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A Case of Improved Insulin Resistance in Type 2 Diabetes After Liver Transplantation

Eugene Han, M.D., Nan Hee Cho, M.D., Ye Yeon Lee, M.D.,
Wang Yong Choi, M.D., In Wook Song, M.D., Ho Chan Cho, M.D.

Division of Endocrinology, Department of Internal Medicine,
Keimyung University School of Medicine, Daegu, Korea

Abstract

Recent studies have reported improvement of glycemic control following liver transplantation in patients with type 2 diabetes mellitus and chronic liver disease, and yet, the underlying mechanism is not well understood. In addition, the validity and effectiveness of such an approach in treating type 2 diabetes have not been addressed in the literature, mainly due to the limited amount of clinical data available. We report a case of patient whose insulin needs significantly reduced from 64 units per day to 0 in 2 years after liver transplantation. A 38 year-old woman had been initially diagnosed with liver cirrhosis; two years later, she was diagnosed with type 2 diabetes. And five years after the diagnosis, her glucose level was not adequately controlled despite the use of exogenous insulin. At the age of 48, liver transplantation was required due to intractable hepatic encephalopathy; since then, significant changes, as evidenced by fasting plasma-insulin and homeostasis model assessment insulin resistance index, have been observed. Therefore, the present case report provides additional data supporting that liver transplantation may alleviate type 2 diabetes in patients with concurrent chronic liver disease, presumably due to the change in insulin resistance, which appears to be a main underlying pathophysiologic feature of hepatogenous diabetes.

Key Words : Hepatogenous diabetes, Insulin resistance, Liver transplantation

Introduction

The prevalence of diabetes mellitus in South Korea was 1.7% in 1971, but by 2010 it rose to 10.1% in adults older than 30 years of age, representing an increase to 4-5 million people [1]. On the other hand, deaths from liver cirrhosis (LC) decreased drastically due to the advent of vaccination and antiviral therapy against the hepatitis B virus, the most common cause (57-73%)

Corresponding Author: Ho Chan Cho, M.D., Department of Internal Medicine, Keimyung University School Medicine
56 Dalseong-ro, Jung-gu, Daegu 700-712, Korea
Tel : +82-53-250-7915 E-mail : ho3632@dsmc.or.kr

of LC in South Korea [2]. It is generally difficult to maintain glucose metabolism homeostasis because most cases of chronic liver disease also present for hepatocellular dysfunction, decreased insulin sensitivity, impaired glucose tolerance, and type 2 diabetes mellitus (T2DM) or hepatogenous diabetes [3,4]. The prevalence of T2DM in LC patients varies, depending on factors such as the degree of hepatic dysfunction, age, and the prevalence of hepatitis C [4,5]. In South Korea, the prevalence of diabetes in LC patients is 22.4% [6]. While hyperglycemic status improves in T2DM and LC patients receiving a liver transplant [7,8], the effectiveness of this approach and its mechanism of action are not yet established, mainly due to the limited amount of clinical data available.

Case Report

A 48-year-old female patient was hospitalized for living-donor liver transplantation (LTx). The patient, who had no family history of disease, alcohol intake, or smoking, was diagnosed with LC a decade prior to hospitalization due to chronic hepatitis B. Two years later she was diagnosed with T2DM and treated with oral hypoglycemic agents, followed by another hospitalization 2 years thereafter for hepatic encephalopathy at which time she was treated conservatively. Except for this event, she remained stable in a condition of compensated LC. The patient was prescribed metformin (500 mg/day) and gliclazide (30 mg, two times/day) to control blood glucose. Three years prior to hospitalization, the patient's glycated hemoglobin (HbA1c) level was 11.1%, homeostasis model assessment of insulin resistance (HOMA-IR) index was 9.85. She was then prescribed insulin (>40 units/day) and metformin (1,000 mg/day). Thereafter, the patient was admitted to our hospital twice due to sustained hyperglycemia (HbA1c>10%). Five months prior to hospitalization, LC progressed to Child-Pugh class C (score 10) and hepatic encephalopathy was evident. The patient underwent a living-donor LTx. During this time, the HbA1c level increased to 12.8%, prompting the daily administration of 14 U of insulin lispro before every meal and 16 U of insulin glargine. The levels of fasting glucose, 2 hour postprandial blood glucose, fasting plasma insulin, fasting C-peptide, C-peptide after oral glucose loading, and HOMA-IR index were 130 mg/dℓ, 362 mg/dℓ, 30.7 μIU/ml, 2.8 ng/ml, 5.8 ng/ml, and 9.85, respectively.

After LTx, the patient was prescribed a triple-drug immunosuppressive regimen of prednisolone (20 mg/day), tacrolimus (4 mg/day) and mycophenolate mofetil (1,000 mg/day) to minimize the chances of graft-versus-host disease (GVHD). At discharge, the patient daily administrated 12 U, 24 U, 28 U of insulin lispro before every meal and 16 U of insulin glargine. Six months after surgery, the dose of tacrolimus was reduced from 4 mg/day to 2 mg/day. The total doses of insulin glargine and insulin lispro were 18 U/day, and 36 U (12 U was administered three times/day before every meal), for each. 1 year after surgery, the doses of insulin glargine and insulin lispro were 14 U/day and 20 U (10 U was administered two times/day before breakfast and dinner). Eighteen months after surgery, both prednisolone and mycophenolate mofetil were discontinued. Two years after LTx, the patient was using only oral hypoglycemic agents (i.e., metformin at 1,000 mg/day and gliclazide at 120 mg/day) to control glucose. The patient's HbA1c level was 6.7% and stable without insulin. Fasting glucose, 2 hour postprandial blood glucose, fasting plasma insulin, fasting C-peptide, C-peptide after oral glucose loading, and HOMA-IR index were 118 mg/dℓ, 341 mg/dℓ, 11.87 μIU/ml,

2.22 ng/ml, 4.14 ng/ml, and 3.45, respectively.

There was no significant difference in body mass index (BMI) before (30.4 kg/㎡) and after (29.3 kg/㎡) surgery.

Discussion

The liver is an organ important in metabolism of insulin and plays an essential role in maintaining a constant blood glucose level through glucose synthesis, glycogen synthesis, storage and degradation [10]. Insulin resistance is a pathologic condition in which both the metabolism of insulin that inhibits gluconeogenesis in the liver as well as the insulin-mediated glucose uptake in muscle and adipose tissue is decreased. And type 2 diabetes is characterized by insulin resistance, impaired insulin secretion, excessive gluconeogenesis in liver and abnormal lipid metabolism [11]. HOMA-IR is a tool to estimate insulin sensitivity, which is a surrogate for insulin resistance. The index was calculated as follow [12].

HOMA-IR : fasting serum insulin (uU/mL) x fasting glucose (mmol/L) / 22.5

It is possible to use HOMA to assess insulin sensitivity in insulin users when glucose and insulin concentration are in a steady state, but not to assess b-cell function in those taking exogenous insulin [13]. In Korean study, the HOMA-IR of Korean diabetic male was 2.6 and that of Korean diabetic female was 3.1 [14].

Transplantation rejection, graft failure, and especially the use of immunosuppressive agents can exacerbate pre-existing diabetes or cause newly-developed diabetes (9-21% reported) by triggering insulin resistance or directly affecting pancreatic β cells [15-17]. Theoretically, a blood glucose level within normal range and a reversal of insulin resistance and/or hepatogenous diabetes is probable for most patients after liver transplantation if immunosuppressive agents are not prescribed [8,9]. In another study, 16 out of 24 (67%) LC patients who underwent an LTx recover from diabetes, leading the authors to conclude that reversal of hepatogenous diabetes is likely in patients with insignificant pancreatic β cell dysfunction and in the absence of immunosuppressive action [9]. There is also a report of a 55-year-old female patient whose T2DM was controlled with oral hypoglycemic agents. Three years after the onset of LC caused by chronic hepatitis C, insulin therapy was prescribed to control blood glucose. And after LTx, five-year follow-up reported that the patient have maintained continuous normal blood glucose level but that she started to undergo hemodialysis four years after LTx and her diabetic nephropathy that was combined before the transplant could proceed after the transplant despite improvement of insulin requirements and diabetes remission that resulted from LTx [8]. Likewise, another study reports remission of diabetes in 16 out of 24 patients (66.6%) with LC and diabetes 2 year after LTx. In addition, even in the patients who did not achieve remission of diabetes, mean HbA1c level was improved (6.9 ± 0.9% vs 7.9 ± 1.1%). The HbA1c level of remission group prior to transplantation was 7.1 ± 0.6%, which was lower than that of not cured group [9]. So, the reversal of hepatic dysfunction in our patient with hepatogenous diabetes was quite astonishing given that her initial HbA1c level was 12.8% with high-dose insulin therapy and significantly decreased HbA1c level of 6.7% with oral hypoglycemic agents after LTx.

The patient was diagnosed with T2DM, but it is possible that the patient had hepatogenous diabetes caused by pre-existing LC instead. Insulin resistance is one of the most important factor in the pathogenesis of hepatogenous diabetes [4]. And

decreased insulin secretion in pancreatic β cells that is insufficient to overcome defects in insulin action as well as hyperinsulinemia caused by decreased insulin degradation due to hepatocellular failure and portosystemic shunt are considered another main pathogenesis of hepatogenous diabetes [4,9]. While the mechanism behind the reversal of diabetes after LTx is not yet clear, it might be related to endogenous glucose synthesis and improved insulin resistance after LTx [9]. In this case, we failed to control the patient's blood glucose level with high dose of exogenous insulin therapy and the patient showed increased level of HOMA-IR before LTx. And the patient is prescribed two oral hypoglycemic agents without insulin and shows a stable HbA1c level at 6.7% and an improved index of insulin resistance (HOMA-IR 9.85 vs. 3.45) 2 years after LTx. In conclusion, as we experienced the representative case showing a significant potential mechanism for improvement of type 2 diabetes or hepatogenous diabetes, presumably due to improved insulin resistance and glucose homeostasis through liver transplantation, we report the case with a review of concerned literatures.

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