Can J Diabetes 39 (2015) 101–104

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Impaired Gallbladder Motility in Adults with Newly Detected Type 2 Diabetes and Lack of Reversibility after Achieving Euglycemia

Faheem Arshad MD [a], Bashir Ahmad Laway DM [a,*], Tanveer Ahmad Rather MD [b], Mohammad Shafi Kuchay MD [a], Shoukat Hussain Khan MD [b]

[a] Department of Endocrinology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India
[b] Department of Nuclear Medicine, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form
31 July 2014
Accepted 31 July 2014

Keywords:
diabetes
gallbladder ejection fraction
^{99m}TC-mebrofenin scintigraphy

ABSTRACT

Objective: The effects of hyperglycemia and normoglycemia on gallbladder emptying have not been studied in detail. This prospective case-control study was designed to investigate the gallbladder ejection fraction in patients with newly detected diabetes and to assess the impact of restoring normoglycemia on gallbladder ejection fraction in such patients.
Methods: ^{99m}Tc-mebrofenin scintigraphy was performed in 22 patients with newly detected type 2 diabetes for measurement of gallbladder ejection fraction. The scintigraphy was performed at the time of first presentation and again 6 months after control of diabetes (glycated hemoglobin [A1C] <7%). Also, gallbladder ejection fraction was measured in 20 age- and sex-matched controls without diabetes.
Results: Gallbladder ejection fraction was lower in patients with newly detected diabetes compared with controls (31.4%±5.9% vs. 70.7%±4.3%, p<0.001). Gallbladder ejection fraction did not improve after the treatment of diabetes mellitus (21.3%±5.7%, p=0.395).
Conclusions: Gallbladder ejection fraction was markedly reduced in patients with newly detected diabetes compared to controls without diabetes. Control of diabetes and normalization of A1C did not reverse the motility defect.

Mots Clés :
diabète
fraction d'éjection de la vésicule biliaire
scintigraphie après injection de mébrofénine-technétium 99m (^{99m} Tc)

RÉSUMÉ

Objectif : Les effets de l'hyperglycémie et de la normoglycémie sur la vidange vésiculaire n'ont pas été étudiés en détail. Cette étude cas-témoins prospective avait pour objet d'examiner la fraction d'éjection de la vésicule biliaire des patients ayant récemment reçu un diagnostic de diabète et d'évaluer les effets du rétablissement de la normoglycémie sur la fraction d'éjection de la vésicule biliaire de ces patients.
Méthodes : Une scintigraphie après injection de mébrofénine-technétium 99m (^{99m} Tc) a été réalisée pour déterminer la fraction d'éjection de la vésicule biliaire de 22 patients ayant récemment reçu un diagnostic de diabète de type 2. La scintigraphie a été réalisée lors du tableau clinique initial et 6 mois après la régulation du diabète (hémoglobine glyquée [A1c] <7 %). La fraction d'éjection de la vésicule biliaire a également été mesurée chez 20 témoins non diabétiques appariés selon l'âge et le sexe.
Résultats : La fraction d'éjection de la vésicule biliaire était plus faible chez les patients ayant récemment reçu un diagnostic de diabète comparativement aux témoins (31,4 %±5,9 % *vs* 70,7%± 4,3 %, p<0,001). La fraction d'éjection de la vésicule biliaire ne s'était pas améliorée après le traitement du diabète sucré (21,3 %±5,7 %, p=0,395).
Conclusions : La fraction d'éjection de la vésicule biliaire a été notablement réduite chez les patients ayant récemment reçu un diagnostic de diabète comparativement aux témoins non diabétiques. La régulation du diabète et la normalisation de l'A1c n'a pas corrigé l'anomalie de la motilité.

Introduction

Hyperglycemia in people with diabetes is associated with alterations in gallbladder ejection fraction. Cholescintigraphy determines the gallbladder ejection fraction (GBEF) and other filling

* Address for correspondence: Bashir Ahmad Laway, DM, Department of Endocrinology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.
E-mail address: drlaway@gmail.com

1499-2671/$ – see front matter © 2015 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.07.223

parameters. GBEF is significantly reduced in patients with diabetes for unclear reasons, though diabetes autonomic neuropathy involving the gallbladder could be a significant contributor (1–3). Release of cholecystokinin (CCK) after a fatty meal causes gallbladder contraction. Impaired gallbladder motility after a fatty meal could occur because of the decreased number or sensitivity of CCK receptors on the gallbladder wall despite its normal postprandial release (4). In healthy men and women, experimentally induced hyperglycemia has been found to cause impairment of gallbladder emptying (5). In people with diabetes, the effects of hyperglycemia and normoglycemia on gallbladder emptying have not been studied in detail. The present prospective case-control study was designed to evaluate GBEF using ^{99m}Tc-mebrofenin scintigraphy in people with newly detected diabetes at the time of hyperglycemia and after achieving euglycemia compared with healthy controls without diabetes.

Methods

The study was performed at a tertiary care hospital in the northern state of Jammu and Kashmir in India. The study was approved by the hospital ethics committee. The purpose of the study was explained, and informed consent was obtained from all the participants.

Study population

We included in the study 22 people with newly detected diabetes and 20 healthy volunteers without diabetes. People in both the groups were comparable in age, gender and body mass index (BMI) and had normal liver function tests. Controls were randomly selected from among the healthy volunteers. Abdominal ultrasonography, performed in patients with diabetes and healthy controls ruled out gallstone disease.

Measurements

We recruited 22 treatment-naive people with recently detected diabetes for the study after informing them about the study and obtaining written consent. The diagnosis of diabetes was based on the presence of fasting hyperglycemia (fasting plasma glucose $\geq$7mmol/L) on more than 2 occasions or on 2-hour postmeal plasma glucose $\geq$11.11 mmol/L and A1C $\geq$6.5%. History of any gut symptoms such as upper abdominal pain or discomfort, especially after a fatty meal in the previous 4 weeks before presenting for medical advice, was enquired for in both the cases and the controls. Menstrual and obstetric histories were noted in women. Physical examinations included measurement of height, weight, BMI, waist/hip ratio and presence of signs of insulin resistance. Systemic examinations included examination of peripheral pulses, fundus, and the presence of peripheral or autonomic neuropathy. The autonomic nervous system was tested in cases and controls by using simple bedside tests, including heart rate response to standing, deep breathing and the Valsalva maneuver; systolic blood pressure response to standing; and diastolic blood pressure response to sustained handgrip. The results of these tests were scored as 0 (normal), 1 (borderline) and 2 (abnormal). The final autonomic nervous system score was calculated by adding the individual scores (6). Venous blood samples were obtained from all patients from the antecubital region between 8 AM and 9 AM after an 8- to 12-hour overnight fast. Glucose levels were determined in serum samples using the hexokinase method (enzymatic ultraviolet test) and original reagents on an auto analyzer. Hemoglobin A1C was measured by high-performance liquid chromatography standardized to the Diabetes Control and Complications Trial assay. Patients with newly detected diabetes were prescribed metformin or metformin plus glimepiride for 24 weeks and were reevaluated. BMI, A1C and gallbladder ejection fraction were again measured at 3 and 6 months into the treatment.

Measurement of gallbladder ejection fraction

Cholescintigraphy was performed after intravenous injection of ^{99m}Tc-mebrofenin. A predefined software was used to calculate the GBEF and time to maximum filling of gallbladder (T max). The standard fatty meal used for stimulating gallbladder contraction consisted of an 8-ounce glass of half cream and half milk (half-and-half milk) containing 11 g of carbohydrate, 28 g of fat, 8 g of protein and 325 calories. The dose of half-and-half milk was adjusted for body weight (240 mL [8 oz.]/70 kg of body weight).

Cholescintigraphy protocol

The subjects fasted for 4 to 6 hours before receiving an intravenous injection of 4 to 6 mCi (1 mCi = 37 MBq) of ^{99m}Tc-mebrofenin (Choletec; Bracco Diagnostics, Monroe Township, New Jersey, USA) prepared immediately before injection. A single detector was used for acquisition of images. The detector was placed anteriorly over the whole abdomen. Dynamic acquisition was started immediately after intravenous injection of ^{99m}Tc-mebrofenin. Continuous frames of 1-minute duration were obtained for 30 minutes. At 30 minutes (the usual time taken by the gallbladder to fill up), the standard meal was administered orally to stimulate the gallbladders' emptying. During the following 60 minutes, dynamic acquisition with 1 frame per minute was continued during gallbladder emptying. Static images of 3 minutes' duration, each at 90 minutes and at 4 hours, were also taken. The images were obtained in the supine position using a large-field-of-view gamma camera (Siemens Hoffman Estate, IL. 60/95, United States of America) equipped with a low-energy, high-resolution parallel hole collimator. The images were stored in a 128 $\times$ 128 matrix in the computer for further processing.

Statistical analysis

Statistical analysis was performed using SPSS for window (v 11, IBM). Results were expressed as mean $\pm$ SD. An independent samples t test was used to compare mean $\pm$ SD values between cases and controls; a paired samples t test was used to compare the patient group before and after treatment. A p value of less than 0.05 was taken as significant.

Results

There was an equal representation of men and women in both the diabetes and the control groups. The mean $\pm$ SD age and BMI were comparable in the 2 groups, but there was a significant difference in A1C. GBEF of >35% was considered normal, regardless of patients' sex; 68.18% of people with diabetes had reduced GBEF at the time of hyperglycemia as compared to normal GBEF in healthy controls. GBEF was significantly lower in patients with diabetes (A1C of 9%) and with hyperglycemia as compared to the normal ejection fraction in healthy controls (GBEF of 70.7$\pm$4.3%) (Table). Serial GBEF at 30, 60, 90 and 240 minutes were lower in the group with diabetes during hyperglycemia than in normal healthy controls without diabetes. Similarly, T max was significantly delayed in men and women with diabetes compared with healthy controls. After achieving euglycemia with oral antidiabetic drugs and normalization of A1C, the gallbladder functional parameters, such as GBEF and T max, studied previously, were repeated. Neither GBEF nor T max revealed any statistically significant improvement at 3 to 6 months after achieving euglycemia.

Discussion

Diabetes, obesity and insulin resistance are associated with increased risk for development of gall stones. Hyperinsulinemia is a