Hepatic Glucose Metabolism of Diabetic Patient Evaluated by 18FDG PET Scan

IV. 9. Hepatic Glucose Metabolism of Diabetic Patient Evaluated by ^{18}FDG PET Scan

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Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized as a condition with high blood glucose level and impairment of its regulation. It causes several severe complications such as nephropathy, retinopaty etc. Its pathophysiology is not fully known. It is generally accepted that insufficient insulin secretion from the pancreatic B cells causes a type of DM (insulin dependent DM, IDDM). Low insulin sensitivity of body tissue also causes DM (non insulin dependent DM, NIDDM). Insulin promotes glucose uptake by skeletal muscle, adipose tissue and myocardium by increasing cell membrane permeability. Metabolism of glucose in the liver is, however, quite different from that in other organs. Influx of glucose into hepatocytes is not restricted by insulin, i.e. insulin independent. In hyperglycemic state, the liver uptakes glucose and changes it into glycogen. In hypoglycemic state, it metabolizes glycogen to glucose and thus maintains the serum glucose at the optimum level. In diabetic patients, glucose uptake by muscles decreases, while glucose uptake by the liver increases for the compensation. We considered hepatic ^{18}FDG uptake or its influx relate to the severity of DM. Estimation of glucose dynamics of the liver and plasma is therefore important to evaluate the mechanism and treatment effect in DM. We attempted it by using ^{18}FDG dynamic PET scan combined with oral glucose loading.

Materials and Methods

Four normal volunteers and two diabetic patients were examined. Clinical profiles of the subjects are shown in Table 1. Fasting blood sugar of two diabetic patients were around 150 mg/dl. Fifty grams glucose was orally administrated 30 minutes before the start of the scanning. PT-711 was employed to measure the hepatic ^{18}FDG activity. The slice is over the right lobe of the liver. Sequential scanning of 150 sec data acquisition started at the time of intravenous injection of 1-4 mCi of ^{18}FDG up to 600 sec, followed by seven 5 min scans.

Venous blood was taken from the warmed forearm during the scans to monitor plasma ^{18}FDG activity, glucose concentration and insulin level.

Using irregular ROIs encompassing right lobe of the liver, hepatic radioactivity was obtained in terms of cps/pixel. Time activity curve was normalized using differential absorption ratio (DAR). Patlak plot, using venous count as input function, was used to determine glucose influx rate (Ki)[= k1 × k3 / (k2+k3)].

Results

- time activity curve and blood data -

Radioactivity of the liver rapidly increased instantaneously after ^{18}FDG injection and then washed out (Figs. 1,2). Figure 1 shows profiles of normal insulin secretion and serum glucose concentration in a typical normal volunteer, while diabetic patients showed low insulin secretion and higher glucose concentration (Fig. 2). Plasma ^{18}FDG clearance normalized by injected dose (mCi) is faster in normal volunteer (Figs. 1, 2).

- DAR and Patlak plot analysis -

Results are summarized in Table 2. Liver DAR of ^{18}FDG at 45 min after injection tended to be higher in diabetic patients than in normal controls. Patlak plot was inadequate in two cases. Linearity of the plot was not good enough because of higher ^{18}FDG wash out from the liver. As a measurement of glucose influx rate, we multiplied Ki by serum glucose. These values were also higher in diabetic patient.

Discussion

As to blood data, adequate insulin secretion turns serum glucose concentration to normal range rapidly in normal volunteer, while diabetic patients showed low insulin secretion and high glucose concentration. The low clearance rate of plasma ^{18}FDG in diabetic patients is probably due to the decrease of cell membrane permeability caused by insufficient insulin secretion in glucose consuming organs other than the liver. Liver metabolizes ^{18}FDG in different way from other organs.

There are some differences between the compartmentmodel of the liver and that of other organs. Hepatic G-6-phase activity is higher than others. ^{18}FDG permeability of hepatocytes does not depend on insulin but on serum glucose concentration. In other organs, ^{18}FDG influx into the cell(k1) depends on insulin. Hexokinase of the liver also has some difference from that of others (Table 3). High Km of hepatic hexokinase enables to manage high glucose level. In diabetic patients, glucose uptake of other organs (skeletal muscles, adipose tissue etc.) decreases because of low insulin secretion. It is thought that hepatic uptake relatively increases to compensate this. In our study, DAR of FDG and Ki*(serum glucose) values of diabetic patients are possibly higher than those of normal control. Glucose uptake by other organs will decrease in proportion to the severity of DM. Conversely liver uptakes more glucose and metabolizes it in a different way to normalize serum glucose concentration.

Relatively increased hepatic ^{18}FDG uptake may have relation with the severity of DM. ^{18}FDG dynamic scan is the possible tool to estimate these glucose dynamics.

References

1) Sokolloff L., Reivich M., Kennedy C,. et al., J. Neurochem. **28**(1977)897.
2) Patlak C. S., Fenstemacher J. D., Blasberg R. G., J. Cereb. Blood. Flow Metabol. 3(1983)1.

Table 1. Profile of the subjects.

Patient ID		age	sex	FBS
1293	diabetes	50	F	152
1320	diabetes	45	M	137
1331	normal	26	M	98
1335	normal	22	M	90
1365	normal	23	M	87
1410	normal	24	M	82

Table 2. ^{18}FDG uptake by the liver.

Patient ID	DAR (45 min)	K1xK3/(K2 + K3) (mℓ/g/min)	[K1xK3/(K2 + K3)]x glu (mg/g/min)
1293	2.57	0.34	86.4
1320	1.83	-----	-----
1331	2.20	-----	-----
1335	2.01	0.50	66.3
1365	0.83	0.29	51.7
1410	1.16	-----	-----

Table 3. Difference of Hexokinase.

	Hepatic hexokinase	hexokinase of other organs
Km to glucose	10mM	0.1mM
Inhibition by G-6-P	-	+
Diabetes	↓↓	→
Insulin	↑↑	→

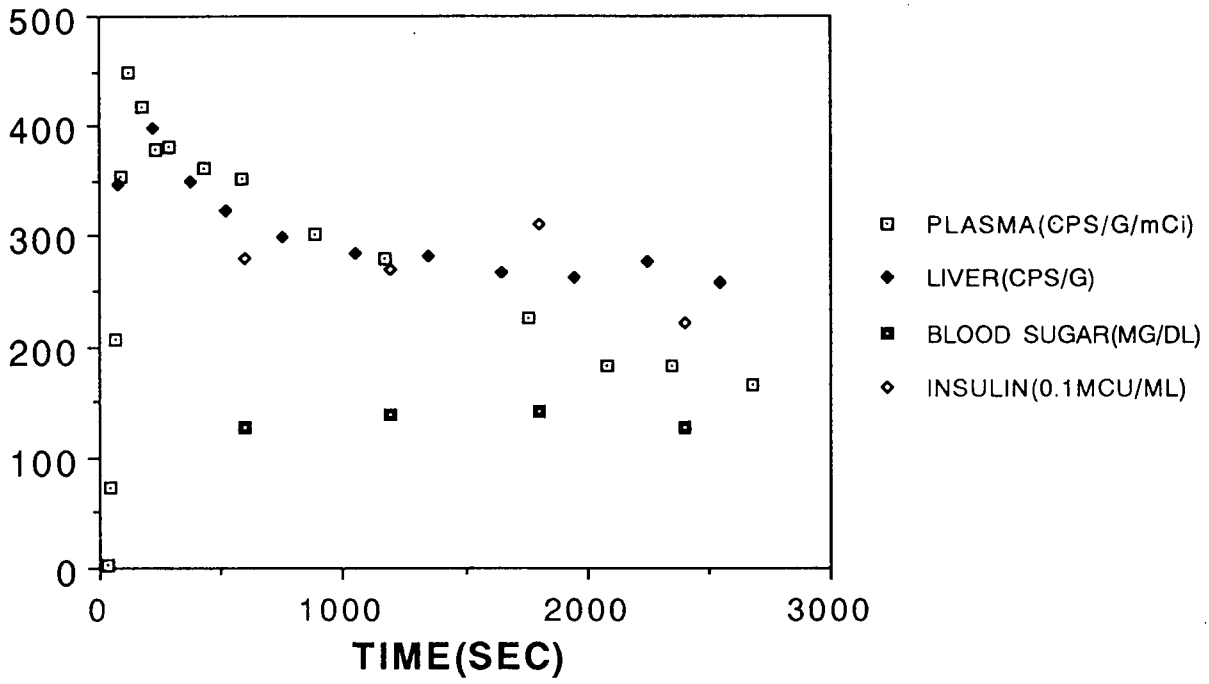

Fig. 1. Time activity curve of normal volunteer

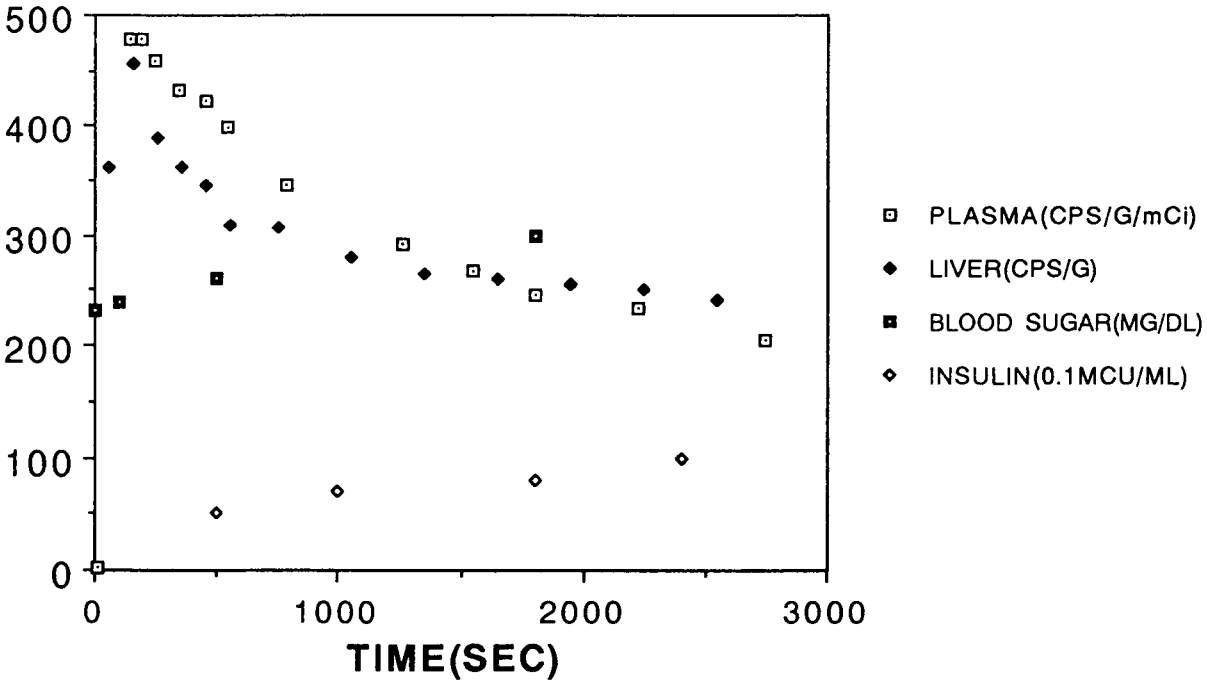

Fig. 2. Time activity curve of DM patient