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Clinical Observations in Patients with Type 1 Diabetes of Over 50 Years Duration in One Practice in Hungary

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ABSTRACT

Within a practice (József Fövényi.), four male and two female patients, aged 54-73 years, with diabetes duration of 51-68 years, received care for 28-53 years, respectively. All physical status data, HbA1c, lipids, and renal parameters were available from 1989 onwards. The bodyweight of three male patients increased, while that of one male and two female patients remained normal. HbA1c levels ranged from 6 to 9%, LDL-cholesterol levels ranged from 1.3 to 3.5 mmol/l, HDL-cholesterol and triglycerides were normal, serum creatinine, eGFR in all but one patient remained within the normal range. All patients were C-peptide negative. One patient was free from retinopathy, four had mild background and one had pre-proliferative retinopathy, four patients had mild, two moderate sensory and autonomic neuropathy. Based on cardiac evaluation and coronary CT angiography, as well as ultrasound examination of the cervical and lower limb arteries, ne0ither the coronaries nor the peripheral arteries showed signs of arteriosclerosis in one woman and two men, while the other three patients had severe atherosclerosis and severe coronary calcifications. All patients had been receiving intensive insulin therapy since the 1980s had been receiving only analogue insulin for 18 years, one female patient had been using an insulin pump (since 2014 with continuous glucose monitoring) for 20 years, and four additional patients used also CGM (continuous glucose monitoring). All patients were taking statins, all patients had well-treated hypertension. All patients – except for one woman – considered their quality of life to be good and had no significant complaints attributable to diabetes.

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KEYWORDS:
complete cross-sectional analysis; continuous glucose monitoring (CGM); diabetes duration 50+ years; duration of care 28-53 years; insulin treatments; insulin pump; longitudinal analysis for 28-33 years; macrovascular & microvascular complications.

INTRODUCTION

It is well known that thanks to modern insulin products and self-monitoring of blood glucose, the life expectancy of people with Type 1 diabetes (T1D) has improved dramatically and more and more people are alive at 50 years and beyond with diabetes.

The Joslin Medalist programme [19] has registered >5,000 T1D patients who have lived with diabetes for 50+ years and >600 who have lived with diabetes for 75+ years. In the scientific literature the oldest patient who lived with diabetes long enough to receive the 75+ year Joslin Victory Award was a Hungarian lady who died at the age of 91 after 86 years with diabetes, and I had the honour to manage her care for 56 of those years [6]. In the FinnDiane 50-year Cohort (based on the Finnish National Register), 729 T1D patients with 50+ years of diabetes were involved in longitudinal and cross-sectional analysis with very detailed physical status and laboratory data, but the follow-up lasted only 15 years [8]. The British Golden Years Cohort was a cross-sectional study of 400 T1D patients with 50+ years of diabetes [4]. In the Swedish Study (based on the Swedish National Diabetes Register) 1.023 T1D patients with 50+ years of diabetes were studied. The follow-up period was 10 years and 6-37% of patients had at least one physical and laboratory parameter (HbA1c, body mass, blood pressure, etc.) missing [1]. A Japanese longitudinal study of 29 T1D patients with 50+ years of diabetes was conducted with a follow-up of 43 years.

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However, only HbA1c and systolic blood pressure data were recorded [16]. In the Parisian Cohort, data from 57 T1D patients with an average diabetes duration of 49.8±7.6 years were processed in great detail, but only a cross-sectional study was performed [2]. In the Canadian Study of Longevity in Type 1 Diabetes, 450 patients with 50+ years of diabetes on the National Register were included, but this was also a cross-sectional study only [10]. In the VISS Study, 447 T1D patients with an average duration of diabetes of 32 years were included. The development of complications was examined, but only as a function of average HbA1c levels [3].

AIM OF OUR STUDY

The aim of the study was to perform A longitudinal and cross-sectional analysis of the medical history of 6 T1D patients with 50+ years of diabetes mellitus managed in one practice.

METHODS

The longitudinal analysis is based on our patient care programme established in 1989 (and developed further several times), in which physical characteristics (body mass, BMI, waist circumference, blood pressure) were recorded during 3 or 4 visits each year, palpation of the distal peripheral arteries, Doppler as needed, neuropathy testing with a calibrated tuning fork, and ophthalmological examination once a year. Three to four times a year, we measured HbA1c, total, HDL, LDL cholesterol, triglycerides, uric acid, C-reactive protein (CRP) and serum creatinine, and from 2011 also estimated glomerular filtration rate (eGFR), and once a year albumin excretion was measured from 24-hour urine. The duration of longitudinal analysis was 28 to 33 years.

During the past year, the cross-sectional study has included carotid and lower limb arterial ultrasound scans to assess vascular status; ECG, echocardiography and stress tests were carried out to assess cardiac status; and coronary CT angiography was performed in five patients. Postprandial C-peptide levels were determined in all patients.

PATIENTS

Patient	1	2*	3	4	5	6
Sex	Male	Female	Female	Male	Male	Male
Duration of diabetes years	69	62	59	53	53**	51**
Age at onset of diabetes, years	2	11	11	19	3	3
Date of diagnosis	1953	1960	1963	1968	1969	1971
Present age, years	71	73	70	73	56	54
Duration of care by the author, years	52	28	34	46	53**	51**

Table 1. Patient's characteristics in order of diabetes duration. * Patient 2 had been cared for 16 years in cooperation with the fourth author (Győző Kocsis). **In patients 5 and 6, the duration of diabetes and the duration of care are the same because they are the first author's own sons, who have been exclusively under his care from the day of their diagnosis.

LONGITUDINAL ANALYSIS

The following figure shows the changes of patients' main physical and laboratory parameters during follow up.
Figure 1.

Figure 1. Changes in body mass, HbA1c levels, HDL and LDL cholesterol, serum creatinine and from 2011 onwards also the eGFR for all 6 patients. Since 3 to 4 examinations and laboratory tests were carried out each year, each data point represents the average of the annual measurements.

In the Table 2. the physical and laboratory parameters can be seen during the observational period

Patient	1	2	3	4	5	6
Baseline* BMI, kg/m^2 / waist circumference, cm	22.1 / 89	23.1 / 82	21.1 / 82	25.8 / 88	26.6 / 92	24.2 / 86
Last visit** BMI, kg/m^2 / waist circumference, cm	23.8 / 91	20.9 / 81	21.4 / 82	31.2 / 106	36.6 / 130	28.1 / 96
HbA1c, %, mean ± SD	7.15±0.75	7.17±0.63	7.28±0.56	7.28±0.62	7.22±0.50	6.91±0.60
HDL-cholesterol, mmol/l, mean ± SD	1.24±0.14	1.52±0.19	1.50±0.24	1.38±0.14	1.21±0.09	1.19±0.11

LDL-cholesterol, mmol/l, mean ± SD	3.09±0.99	3,15±0.62	2,52±0.56	2,35±0.41	2,51±0.36	2,18±0.33
Triglycerides, mmol/l, mean ± SD	1.28±0.36	1.15±0,35	0,78±0,33	1,05±0,39	1,62±0,46	0,63±0,18
Creatinine, µmol/l / eGFR ml/min/1,73 m^2, mean ± SD	91,2±7,8 / 74.0±4.6	82,7±8.2 / 63.2±5.2	62.2±7.3 / 90.8±6.0	80.6±5.7 / 88.8±3.6	85.5±6.3 / 82.6±7.1	84.2±5.9 / 87.1±5.6
24 hrs albumin excretion, mg, mean ± SD	22.7±10.5 ***	32.1±16.9 ***	13.4±8.6	20.2±10.3 ***	3.9±1.3	3.8±2.3
CRP, mg/l, mean ± SD	3.33±4.79	1.25±0.86	1.41±0.51	1.58±0.66	4.08±1.24	2.16±1.19

Table 2. Changes in physical parameters during follow up and mean ± SD of all laboratory parameters. * Since the creation of our first computerized care program in 1989, ** In 2022
*** Moderate microalbuminuria (<50 mg/24 hrs) during the last 5 years

CROSS SECTIONAL ANALYSIS

Table 3 shows the late diabetic complications, comorbidities and cardiovascular status of our patients.

Patient	1	2	3	4*	5	6
Retinopathy	Back-ground	Pre-proliferative	Back-ground	No	Back-ground	Back-ground
Neuropathy	Yes +++	Yes +++	Yes +	Yes +	Yes +	Yes +
Nephropathy	Yes +	Yes +	No	Yes +	No	No
Hypertension	Yes, well treated	Yes, well treated	Yes, well treated	Yes, well treated	Yes, well treated	Yes, well treated
Statin treatment	Yes	Yes	No	Yes	Yes	Yes
Carotid / lower limb atherosclerosis	Yes+++/ Yes+++	Yes+++/ Yes+++	No	Yes++/ Yes++	No	No
Cardiac functional abnormalities	Yes++	Yes+	No	Yes++	No	No
Coronary CT abnormalities	**	Yes+++	No	Yes+++	Yes+	Yes+

Table 3. Diabetic late complications, comorbidities & cardiovascular status. * Smoked for 40 years. ** Coronary bypass surgery performed in 2003. + mild, ++ moderate, +++ severe impairment

As for retinopathy, patient 2 is in the pre-proliferative stage without visual impairment, patient 4 had none, and the other four patients had mild background retinopathy. Patients 1 and 2 had severe neuropathy, the other four patients had very mild neuropathic symptoms. Three patients had a very mild form of nephropathy, the other three had completely normal kidney function. All six patients had hypertension, but with appropriate therapy near normal blood pressure values could be maintained. Because of the elevated LDL cholesterol levels, all (but patient 3) were taking a statin preparation, although patient 2 avoided taking it most of the time. Half of the patients had severe atherosclerotic lesions of the carotid and lower limb arteries, the other three patients had completely intact arteries. In patients 2 due to severe peripheral arteriosclerosis percutaneous transluminal angioplasty was also performed on right lower limb. She had previously cerebral and peripheral arterial events as well. From a cardiological point of view, functional impairment was found in patients 1, 2 and 4. Patient 3 had completely intact coronaries, patients 2 and 4 had severe coronary calcification and multiple severe stenoses, while patients 5 and 6 had only minimal coronary wall irregularities. Finally, female patient 3 had the best status, with the fewest diabetic lesions. Here I would also point out that she is the only one without a university degree.

Patient	1	2	3	4	5	6
Basal insulin IU/day	glargine 26	aspart 11 (Pump)	degludec 11	degludec 28	glargine 73	degludec 28
Bolus insulin IU/day	lispro 24	aspart 10	aspart 10	lispro 28	lispro 70	lispro 22
Insulin IU/kg	0.68	0.41	0.36	0.57	1.16	0.53
Use of CGM	Guardian	Guardian	Guardian	No	Guardian	Libre 3

Table 4. Insulin treatment and use of CGM & insulin pump

Regarding the patients' insulin therapy and device use: except for patient 2, who had been using an insulin pump for 20 years, guided by CGM for the last 6 years, the rest of the patients are all on intensive insulin therapy (MDI). All but patient 4 used CGM, four patients used Guardian 3, and one patient used Libre 3 sensors.

DISCUSSION

In the present study, we analysed the cases of six patients of ours with T1D present for 51-69 years. Half of them had normal body mass, while the other half were overweight or obese. This rate exceeds the body mass rates reported in a previous study performed in Hungary [14], where metabolic syndrome was found in 29.7% of men and 32.7% of women with T1D. 50% of our patients - all three of them were men - metabolic syndrome developed over time due to a gradual increase in body mass.

Although the number of cases presented is this study is much lower than in the studies discussed in the introduction, there are fundamental differences in the way they were processed.

While in the Parisian Cohort Study the average HbA1c level of the patients was 8.7%, those of our patients ranged between 6.9% and 7.3%.

In a 30-year long observational study [13] HbA1c levels were measured on an average of 6 times in 536 patients, whereas in the Pittsburgh Study [17], HbA1c levels were recorded only at the beginning and end of the study in 658 patients over a 16-year follow-up period, i.e. a total of 2-times, and those data were used to draw conclusions about the risk of micro- and macroangiopathic complications.

In the repeated comparison of the Pittsburgh study and the DCCT/EDIC [12], a very limited number of metabolic parameters have been evaluated to establish the risk factors for cardiovascular complications.

In contrast, our patients had 3 to 4 HbA1c, total cholesterol, HDL- cholesterol, LDL-cholesterol, triglycerides, serum creatinine and CRP tests and one 24-h urine albumin test each year for 28-33 years, and 3 to 4 eGFR determinations per year for the last 11 years.

Frozen shoulder, the prevalence of which according to some studies can be as high as 60% in patients with >45 years of diabetes [9], did not occur in any of our patients.

Several studies emphasize that minimal residual insulin secretion [15], mainly after carbohydrate intake, can be detected in a significant proportion of type 1 diabetics with a very long duration of diabetes and without severe late complications. None of our six patients had residual insulin secretion, and all were C-peptide negative.

In a study analysing data from 27,805 T1D patients with 45+ years of diabetes [18], the estimated prevalence of microalbuminuria was 25% and that of macroalbuminuria and end-stage renal disease was 9.4%. Only 50% of our patients had mild (<50 mg/day) microalbuminuria during the past 5 years.

It is likely that cardiovascular lesions are more common in long-standing diabetes than those suggested by the known cases, as only a small proportion of cases are properly diagnosed [8]. Our own cases are proof of this: in two of our patients serious cardiovascular lesions have just been diagnosed by a recently completed full work-up.

According to the DCCT/EDIC study (DCCT/EDIC, 2016) and the FinnDiane 50-year Cohort [7], the most important risk factors for cardiovascular lesions are diabetes duration and HbA1c levels. In our patients 1 and 2 with the longest duration of diabetes (69 years and 62 years, respectively), the predominant role of duration is clear, but the next female patient, patient 3 has a diabetes duration (59 years) barely less than the previous patient, yet she has a completely intact cardiovascular system. HDL-cholesterol levels are equally high in female patients 2 and 3 (female patient 3), therefore this factor does not explain the differences in vascular abnormalities. Similarly, there are no major differences in the average HbA1c levels of our patients.

However, it should be added that our patient 2, who had the worst overall health status in the group, had very poor metabolic status during the first 34 years of her diabetes, according to her own account, and the toll of that could not be significantly corrected by the last 28 years spent under our care, including 20 years of pump use. In the case of our third severely atherosclerotic patient, patient 4, the noteworthy factor is 40 years of smoking, which he had quit just 2 years ago.

According to some studies [11], the incidence of fractures in long-standing T1D is not higher than among control subjects of similar age. Among our six patients, only female patient 2 had bilateral femoral head necrosis requiring surgical intervention in 1993 and a left proximal humerus fracture in 2011.

Finally: all patients – except for one woman – considered their quality of life to be good and had no significant complaints attributable to diabetes.

CONCLUSION

Although we have only processed data from six patients with diabetes of 50+ years, the volume of data processed is at least an order of magnitude higher than that found in the literature. We hope that, despite the small number of cases, we have successfully contributed to increasing the life expectancy of people with long-term T1D and to improve overall patient care.

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CONFLICT OF INTEREST: The authors have declared that no competing interests exist.

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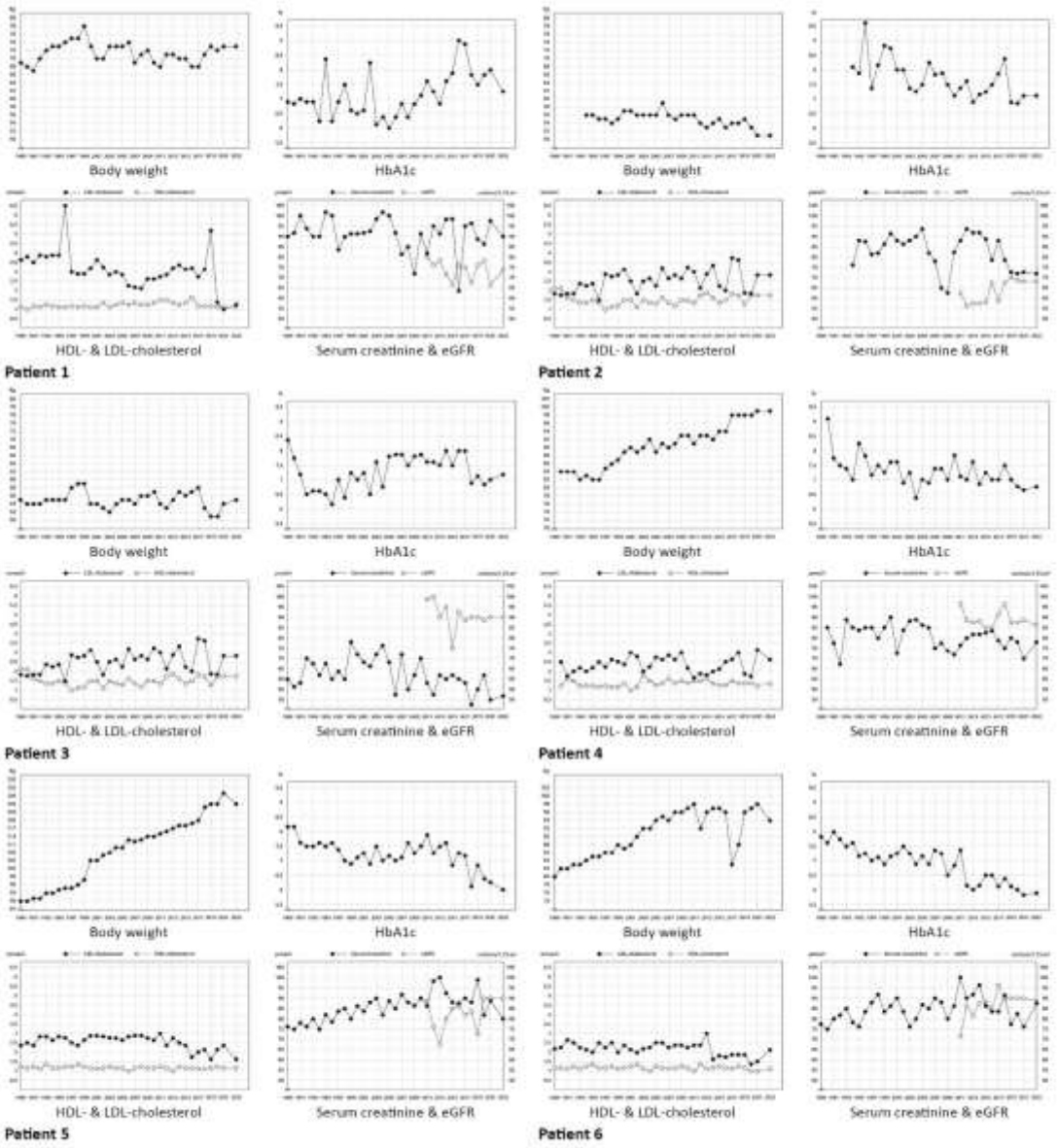

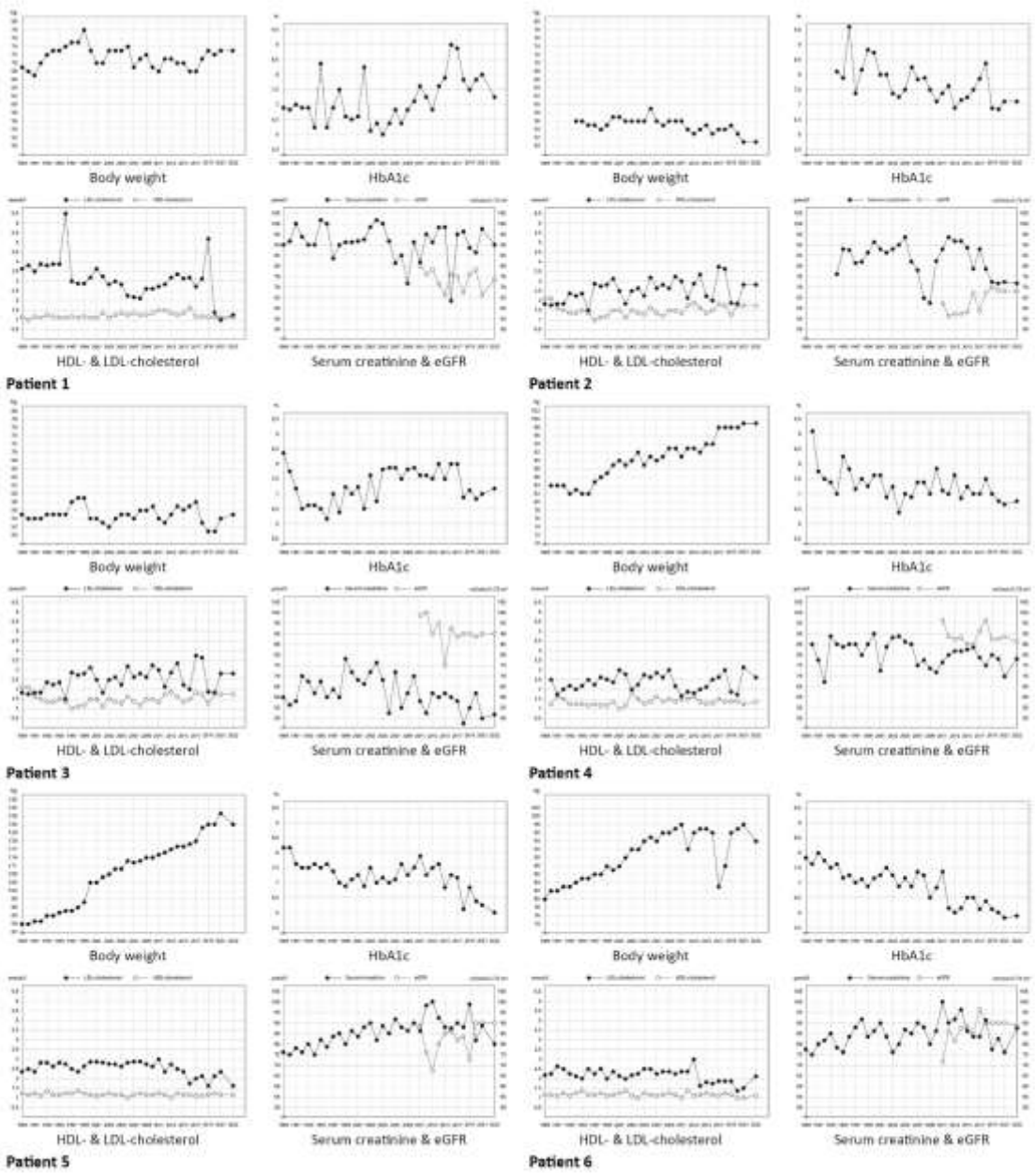
Body weight
HbA1c
Body weight
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HDL- & LDL-cholesterol
Serum creatinine & eGFR
HDL- & LDL-cholesterol
Serum creatinine & eGFR
Patient 1
Patient 2
Body weight
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Body weight
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Serum creatinine & eGFR
HDL- & LDL-cholesterol
Serum creatinine & eGFR
Patient 3
Patient 4
Body weight
HbA1c
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HDL- & LDL-cholesterol
Serum creatinine & eGFR
Patient 5
Patient 6