulin triggers the liver to produce more insulin-like growth factor (IGF) which is believed to be the stimulator of prostate growth.

Case presentation

A 64-year-old Black male presented in the clinic approximately 13 months prior with complaints of mild abdominal discomfort, fatigue, and increased urinary urgency and hesitancy characterized by initial dribbling and weak stream of urine flow, and inability to completely empty his bladder for 4-month duration.

Patient's medical history is significant for DM-2 for 22 years and is managed with daily oral hypoglycemic medication – metformin, hypertensive heart disease, osteoarthritis, essential tremor in both hands, and diabetic retinopathy. He is a non-smoker and does not consume alcohol. BMI was 29 kg/m^{2,} indicative of obesity. Physical examination at that time revealed protruded abdomen, dull pain on palpation on right upper quadrant, and pain on the suprapubic region. Percussion of the liver revealed firmness and increased lower border of the liver with tympany over the umbilical area indicative of liver enlargement with ascites. Patient denied jaundice, itchiness, nausea, and vomiting but endorsed constipation which relieves with over-the-counter laxatives. Vital signs on admission were blood pressure 156/92 mmHg, respiratory rate 18 b.p.m, and afebrile. Patient was admitted to the hospital for detailed diagnostic investigations and treatments.

Investigation

Patient's liver function test (Table 1) appeared normal except for slight increase in gamma glutamyl transferase (GGT) which was indicative of liver disease or possible damage to the bile ducts. Lipid profile (Table 2) showed increased levels of LDL and VLDL cholesterol which could be due to poor liver functioning. HgA1c was 8.4% (normal < 5.6%), prostate-specific antigen (PSA) was 0.6 ng/mL (normal: 0–4 ng/L), and urinalysis was positive for glucose but otherwise normal. Ultrasound of the liver showed an enlarged liver (span 18.8 cm) with a raised parenchymal echogenicity and smooth borders. The intrahepatic, vascular, and biliary channels were preserved. The gallbladder appeared distended with clear content and no stones and showed normal wall thickness. The pancreas and spleen were normal. The right and left kidneys measured 11.8 × 5.1 cm and 12.0 × 6.5 cm, respectively. Their cortical echo pattern and corticomedullary differentiations are preserved. Small amount of free fluid was evident in abdominal cavity.

The prostate gland was enlarged and measured 4.2 × 5.1 × 4.8 cm with a prostatic volume of 53.4 cm^3, well-defined borders, and homogeneous parenchymal echo pattern. The urinary bladder appeared distended with urine and normal wall thickness; prevoid volume of ~231 cm^3 and postvoid volume of ~67 cm^3. Patient was also given the International Prostate Symptom Score (IPSS) assessment test which returned with a score of 21, which was considered severe (Table 3). A uroflowmetry test was recommended by the urologist. Patient was advised not to urinate for 3 h and was given 1 L of water to drink during that time. Afterward, he was allowed to urinate in a funnel connected to the electronic uroflowmeter. The results were as follows: voided volume 210 mL; max flow rate 10.5 mL/s; average flow rate 5 mL/s; voiding time 55 s; and time to max flow 28 s. A final diagnosis of bladder outlet obstruction due to prostatic hyperplasia (BPH) was made based on patient's clinical symptoms and age. A secondary diagnosis with fatty infiltration of the liver (NAFLD) was also made.

Treatment

The initial management began with urinary catheterization which relieved suprapubic pressure. There was no sign of infection, and so, no antibiotic regimen was prescribed. Patient blood pressure was normalized

Table 1 Liver function test showing increased level of GGT indicative of liver disease.

Tests	Patient	Normal range
Bilirubin (total), µmol/L	11.2	2–17
Direct bilirubin, µmol/L	4.9	2–7
Albumin, g/L	45	36–52
Total proteins, g/L	69	62–82
Globulin, g/L	24	18–36
Aspartate aminotransferase, µ/L	36	Up to 37
Alanine aminotransferase, µ/L	34	Up to 42
Alkaline phosphatase, µ/L	102	60–306
Gamma glutamyl transferase, µ/L	58	10–55

Table 2 Lipid profile of patient showing low level of HDL with elevated levels of LDL and VLDL cholesterol.

Laboratory parameters	Patient	Normal range
Total cholesterol, mmol/L	4.3	<5.2
HDL cholesterol, mmol/L	0.7	>1.5
LDL cholesterol, mmol/L	2.9	<2.6
VLDL cholesterol, mmol/L	0.72	0.10–0.60
Triglyceride, mmol/L	1.62	0–1.7

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

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Table 3 Patient's IPSS questionnaire score card.

In the past month	Not at all	At least once	Twice	Up to three times	Up to four times	Up to five times
How often do you feel like you didn't completely empty your bladder?						5
How often do you feel like peeing less than an hour after you have peed?		1				
How often have you found that you stopped and started peeing again during urination?						4
How often have you had weak urine stream or weak urine flow?						5
How often have you had trouble holding your urine?		1				
How often have you had the need to push or strain during urination?					4	
How many times during the night have you had to urinate?		1				

Severity score is calculated as mild: 0–7; moderate: 8–19; severe: 20–35.

with spironolactone and i.v. fluid and was monitored overnight in the hospital. He was discharged after 36 h in-hospital care with prescriptions of Co-Diovan (valsartan/hydrochlorothiazide) 160/25 one tablet daily for the management of hypertension, metformin (1 mg) twice/day, insulin flexpen 30 IU morning and 20 IU evening for his diabetes management, duodart (dutasteride/tamsulosin) one tablet/day for his BPH, and actos (pioglitazone) 15 mg one tablet daily plus neurovite forte to help slow the progression of NAFLD. He was also prescribed a daily eye cap for his sight, rivotril 0.5 mg (clonazepam) twice a week for essential tremor management, and athrotec 75 (diclofenac/misoprostol) as needed for his arthritic pains.

Outcome and follow-up

Patient's PSA level remained normal and urinary symptoms resolved completely on his 13-month follow-up. Patient's IPSS test score on follow-up was recorded as 1. Complete blood count was normal. HgA1c decreased to 6.7%, cholesterol levels returned to normal levels with diet modifications, and liver size measured as 16.2 cm on liver ultrasound. Patient showed significant progress with the above-mentioned treatment regimens and there was not any need for additional medications.

Discussion

Several studies have shown that DM-2 is associated with a significantly low serum total PSA level than in non-diabetic individuals due to lower androgen levels found in diabetic men (2). Likewise, another study by Muller *et al.* (3, 4) reported that men with very high level of hemoglobin A1c (like in our patient) had 29% lower serum levels of PSA at later stages of diabetes. There have been additional reports on the decrease in testosterone level in men with DM-2 due to hypogonadism evident with low PSA values (4). Thus, it is recommended that testosterone level should be measured in men with DM-2 (5, 6). These may be attributed to the low levels of PSA (0.6 ng/dL) and elevated HgA1c (8.4%) seen in our patient. Large prostate volume as also seen in our patient has been associated with components of metabolic syndrome, particularly diabetes, a positive correlation to a study which showed a link between prolonged diabetes treatment and increase in the size of the prostate resulting in BPH (7).

Diabetes-induced NAFLD is also a known contributing factor to increase microvascular complications such as chronic kidney disease/end-stage renal disease and retinopathy (8). Similarly, glucotoxicity promotes the pathogenesis of NASH via accelerated *de novo* lipogenesis, hepatocellular dysfunction, and insulin resistance (9). Several methods used in evaluating patients with lower urinary tract syndrome (LUTS) have been reported to be very effective which include the measurements of detrusor wall thickness with ultrasound and intravescical prostate protrusion (IPP) for predicting BPO in patients presenting with LUTS as non-invasive methods (10). It is also imperative to determine the severity of the bladder obstruction with the IPSS which helps guide treatment protocol in these patients. The IPSS consists of series of questions which determines how well a patient could empty his urinary bladder, and the total score is used in determining the severity of the obstruction before treatment and relief of the symptoms (efficacy of the treatment) after post-treatment (11, 12).

In summary, it is evident that there is a bidirectional relationship between NAFLD and DM-2. Diabetes mellitus results in the development and progression of NAFLD to NASH with subsequent development of liver cirrhosis and hepatocellular carcinoma when not promptly and effectively managed. Alternatively, NAFLD in obese individuals is associated with an increased risk of developing DM-2.

Therefore, diabetes specialists should be fully aware about NASH-related complications. Diabetic patients with NASH/NAFLD should be managed effectively in diabetes clinic and hepatology clinic with early diagnosis of NAFLD/NASH using laboratory markers, imaging studies, and prospective NASH-specific therapies currently in phase 3 clinical trials (elfibranor, resmetirom, and aramchol) when approved by the US food and drugs administration for human consumption.

Patient's perspective

I am grateful for the care I received during my hospital visit. I was happy to learn that my A1c is down to near normal level and hope to continue making progress in my overall health as I continue to feel much better every day.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of clinical details was obtained from the patient.

Author contribution statement

As a sole author and treating physician of the patient, I appreciate the nurses and all other health professionals who were involved in the patient in-hospital care.

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