Microvascular Outcomes of Pediatric-Onset Type 1 Diabetes Mellitus: A Single-Center Observational Case Reviews in Sana'a, Yemen

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ABSTRACT: Microvascular complications of pediatric-onset type 1 diabetes are common in low-income countries. In this study, we aimed at reviewing microvascular outcomes in 6 cases with type 1 diabetes over 14 to 31 years of follow-up. Severe proliferative diabetic retinopathy (PDR) and/or diabetic macular edema (maculopathy) (DME) and overt diabetic nephropathy (macroalbuminuria) were seen among 4 of 6 patients, whereas severe diabetic peripheral neuropathy with Charcot neuroarthropathy was seen in 1 patient only, who had the longest duration of follow-up. The weighted mean (SD) (95% confidence interval) hemoglobin A_{1c} was 8.9 (1.6) (8.4-9.4)% [74 (17) (68-80) mmol/mol] for PDR/DME and 8.6 (1.7) (8.0-9.0)% [71 (19) (65-77) mmol/mol] for macroalbuminuria. Thyroid autoimmunity was positive in 3 patients with overt hypothyroidism in 2 of them. Worse microvascular outcomes among these cases might be attributed to poor glycemic control, lack of knowledge, and limited financial resources.

KEYWORDS: Type 1 diabetes mellitus, microvascular outcomes, diabetic retinopathy, diabetic kidney disease, diabetic peripheral neuropathy

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Introduction

Type 1 diabetes (T1D) is predominantly a disease of children, adolescents, and young adults. It is a clinically *exclusive* disease, encompassing patients with diabetes-associated autoantibodies (DAA), plus absolute insulin deficiency.[1] The classical trio of symptoms associated with disease onset (polydipsia, polyphagia, and polyuria) along with overt hyperglycemia and immediate need for exogenous insulin replacement remains the diagnostic hallmarks in children and adolescents with T1D.[2] Three classes of biomarkers characterize T1D: DAA as an immune marker, C-peptide as a proxy for level of insulin secretion, and HLA genotypes as a genetic marker.[1] Diabetes of all types can damage the heart, blood vessels, eyes, kidney, and nerves, leading to disability and premature death.[2] In Diabetes Control and Complications Trial (DCCT), the effect of intensive glucose control on the development and progression of microvascular complications in terms of diabetic retinopathy (DR), nephropathy, and neuropathy showed benefit after a mean of 6.5 years follow-up.[3] The trials also demonstrate that those patients with good β-cell function do better in terms of glucose control and complications.[4] To the best of our knowledge, very few similar prospective cohort studies have been published in the literature on microvascular complications in low-income countries like Yemen. Therefore, we aimed in this study to present the natural history and the development of diabetes-specific microvascular pathology in the retina, renal glomerulus, and peripheral nerves among 6 cases with T1D over several years of follow-up from childhood and adolescence to adulthood.

Study Design and Methods

This study was conducted in a diabetic center in Yemen. In our childhood and adolescence diabetes registry, we have about 450 patients registered for treatment and follow-up from the age of symptomatic onset between ≤6 months and 18 years to adulthood. In this study, we have identified 6 cases in this cohort for whom complete data on the development of microvascular complications were available over the years of follow-up. They were followed from the age at onset of the disease to the last clinic visit, over duration between 14 and 31 years after diagnosis. Follow-up observation included comprehensive clinical assessment, laboratory investigations, and surveillance for microvascular complications. Diagnosis of T1D was established with history of symptoms of hyperglycemia and the first high blood glucose (BG) level and first insulin injection. Islet autoantibodies test was available at diagnosis for 1 patient and C-peptide measurements were available for all patients during the course of the disease. Hemoglobin A_{1c} (HbA_{1c}) was measured in each visit during years of follow-up for all patients.[5] We used dual reporting of HbA_{1c} in both NGSP/DCCT units (%-one decimal) and the IFCC-SI units defined as millimoles per mole of unglycated hemoglobin (mmol/mol-no decimal) according to the recommendation of the International HbA_{1c} Consensus Committee.[3,6] It has been expressed as mean with SD and 95% confidence interval (95% CI). The HbA_{1c}-derived estimated average glucose (eAG) concentration (mg/dL) (mmol/L) was calculated as recommended by American Diabetes Association (ADA).[7] Glycemic variability is the long-term fluctuation of glycemia and has been defined as HbA_{1c}%-SD.[8,9] The adjusted HbA_{1c}%-SD over the number of clinic visits during years of follow-up was calculated using the DCCT formula[8] as HbA_{1c}-SD for all visits: SD/SQR [n/(n−1)]. As the number of visits an individual patient had could also influence this SD (such that few visits

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would make the SD apparently greater than many visits), the SD value was divided by SQR [n/(n – 1)] to adjust for this possibility.[9] It is an HbA_{1c}-independent risk factor to the development of DR and diabetic kidney disease (DKD) in patients with T1D.[7,8] Biochemical studies included serum creatinine (μmol/L) for calculating estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for identifying the grade of GFR and urine albumin to creatinine ratio (ACR) (mg/g) for identifying the stage of albuminuria. Stimulated C-peptide level was measured in urine as 2-hour postmeal urine C-peptide to creatinine ratio (UCPCR; nmol/mmol).[10] All laboratory investigations were conducted in Abbott Automated Laboratories in Sana'a, Yemen. Grading of eGFR and staging of albuminuria were established as mentioned elsewhere.[11,12] We considered using $eGFR_{cystatinC}$ for patients with chronic kidney disease (CKD) stage G3aA1 and more as recommended by NICE (National Institute for Health and Care Excellence) guidelines.[11] To improve CKD classification, all levels of reduced eGFR were complemented by urinary ACR, even in the range of microalbuminuric values.[12] Eye assessment and care were provided by a specialized eye center in Sana'a city. Diabetic retinopathy and diabetic macular edema were classified as recommended by the International Council of Ophthalmology Guidelines.[13] Diabetic neuropathy was assessed by clinical examination and confirmed by biothesiometry and/or nerve conduction velocity studies. Confirmed clinical neuropathy was defined as vibration perception threshold >25 V and/or the presence of abnormalities in nerve conduction of sural sensory and peroneal motor nerves in the lower limbs. Statistical analysis was computed using SPSS for windows, version 19 (SPSS Inc.). Data were presented as mean with SD (SD around the mean value) and 95% CI of the mean. Long-term mean HbA_{1c}, as a measure of glycemic control, was calculated and weighted for the time between the measurements ($wHbA_{1c}$).[14] Unlike arithmetic mean where each data point contributes equally to the final mean, in weighted mean, some data points contribute more "weight" than others to the final mean.[15] For identifying weighted mean HbA_{1c}, all the HbA_{1c} values, from time of diabetes diagnosis to the last follow-up clinic visit, or time of onset of proliferative diabetic retinopathy (PDR) or macroalbuminuria (MAU), were used for calculations. The psychological stress caused by diabetes was evaluated by the Hospital Anxiety and Depression Scale (HADS) as a validated instrument for detecting states of depression and anxiety.[16] The quality of life (QoL) was measured by Ferrans and Powers QoL index, Diabetes version III (Arabic).[17]

Results

Table 1 presents 6 patients who developed T1D in childhood or adolescence and have been followed up to adulthood. They had a diagnosis of T1D based on the classical trio of symptoms at diagnosis, overt hyperglycemia, absolute requirement for insulin therapy, and history of diabetic ketoacidosis (DKA) at presentation. All 6 patients had declining β-cell function with increasing duration of diabetes for >5 years, defined as absent or very low postmeal-stimulated UCPCR. Among these patients, 3 were observed for more than 20 years and the other 3 between 14 and 18 years. Severe PDR and/or diabetic macular edema (maculopathy) (DME) and overt diabetic nephropathy (MAU) were seen among 4 of 6 patients, whereas severe diabetic peripheral neuropathy (DPN) with Charcot neuroarthropathy was seen only in 1 patient who had the longest duration of follow-up. A total of 36 HbA_{1c} values were collected from patients till the time of development of PDR and 39 values till the time of development of MAU. The weighted mean (SD) (95% CI) HbA_{1c} was 8.9 (1.6) (8.4-9.4)% [74 (17) (68-80) mmol/mol] for PDR and 8.6 (1.7) (8.0-9.0)% [71 (19) (65-77) mmol/mol] for MAU. Thyroid autoimmunity was positive in 3 patients with overt hypothyroidism in 2 of them. Anxiety and depression were noted among 4 cases and low Qol index among 2 cases. Narrative of the individual patients is provided in the following table.

Case 1

Case 1 was 5 years old when first diagnosed as having T1D. She presented with severe hyperglycemia and DKA. After hospital admission for a few days, she was discharged on 2 to 3 premixed human insulin injections per day given by her mother. The newer insulin analogues were introduced in treatment as basal-bolus regimen later in the course of the disease. Occasional self-monitoring of BG (SMBG) was performed with her BG levels out of goals most of the time. Transition from family care to self-care was established at the age of 16 years. Early morning mild hypoglycemic episodes were recurrent more than 3 times per week. Old-onset type 2 diabetes was reported in maternal grandfather and young-onset diabetes in her brother and sister. During the first 17 years after diagnosis, she was not on regular follow-up with recurrent periods of loss of contact. Over the years of observation up to 31 years after diagnosis, there was evidence of poor glycemic control obtained from weighted mean (SD) (95% CI) HbA_{1c} value of 8.8 (2.4) (7.6-10)% [72 (26) (59-85) mmol/mol]. The corresponding mean (SD) (95% CI) value of HbA_{1c}-derived (eAG) concentration over the years of follow-up was 250 (86) (206-295) mg/dL [13.9 (4.8) (11.4-16.4) mmol/L]. There was also significant glycemic variability or fluctuations of mean HbA_{1c} over the years of follow-up, defined as adjusted HbA_{1c}-SD value of 2.3% (25 mmol/mol) for all visits (Figure 1). Surprisingly, the patient was still having a residual β-cell function at 31 years after diagnosis as shown by a 2-hour postmeal-stimulated UCPCR value of <0.02 (0.0012) nmol/L indicating a residual but very low endogenous insulin secretion (microsecretion).

Diabetic eye complications started as early as 4 years after diagnosis with a bilateral diabetic cataract that was surgically treated. First retinal screen was performed about 22 years after diagnosis and continued on yearly basis. Mild nonproliferative

Table 1. Clinical and biochemical characteristics of type 1 diabetes cases.

CASE	1	2	3	4	5	6
Age at diagnosis, y	5.0	12	12	15	13	17
Years of follow-up	31	18	23	17	22	14
Weighted mean (n)	17	10	13	23	17	15
HbA_{1c} weighted mean (SD) (95% CI)						
NGSP units (%)	8.8 (2.4) (7.6-10)	8.3 (2) (6.9-9.7)	9.3 (0.9) (8.8-9.9)	8.2 (1.10) (7.8-8.6)	7.5 (1.6) (6.7-8.3)	6.9 (0.7) (6.5-7.3)
SI units (mmol/mol)	72 (26) (59-85)	68 (22) (52-84)	78 (10) (72-84)	66 (11) (61-71)	59 (17) (50-68)	52 (8) (48-56)
eAG, mg/dL						
Mean (SD)	250 (86)	231 (83)	238 (38)	206 (32)	200 (60)	167 (29)
95% CI	206-295	171-290	215-261	192-219	167-230	151-183
Adjusted HbA_{1c}%-SD	2.3	1.9	0.86	0.98	1.55	0.68
UCPCR—years after diagnosis, nmol/mmol	0.0012 (at 31 y)	0.17 (at 6 y)	0.001-0.000 (at 17 and 23 y)	0.002 (at 13-17 y)	0.000 (at 22 y)	0.035-0.02 (at 9 and 14 y)
Microvascular complications	PDR + DME	PDR + DME	PDR + DME	NPDR + DME	DN-(PMA)	DN-(PMA)
	DN-(PMA)/(MAU)	DN-(MAU)-CKD + CRF	DN-(MAU)	DN-(MAU)		
	Severe DPN + CT + Charcot feet	Mild DPN	Mild DPN	Mild DPN + CTS		
Thyroid						
TPOAb/TgAb	Negative	TPOAb +	TPOAb/TgAb +	Negative	TPOAb +	Negative
TSH/FT4	Euthyroid	Hypothyroid	Euthyroid	Euthyroid	Hypothyroid	Euthyroid
HADS						
Anxiety	Definite	Noncase	Definite	Definite	Not tested	Definite
Depression	Definite	Noncase	Borderline	Definite	Not tested	Borderline

Abbreviations: CKD, chronic kidney disease; CRF, chronic renal failure; CTS, carpal tunnel syndrome; DME, diabetic macular edema (maculopathy); DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; eAG, estimated average glucose; HADS, Hospital Anxiety Depression Scale; MAU, macroalbuminuria; n: Number of samples per patient; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PMA, persistent microalbuminuria; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; UCPCR, urine C-peptide to creatinine ratio.

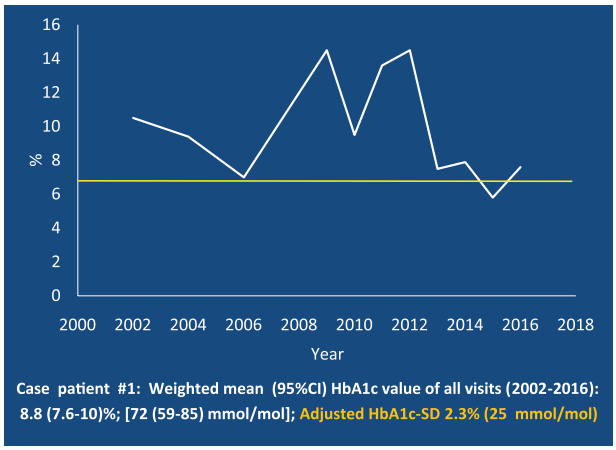

Figure 1. HbA_{1c} (%)—case 1. HbA_{1c} indicates hemoglobin A_{1c}.

diabetic retinopathy (NPDR) was first detected 1 year later, with progression within a couple of years to severe NPDR, high-risk PDR (HRPDR), and DME at 25 years duration. She had laser photocoagulation and intravitreous bevacizumab (Avastin) injection. Her PDR was then stabilized, except for recent small vitreous hemorrhage in the right eye.

The devastating microvascular complication of diabetes in this particular patient was diabetic neuropathy. At 25 years duration, she presented with symptoms of severe painful neuropathy that was confirmed by biothesiometry and electrophysiological study. After 3 years, she had horizontal diplopia caused by right cranial nerve VI palsy that resolved spontaneously within 2 months time. This trivial event was followed a few months later by rapid development of painful, swollen, warm, and red left foot. A diagnosis of acute stage of Charcot neuroarthropathy was established. Further evaluation with X-ray and magnetic resonance imaging (MRI) of the foot confirmed the diagnosis of mid-foot and rear-foot Charcot with destruction and deformity of tarsal bones, mainly calcaneus and navicular bones and lower aspect of talus bone associated with joint distortion (Figures 2 and 3). While on treatment for Charcot left foot, she had a trivial trauma of the right foot big toe, with subsequent neuropathic foot ulcer penetrating to distal phalanx bone (grade III) and associated with infection (stage B). The ulcer healed by wound management leaving the big toe deformed due to sclerosis and deformity of distal phalanx. The same sequence of symptoms and signs of Charcot neuroarthropathy developed 1 year later in the right foot. An X-ray and MRI confirmed the diagnosis of mid-foot Charcot disease causing destruction of cuneiform, navicular, and cuboid bones, as well as heads of the third and fourth metatarsal bones.

Diabetic kidney disease was less aggressive than either DR or neuropathy but all were noted almost at the same time at 25 years after diagnosis. Persistent microalbuminuria (PMA), a sign of early kidney damage, was defined as urine ACR between 130 and 255 mg/g, during multiple measurements over 4 years. Meanwhile, eGFR continued to range between 60 and 89 mL/min/1.73 m^2. Therefore, she was classified as having CKD G2/

Figure 2. Case 1. Charcot left foot- swelling and deformity of the rear foot and ankle.

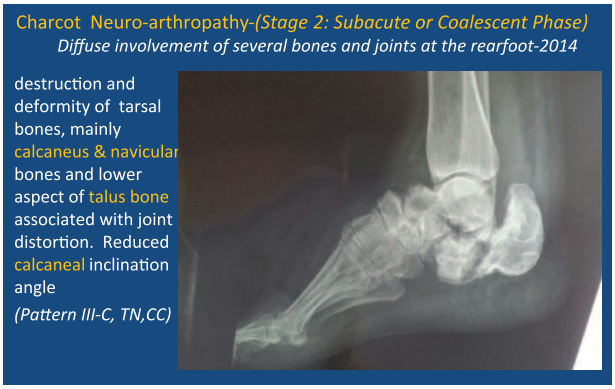

Figure 3. Case 1: Charcot left foot—lateral view: destruction and deformity of tarsal bones, mainly calcaneus and navicular bones and lower aspect of talus bone associated with joint distortion. Reduced calcaneal inclination angle (pattern III-C, TN, CC).

A2. Ambulatory blood pressure (BP) monitoring (ABPM) performed during this stage showed normal BP with 24-hour mean systolic BP/diastolic BP (SBP/DBP) value of 112/72 mm Hg. She was treated with angiotensin-converting enzyme inhibitor, ramipril, and strict glycemic control. Persistent microalbuminuria progressed over the last 6 years follow-up to MAU (ACR: 480 mg/g) combined with mild decline of eGFR to (57 mL/min/1.73 m^2) putting her in CKD G3a/A3.

The burden of long-standing diabetes and its microvascular complications in this young patient was associated with low QoL score (0.53) on Ferrans and Powers QoL index and moderately severe combined anxiety and depression on the HADS.

Case 2

Case 2 was 12 years old when she developed diabetes. She was classified as having T1D based on clinical criteria of rapid onset, severe symptoms, severe hyperglycemia, ketones in urine, and positive glutamic acid decarboxylase antibody testing. No other family members were affected with diabetes. She lost contact between 4 and 8 years after diagnosis and then became adherent to regular clinic visits during the remaining years of follow-up. Over the years of observation up to 18 years after diagnosis, she was treated with human premixed insulin with lack of satisfactory glycemic control as suggested by weighted

mean (SD) (95% CI) HbA_{1c} value of 8.3 (2.0) (6.9-9.7)% [68 (22) (52-84) mmol/mol]. The corresponding mean (SD) (95% CI) value of HbA_{1c}-derived eAG concentration over the years of follow-up was 231 (83) (171-290) mg/dL [12.8 (4.6) (9.5-16.1) mmol/L]. The adjusted HbA_{1c}-SD over the number of visits during follow-up years was 1.9% (21 mmol/mol) denoting a substantial long-term variability of HbA_{1c} concentration. Endogenous insulin secretion started to decline to an absolute deficiency status at 6 years after diagnosis, with a fasting serum C-peptide (FCP) < 0.08 (0.03) vs fasting plasma glucose (FPG) > 8.0 mmol/L and 2-hour postmeal-stimulated UCPCR value of <0.2 (0.17) nmol/mol, indicating low endogenous insulin secretion. Recurrent attacks of DKA were noted during the initial 4 years of the disease. Mild hypoglycemic episodes were reported throughout the course of the disease, initially due probably to insulin excess from time to time in the context food intake or exercise and later with advanced disease due to DKD and progressive renal impairment.

At 3 years after diagnosis, thyroid screening showed a strongly positive thyroid peroxidase antibody (TPOAb) (898 IU/mL) and thyroglobulin antibody (TgAb) (1938 IU/mL) with raised thyrotropin (TSH) (8.2 μIU/L vs normal FT4 level: 12 pmol/L), indicating the presence of chronic autoimmune thyroiditis with subclinical hypothyroidism. It progressed over time to overt hypothyroidism with levothyroxine dose adjustment based on TSH level monitoring.

At 9 years after diagnosis, she showed again after being absent for 6 years. There was a problem with her eyes. On clinical evaluation of her status, there was bilateral HRPDR with left eye DME, MAU (ACR 475 mg/g) with G2 eGFR (68 mL/min/1.73 m^2) and hypertension. Office BP was 180/110 mm Hg and ABPM 24 hours mean SBP/DBP value was 142/89 mm Hg. She was 21 years old at the time of diagnosis of hypertension, eye, and renal complications. Hypertension and diabetic nephropathy were treated with 3 antihypertensive drug combinations including angiotensin receptor blocker (losartan), calcium channel blocker (amlodipine), and selective β-blocker (atenolol), together with low-protein and low-salt diet.

Despite the burden of diabetes and its complications, the patient was psychologically stable when assessed with the HADS.

Diabetic retinopathy was discovered at first eye screen as an advanced PDR and DME. Urgent laser photocoagulation was recommended by the ophthalmologist but not done. After 6 months, her condition became worse with the left eye showing advanced combined renal and diabetic PDR, traction retinal detachment, and cystoids macular edema. This was treated surgically by pars plana vitrectomy and silicon oil injection. The right eye was managed with 3 sessions of laser photocoagulation.

The clinical diagnosis of mild sensory diabetic neuropathy was based on symptoms of numbness and burning of feet and toes. Clinical examinations elicited diminished pain, thermal, and touch sensations. Vibration perception was preserved. These findings were suggestive of small-fiber peripheral neuropathy (PN).

The devastating microvascular complication of diabetes in this particular patient was DKD. There was a steady progressive decline of eGFR combined with persistent MAU between 9 and 18 years after diagnosis ending into stage 5 CKD (kidney failure). The patient experienced a decline of 6 mL/min/1.73 m^2 per year in kidney function, defined as eGFR, over 9 years of treatment and follow-up. The natural history of her CKD started as G2/A3 (eGFR: 68 mL/min/1.73 m^2, ACR: 475 mg/g) at year 9, to CKD G3a/A3 (eGFR: 52 mL/min/1.73 m^2, ACR: 828 mg/g) at year 10, CKD G3b/A3 (eGFR: 39 mL/min/1.73 m^2, ACR: 2100 mg/g) at year 12, CKD G4/A3 (eGFR: 25 mL/min/1.73 m^2, ACR: 2185 mg/g) at year 14, CKD G4/A3 (eGFR: 22 mL/min/1.73 m^2, ACR: 1920 mg/g) at year 15, and ultimately kidney failure requiring dialysis or transplant defined as CKD G5/A3 (eGFR: 14 mL/min/1.73 m^2, ACR: 1134 mg/g) at year 18. Although treated extensively twice for deteriorating kidney function at 10 and 12 years after diagnosis, the nature of her glomerular disease was not appropriately investigated by specific laboratory studies and kidney biopsy. According to the recent KDIGO (Kidney Disease: Improving Global Outcomes) guidelines,[12] she was referred at CKD stage G3b/A3 to the nephrologist for specialist care. Her CKD progressed from stage G3b/A3 to stage G4/A3 within a couple of years and then to stage G5/A3 (kidney failure) within the subsequent 4 years. The decision of kidney dialysis or transplant was then considered. Her family decided to go first for dialysis. Unfortunately, she died after the first session of hemodialysis at the age of 32 years after 20 years of having T1D and its complications.

Case 3

Case 3 developed T1D at the age of 12 years, and she was 18 years old when first registered in our diabetic center. There was a history of severe symptoms at onset of the disease with hospital admission in coma, due probably to DKA. Since then, she was taking human premixed insulin injection twice daily, but this was changed in our center to insulin analogues with basal-bolus regimen. No other family members were affected with diabetes, but one of her sisters has autoimmune thyroiditis. There was evidence of poor glycemic control over the years of follow-up obtained from weighted mean (SD) (95% CI) HbA_{1c} value of 9.3 (0.9) (8.8-9.9)% [78 (10) (72-84) mmol/mol]. The corresponding mean (SD) (95% CI) value of HbA_{1c}-derived eAG concentration over the years of follow-up was 238 (38) (215-261) mg/dL [13.2 (2.1) (11.9-14.5) mmol/L]. The adjusted HbA_{1c}%-SD over the number of visits during follow-up years was 0.86% (10 mmol/mol), denoting long-term variability of HbA_{1c} concentration. The patient lost contact and follow-up for several years to show

again at 17 years after diagnosis with poor glycemic control (HbA_{1c}: 11.0%) and frequent hypoglycemic episodes particularly during night. Insulin secretion declined to a very low level with serum FCP < 0.1 (0.07) vs FPG > 8.0 nmol/L and 2-hour postmeal UCPCR value of <0.02 (0.001) nmol/mol. Ultimately, she became C-peptide negative at 23 years after diagnosis with 0 serum FCP value vs FPG > 8 mmol/L. Two more morbidities developed at this stage: autoimmune thyroiditis and severe microvascular complications in the retina and renal glomerulus. Thyroid autoimmunity was noted at 22 years after diagnosis with positive TPOAb (197 IU/mL) and TgAb (2300 IU/mL) but normal thyroid function.

Diabetic eye complications started with bilateral diabetic cataract at 10 years after diagnosis, which required cataract surgery for both eyes. Bilateral mild NPDR and DME were first diagnosed at 17 years after diagnosis, with laser photocoagulation for DME. Diabetic retinopathy then progressed rapidly within a couple of years to a more severe grade of PDR affecting both eyes. She had 2 more sessions of laser therapy with subsequent stability of retinal lesions over several years.

Diabetic kidney disease was even more severe than DR with persistent MAU and gradual decline in eGFR between 17 and 23 years after diagnosis, from CKD G2/A3 (eGFR: 67 mL/min/1.73 m^2, ACR: 946 mg/g) at year 17 to CKD G3b/A3 (eGFR: 38 mL/min/1.73 m^2, ACR: 858 mg/g) in her last clinic visit at 23 years after diagnosis. There was decline of 1.7 mL/min/1.73 m^2 per year in kidney function, defined as eGFR, over 7 years of treatment and follow-up. Macroalbuminuria and progressive decline of eGFR were associated with the development of hypertension. She was treated with angiotensin receptor blocker losartan and calcium channel blockers amlodipine and atorvastatin aiming at controlling the BP and reducing high levels of albumin excretion. More frequent episodes of severe hypoglycemia were reported in association with progressive renal impairment and absolute insulin deficiency. She was 35 years old at time of closure of follow-up after 23 years of struggle with diabetes and its complications.

Diabetic neuropathy was less severe than eye and renal diseases. The patient presented with mild numbness, burning, and pinprick sensations in her feet at 17 year after diagnosis. Clinical assessment was suggestive of mild small-fiber DPN.

The psychological impact of long-standing diabetes and its microvascular complications in this particular patient was manifested as low QoL score (0.53) on Ferrans and Power QoL index and mild anxiety and depression on the HADS.

Case 4

Case 4 was 15 years old when she first had symptoms related to high BG. Diagnosis of diabetes was confirmed within a few days by home BG test. She came from a family with some close relatives affected with diabetes and other autoimmune diseases. Both paternal and maternal grandfathers were affected with type 2 diabetes. Mother was on treatment for T2D and had at one time Graves disease. Maternal aunt developed T1D at the age of 20 years with subsequent chronic autoimmune thyroiditis and hypothyroidism, and maternal grandmother had old-onset autoimmune thyroiditis and hypothyroidism. A male cousin of her had T1D at the age of 2.0 years and celiac disease later on at the age of 11 years. However, the index patient screen ruled out other autoimmune diseases.

She took over the responsibility of self-care from the beginning of her diabetes, injecting insulin, monitoring BG at home, and visiting our center on regular basis for clinical follow-up. She was treated from the start with human intermediate-acting insulin (Insulatard) twice daily and regular insulin (Actrapid) before each meal. Hypoglycemic attacks continued to be mild and frequent for several years. The use of insulin analogues glargine and aspart as basal-bolus regimen was established at 14 years after diagnosis. There was evidence of unsatisfactory long-term glycemic control obtained from weighted mean (SD) (95% CI) HbA_{1c} value of 8.2 (1.1) (7.8-8.6)% [66 (11) (61-71) mmol/mol] of 23 visits over 17 years follow-up. The corresponding mean (SD) (95% CI) value of HbA_{1c}-derived eAG concentration over years of follow-up was 206 (32) (192-219) mg/dL [11.4 (1.8) (10.7-12.2) mmol/L]. The adjusted HbA_{1c}%-SD over the number of visits during follow-up years was 0.98% (11 mmol/mol) denoting considerable long-term variability of HbA_{1c} concentration. The β-cell function, defined as 2-hour postmeal UCPCR, was measured every year in the duration between 13 and 17 years. The value was <0.02 (0.002) nmol/mol indicating a residual but very low endogenous insulin secretion (microsecretion).

She was married at the age of 25 years (10 years after diagnosis) with unplanned conception, threatened abortion during early pregnancy, and full-term labor induction by cesarean delivery with normal baby. Diabetic and antenatal cares were provided throughout pregnancy. Diabetes care included SMBG, regular HbA_{1c} measurements, intensive insulin therapy, BP monitoring, and periodic eye and kidney screening. With more intensive insulin therapy, glycemic control improved during pregnancy. Thyroid screening during pregnancy showed normal TSH and negative TPOAb. Blood pressure increased during the last few weeks of pregnancy but returned back to normal after delivery. During the first postpartum year, she breastfed her baby for 6 months only due to sequential development of major health events of carpal tunnel syndrome (CTS), DKD, hypertension, and DME.

The CTS affected mainly right hand, about 3 months after delivery, that substantially resolved by treatment within 8 weeks. She also had symptoms of mild painful DPN during subsequent years.

Diabetic kidney disease developed shortly after the CTS, at 12 years after diagnosis, when she was 27 years old. The patient presented with 4 weeks history of profound weakness, lower limb edema, and dyspnea on moderate exertion. On clinical

examination, there was hypertension (BP: 160/90 mm Hg) and moderate lower limb edema. Urine testing was positive for protein, blood, and granular casts. There was MAU (ACR 1750 mg/g) and mildly decreased GFR (eGFR: 60 mL/min/1.73 m^2). Measuring 24 hours urine protein excretion showed high proteinuria in the nephrotic range (>3.5 g/24 h). Further extensive investigations included immune markers for glomerular disease and renal biopsy. All serological tests (antinuclear antibodies, anti–double-stranded DNA, and antineutrophil cytoplasmic antibodies; antistreptolysin O titer; hepatitis C virus antibodies; hepatitis B surface antigen) and serum complement C3 and C4 levels were negative or normal. The kidney biopsy revealed a picture suggestive of *membranoproliferative glomerulonephritis* on light microscopy. However, electron microscopy did not show any dense deposits in either the basement membrane or the mesangium, and thus the picture was more consistent with *severe mesangial expansion (class IIb diabetic glomerular lesion) that is analogous to the previously used term* "*diffuse diabetic glomerulosclerosis*." Hypertension was controlled with combined losartan and amlodipine therapy. After 1 year, off-treatment ABPM showed normal 24 hours mean BP (107/69 mm Hg). Over the next 4 years, BP continued to be normal, proteinuria regressed to PMA, and eGFR was stable between 70 and 90 mL/min/1.73 m^2.

Diabetic eye disease presented as blurred vision almost at the same time of diagnosis of diabetic nephropathy. Fundus photography and fluorescein angiography confirmed the diagnosis of bilateral clinically significant macular edema (DME). This was treated with laser photocoagulation and intravitreal injection of VEGF-A (Avastin) for both eyes. It resolved quickly, followed 1 year later, by development of mild NPDR. No progression to more severe forms of retinopathy was found till closure of the study at 17 years after diagnosis.

When last seen, our patient was 32 years old. The psychological burden of long-standing diabetes was associated with high levels of depression and anxiety on the HADS and Generalized Anxiety Disorder 7-item (GAD-7) scale.

Case 5

Case 5 was 13 years old when presented with a recent diagnosis of diabetes, 2 months after a previous hospital admission for probable DKA with preserved consciousness. She was already injecting herself human premixed insulin twice daily under supervision of her father, but no SMBG was done. There was a family history of thyroid autoimmunity with her father having autoimmune thyroiditis and hypothyroidism and her younger sister having Graves disease and hyperthyroidism. As for diabetes, her maternal grandfather had older adult-onset type 2 diabetes.

In view of poor glycemic control, there were no hypoglycemic episodes during the initial 5 years of the disease. However, with improved glycemic control during the last 8 years of follow-up, and with gradual decline of residual endogenous insulin secretion, more hypoglycemic episodes 2 to 4 times per week were reported. Hypoglycemic episodes were mild during daytime and severe during night. Impaired awareness of hypoglycemia with low BG levels between 50 and 60 mg/dL without symptoms was also noted especially in the evening. Then, she agreed to shift to insulin analogues as basal-bolus regimen. Evidence of satisfactory long-term overall glycemic control was obtained from weighted mean (SD) (95% CI) HbA_{1c} value of 7.5 (1.6) (6.7-8.3)% [59 (17) (50-68) mmol/mol] of 17 visits over 22 years follow-up. The corresponding mean (SD) (95% CI) value of HbA_{1c}-derived eAG concentration over years of follow-up was 200 (60) (167-230) mg/dL [11.1 (3.3) (9.3-12.8) mmol/L]. The adjusted HbA_{1c}-SD over the number of visits during follow-up years was 1.55% (17 mmol/mol) denoting significant long-term variability of HbA_{1c} concentration over years of follow-up. The stimulated C-peptide, defined as UCPCR at 2 hours after the largest day meal was undetectable indicating a C-peptide negative status after 22 years duration.

First thyroid autoimmunity screen was performed at 6 years after diagnosis when she was 19 years old. As expected, there was a strongly positive TPOAb (>1000 IU/mL) with elevated TSH (20.7 μIU/L) vs normal FT4 (11.6 pmol/L), suggestive of chronic autoimmune thyroiditis and subclinical hypothyroidism. It progressed over time to overt hypothyroidism with levothyroxine dose adjustment based on TSH level monitoring.

Clinical follow-up and surveillance over 22 years after diagnosis of diabetes failed to show evidence of clinically significant microvascular complications. Eye screening was conducted every 1 to 2 years till the last visit without any sign of DR. Early cataract was reported in the left eye but not treated. There was mild diabetic nephropathy defined as CKD G2/A2 (eGFR: 75-88 mL/min/1.73 m^2, ACR: 50-60 mg/g) till the last visit at 22 years after diagnosis. There was no evidence of DPN over follow-up years.

Case 6

Case 6 was 17 years old when first diagnosed as having diabetes. There was severe hyperglycemia but no ketoacidosis at initial presentation. She was admitted to the hospital for a few days for control of BG and training on insulin injection. Among her close family members, only the maternal grandfather had old-onset type 2 diabetes. Since then, she is on regular annual follow-up in our center. Over the years of follow-up, she was adherent to twice daily premixed human insulin and regular insulin (Actrapid) at prelunch time, but infrequent SMBG. Hypoglycemic episodes were reported to be recurrent 2 to 3 times per week, claimed to be mild, during daytime and night. No history of increasing frequency or severity of hypoglycemia with increasing duration of the disease was found. Evidence of long-term overall strict glycemic control was obtained from weighted mean (SD) (95% CI) HbA_{1c} value of 6.9 (0.7) (6.5-7.6)% [52 (8) (48-56) mmol/mol] of 15 visits over 14 years follow-up. The corresponding mean (SD) (95% CI) value of

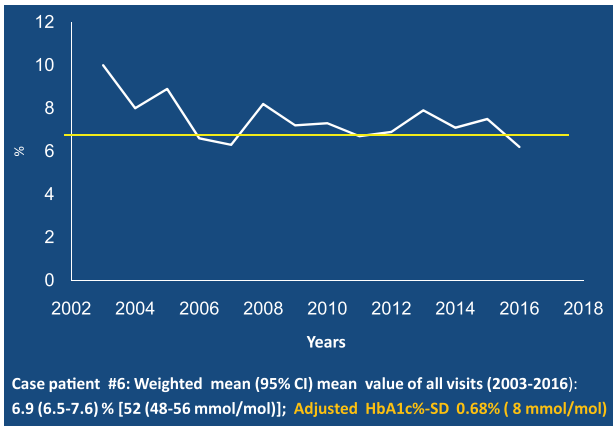

Figure 4. HbA_{1c} (%)—case 6. HbA_{1c} indicates hemoglobin A_{1c}.

HbA_{1c}-derived eAG concentration over years of follow-up was 167 (29) (151-183) mg/dL [9.3 (1.6) (8.4-10.2) mmol/L]. The adjusted HbA_{1c}%-SD over the number of visits during follow-up years was 0.68% (8 mmol/mol) denoting low long-term fluctuations of mean HbA_{1c}% over the years of follow-up (Figure 4). The C-peptide was measured as an index of endogenous insulin secretion at different durations of the disease. At time of diagnosis, FCP was <0.25 (0.2) nmol/L, a value suggestive of early (<3 years) T1D. Later in the course of the disease, the 2-hour postmeal UCPCR value was low <0.2 (0.035) nmol/mmol at 9 years and 0.02 nmol/mmol at 15 years after diagnosis indicating a residual but low endogenous insulin secretion.

Interestingly, this patient was negative for thyroid autoimmunity, and she was free from significant microvascular complications over 14 years of follow-up. She had annual eye screening till the last visit with no evidence of DR. Annual kidney screen used to show intermittent microalbuminuria (stage A2) during the first 9 years of the disease and then became persistent (PMA) during the last 5 years at 11 to 14 years after diagnosis with ACR value ranging between 93 and 102 mg/g (stage A2). The eGFR continued to be normal over the years of follow-up at (grade G1) with a value ranging between 94 and 107 mL/min/1.73 m^2. Neurologic assessment was conducted in each visit, with absence of subjective and objective features suggestive of a clinically meaningful diabetic neuropathy.

When exposed to psychometric and QoL tests, this case with good glycemic control and absence of significant microvascular complications had much less anxiety and depression score on the HADS and higher QoL score (0.65) on Ferrans and Power QoL index as compared with case no. 1 who had poorer glycemic control, severe PN with Charcot feet, and advanced retinopathy.

Discussion

We presented here 6 case studies that are rather patients' journeys with T1D from childhood or adolescence to adulthood. The long-term follow-up made it possible to understand their overall glycemic control, observe over time decline of β-cell function, and monitor the time of development and progression of microvascular complications. A recent scientific statement from the Endocrine Society notes that microvascular complications of diabetes result from interaction between systemic metabolic abnormalities such hyperglycemia, dyslipidemia, and genetic and epigenetic modulators and local tissue responses to toxic metabolites.[18]

Hemoglobin A_{1c} is the best characterized marker of long-term glycemic control in patients with diabetes that is strongly related to the development of diabetic complications. In the DCCT, 6.5 years of intensive treatment vs conventional treatment in T1D was associated with a significant reduction in incident retinopathy, nephropathy, and neuropathy.[19] The median HbA_{1c} at DCCT closure was 7% with intensive treatment and 9% with conventional treatment and rose to 8.0% in both groups over the years of the follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) study.[20] In a recent study from Sweden, Nordwall et al[14] found that in patients with T1D, keeping average HbA_{1c} below 7.6% (60 mmol/mol) as a treatment target can prevent both MAU and PDR for at least 20 years. Consistent with the results of Nordwall et al, we found in our study that weighted mean HbA_{1c} value more than 8% (64 mmol/mol) in cases 1, 2, 3, and 4 was associated with severe microvascular complications, whereas mean value less than 7.6% (60 mmol/mol) in cases 5 and 6 was associated with microalbuminuria only.

Glycemic variability, the long-term fluctuation of glycemia, determined by adjusted HbA_{1c}%-SD, is thought to be an HbA_{1c}-independent risk factor to the development of DR and nephropathy.[9] In the DCCT, HbA_{1c}%-SD was 0.59% in intensive treatment group vs 0.86% in convention treatment group.[9] Similarly, the adjusted HbA_{1c}%-SD in our study was equal or higher than that of conventionally treated group in the DCCT[9] in 5 cases who had severe microvascular complications, with the peak value in case 1 (2.3%), and the lowest value was slightly higher than that of intensively treated group in the DCCT[9] in case 6 (0.68%) who had microalbuminuria only.

Hypoglycemia is the commonest acute complication of T1D that results from interplay of relative or absolute insulin excess in the context of an array of factors such as food intake, exercise, and altered insulin sensitivity or clearance. It is best defined as a fall in BG level that exposes the patient with diabetes to potential harm.[21] Frequent hypoglycemic episodes were common in all cases with glucose alert values between 50 and 70 mg/dL (2.8-3.9 mmol/L), particularly during night and early morning time, with increasing trend with advanced duration and renal impairment.

Connecting peptide (C-peptide) is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion in patients with diabetes. It is a marker of insulin deficiency and has a greater utility further from diagnosis when rapid decline is less likely.[10] Most patients with long-duration T1D continue to secret very low levels of endogenous insulin, which increases after

meal, indicating the presence of a small number of functional β cells that have escaped immune attack or undergoing regeneration.[22] Recently developed ultrasensitive assays capable of detecting C-peptide under 0.03 nmol/L (UCPCR: ≥0.001-<0.03 nmol/L) now allow residual very low levels of C-peptide to be detected in patients with long-standing T1D.[23] In our case series, cases 1, 3, and 4 were insulin microsecretors at diabetes durations of 31, 17, and 13 to 17 years, respectively. Insulin secretion in case 3 declined more and became undetectable after further 6 years. In case 5, insulin secretion was first measured at 22 years after diagnosis and it was undetectable. Case 6 had a low-detectable insulin secretion at 9 years till the last clinic visit at 14 years after diagnosis. These findings are consistent with the T1D Exchange Clinic Network data suggesting that the frequency of residual C-peptide in patients with T1D decreases with time from diagnosis regardless of age at diagnosis.[24]

In our series of cases, diabetic eye and kidney diseases were rather the most common microvascular complications with worse outcomes. Severe diabetic neuropathy with Charcot neuroarthropathy was seen in 1 patient only. The occurrence of these complications in our cases might be attributed to poor BG control, glycemic variability, lack of regular clinical surveillance, and long duration of diabetes. Diabetic or metabolic cataract was reported in 3 patients and operated on in 2 patients. It occurred early at 4 years after diagnosis in case 1 and at 10 years after diagnosis in cases 3 and 5. Sorbitol accumulation in the lens, via polyol pathway, is believed to be the major cause in the development of diabetic cataract.[25]

All of the 4 patients reported here with vision-threatening retinal complications, defined as PDR and/or diabetic macular edema, were appropriately treated with subsequent stable retinal lesions. They had various degrees of visual impairment but no blindness. The possibility that long-term harms of raised glucose concentration are mediated through reduced capillary perfusion is suggested by a strong epidemiologic links between capillary changes in the retina and other microvascular complications.[26] In the DCCT/EDIC, optimizing glycemic control as early as possible was found to delay the onset and slow the progression of DR over many years of follow-up in patients with T1D.[27]

Each of the 4 patients reported here with severe DKD, defined as MAU, impaired glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2), or both, was associated with severe diabetic eye disease and had different renal outcomes. In case 1, PMA progressed over the last 6 years follow-up to MAU (ACR: 480 mg/g) combined with mild decline of eGFR to (57 mL/min/1.73 m^2) putting her in CKD G3a/A3. Case 2 with kidney failure died after first hemodialysis. Case 3 with MAU and CKD G3b has responded well to treatment with less albuminuria (ACR: 385 mg/g) and stability of CKD at grade G3b. Case 4 had rapid development of MAU, hypertension, and DME that resolved completely on treatment with regression of nephrotic range albuminuria to microalbuminuria and normalization of hypertension. In the DCCT/EDIC cohort, there was 3.2-fold higher risk of CKD MAU and 2.8-fold higher risk of CKD renal impairment associated with retinal disease vs nonretinal disease.[28] In the DCCT/EDIC, early intensive treatment of T1D also resulted in clinically important, durable reductions in the risks of microalbuminuria, MAU, impaired GFR, and hypertension.[29]

Clinically significant DPN has been reported in case 1 only. It progressed over the years of the disease from confirmed sensory PN, to left mid-rear Charcot neuroarthropathy, to right foot big toe ulcer, and ultimately right mid-foot Charcot neuroarthropathy. The risk factors behind limb complication were poor glycemic control and long duration of the disease. As with diabetic nephropathy, it was reported by one study that early microvascular dysfunction, evident in the retina, is an independent risk factor for DPN with 1.8-fold higher risk of incidence of DPN in patients with retinal changes vs no retinal changes.[30] Intensive therapy during the DCCT significantly reduced the risk of DPN at trial closure, with the prevalence and incidence of DPN remaining significantly lower in intensive therapy group vs conventional therapy group through EDIC year 13/14.[31]

There are a number of limitations that can be addressed in this case series study on T1D. First, the study is rather an observational follow-up of 6 cases. Second, the patients' clinic visits were not regular due to social and financial reasons. Third, lack of knowledge about diabetes and its complications has probably affected the attitude of patients and their families toward diabetes health care and follow-up.

In conclusion, worse microvascular outcomes of pediatric-onset T1D, especially severe diabetic eye and kidney disease, were noted among 4 of 6 of our cases during their young age of life. The reason was probably related to long-term poor glycemic control, lack of knowledge, and limited financial resources. In view of lifelong burden of diabetes, our young cases were adversely affected by depression and anxiety and low QoL, which can affect attitudes toward self-management, in turn, poor disease outcomes.

Author Contributions

AAG contributed to the following: planning, study design, examining the patients, data collection, statistical analysis of the data, and writing the manuscript.

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