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CLINICAL REPORT

Phimosis with Preputial Fissures as a Predictor of Undiagnosed Type 2 Diabetes in Adults

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Diabetes is usually asymptomatic in its early stage. Early diagnosis may improve outcomes by enabling initiation of treatment before end organ damage has progressed. The aim of this study was to determine whether the clinical sign of phimosis with preputial fissures is predictive of type 2 diabetes in patients not previously diagnosed with diabetes. Twenty-eight patients with acquired phimosis and preputial fissures were collected prospectively. Twenty-eight controls with acquired phimosis without preputial fissures were selected. Statistically significant differences were found in body mass index, random plasma glucose, glucosuria and glycosylated haemoglobin levels, but not in age, family history of diabetes, hypertension and classical hyperglycaemic symptoms. Diabetes was confirmed in all 28 patients in the preputial fissures group, but only 2 (7.1%) patients in the non-preputial fissures group ($p<0.0001$). In conclusion, phimosis with preputial fissures may be a specific sign of undiagnosed diabetes mellitus. ***Key words: diabetes; phimosis; preputial fissure.***

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Type 1 and type 2 diabetes mellitus (DM) is a common metabolic disease characterized by hyperglycaemia resulting from β-cell destruction and a progressive insulin secretory defect on the background of insulin resistance, respectively (1). The prevalence and incidence of DM is increasing epidemically; recent prevalence data from the USA suggests that DM is present in 9.6% of persons over the age of 20 years (2). The prevalence of DM increases with age (3). The attendant economic burden for healthcare systems is increasing rapidly, owing to the costs associated with treatment and diabetes complications (4). To reduce the cost and prevent diabetes complications, early diagnosis and intensive blood sugar control are of clear benefit (5). However, DM is usually silent in its initial stages, and irreversible complications may develop before the disease is recognized and treatment started (6); thus, early methods of detection are needed.

Diagnosis of diabetes is confirmed by blood testing, such as glycosylated haemoglobin (HbA1C) and fasting plasma glucose (7). To determine which subjects may benefit from testing for diabetes it is desirable to screen for clinical symptoms of the disorder. Polyuria, polydipsia, fatigue, and weight loss are common symptoms in people with DM; however, these symptoms are ambiguous and non-specific (1). More specific clinical signs would help expedite appropriate testing.

Many patients with diabetes develop cutaneous disease (8). Phimosis has been reported in association with diabetes since 1971 (9, 10). Balanitis and related phimosis may be present in up to 12% of newly diagnosed cases of diabetes (11, 12). Furthermore, diabetes is present in up to 22% of men with acquired and lifelong phimosis (13).

In 2007, a 47-year-old man with no personal history of diabetes presented to our urology clinic with itching, burning, and pain related to a contracted foreskin. Physical examination revealed phimosis with balanoposthitis and preputial fissures. Routine urinalysis revealed glucosuria. Blood HbA1C and random plasma glucose levels were 10.2% and 218 mg/dl, respectively. Based on our clinical observation, we hypothesized that phimosis with preputial fissures may be a highly specific finding that is predictive of undiagnosed diabetes in young men.

MATERIALS AND METHODS

Patient population

The study procedure was in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Chang Gung Memorial Hospital at Chiayi, Taiwan (104-0042B). From June 2010 to November 2014, data were prospectively collected on 28 men who were referred to our urology clinic for circumcision with a combination of acquired phimosis and preputial fissures (Fissure group). Twenty-eight men with acquired phimosis but no preputial fissures were selected as the control group (Non-fissure group). Exclusion criteria were: age under 20 years, previously diagnosed diabetes, other glycaemic disorder, and prior circumcision. Demographic data included: age, body mass index (BMI), family history of

diabetes (first-degree relative with diabetes), hypertension, and typical symptoms of hyperglycaemia (polyuria, polydipsia, fatigue and weight loss).

Biochemical evaluation

The subjects' random plasma glucose and HbA1C were measured immediately after they attended clinic, by assay of venous blood drawn by phlebotomy. The reference ranges of random plasma glucose and A1C levels were 70–140 mg/dl and 4.6–5.6%, respectively. Urine samples were tested for glucose immediately after the subject attended clinic, using the same commercial urine analysis machine.

Diabetes was diagnosed using any of the following criteria: (*i*) A1C $\geq$ 6.5%; (*ii*) symptoms of diabetes (polyuria, polydipsia, fatigue, weight loss) and a random plasma glucose level of $\geq$ 200 mg/dl (7).

Follow-up regimen

Patients were generally followed up 1 week after first attending the urology clinic, and then one month later. Follow-up consisted of physical examination of the phimosis and preputial fissures. All of the patients with newly diagnosed diabetes were referred to the endocrinology department for blood sugar control.

Statistical analysis

Fisher's exact test with χ^2 and *t*-tests were used for comparisons between groups in categorical and continuous variables, respectively. All statistical analyses were performed using Prism 6 (GraphPad Software, Inc. CA, USA). Data are given as means $\pm$ standard deviation (SD). Statistical significance was set at $p < 0.05$.

RESULTS

Representative phimosis with and without preputial fissures are shown in Fig. 1. The demographic characteristics of the patient population are summarized in Table I.

There were no significant differences between the 2 groups in terms of age, family history of diabetes, hypertension and hyperglycaemic symptoms. Mean BMI, random plasma glucose, and HbA1C levels were significantly higher in the Fissure group compared with the Non-fissure group. Routine urinalysis was positive for glucosuria in the Fissure (100%) and Non-fissure (10.7%) groups, and this was a significant difference ($p < 0.0001$). One subject in the Fissure group had a random plasma glucose level below 200 mg/dl, but his HbA1C was over 6.5%. All 28 patients in the Fissure group, but only 2 patients in the Non-fissure group, had A1C over 6.5%. Therefore, diabetes was confirmed in all 28 patients in the Fissure group compared with 2 in the Non-fissure group ($p < 0.0001$). Classical hyperglycaemic symptoms, such as polyuria (28.6%),

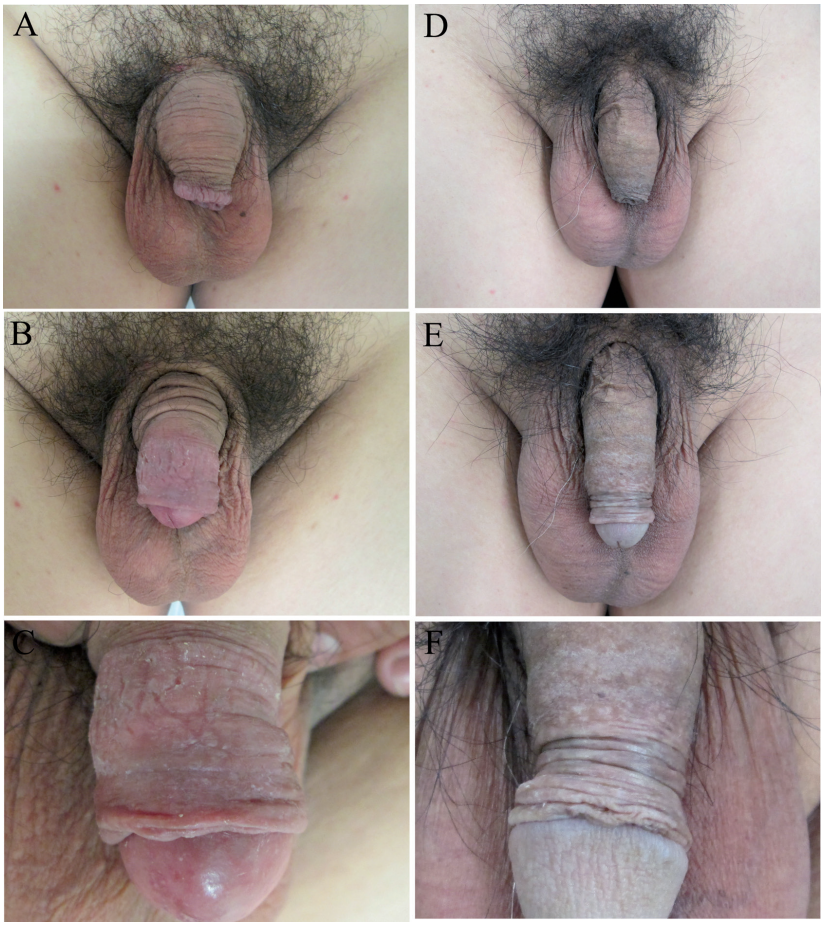

Fig. 1. Examples of phimosis with and without preputial fissures. (A–C) One patient with a combination of phimosis and preputial fissures: (A) erythema, oedema, maceration and vertical fissures circling the entire preputial ring in unretracted foreskin, (B) mild retracting foreskin, and (C) total retracting foreskin. (D–F) Another patient with phimosis without preputial fissures: (D) contracted foreskin without vertical fissures in unretracted foreskin, (E) mild retracting foreskin, and (F) total retracting foreskin.

Table I. *Baseline demographics, pre-diagnostic symptoms and biochemical characteristics*

	Fissure (*n*=28)	Non-fissure (*n*=28)	*p*-value
Age, mean ± SD (range)	40.9 ± 11.09 (26–66)	39.0 ± 12.76 (20–70)	0.5559
≥45 years, *n* (%)	11 (39.3)	8 (28.6)	0.5731
<45 years, *n* (%)	17 (60.7)	20 (71.4)	
Body mass index, kg/m^2, mean ± SD (range)	29.1 ± 3.96 (23.6–38.0)	26.6 ± 3.94 (19.6– 35.7)	**0.0458**
Family history of diabetes, *n* (%)	10 (35.7)	8 (28.6)	0.7753
Hypertension, *n* (%)	9 (32.1)	6 (21.4)	0.5472
Hyperglycaemic symptoms, *n* (%)[a]	17 (60.7)	13 (46.4)	0.4218
Polyuria	8 (28.6)	6 (21.4)	0.7585
Polydipsia	7 (25.0)	5 (17.9)	0.7458
Fatigue	8 (28.6)	7 (25.0)	1.0000
Body weight loss	4 (14.3)	1 (3.6)	0.3516
Glucosuria, *n* (%)	28 (100)	3 (10.7)	**<0.0001**
Random plasma glucose, mg/dl, mean ± SD	351.0 ± 114.5	106.5 ± 25.93	**<0.0001**
≥200 mg/dl, *n* (%)	27 (96.4)	0 (0)	**<0.0001**
<200 mg/dl, *n* (%)	1 (3.6)	28 (100)	
Glycosylated haemoglobin, mean ± SD, % (range)	11.1 ± 1.92 (6.8–14.8)	5.9 ± 0.97 (5.1–9.3)	**<0.0001**
≥6.5%, *n* (%)	28 (100)	2 (7.1)	**<0.0001**
<6.5%, *n* (%)	0 (0)	26 (92.9)	

[a]Patients presented with at least one of: polyuria, polydipsia, fatigue and body weight loss.
Random plasma glucose and glycosylated haemoglobin were measured immediately after attending clinic. Reference ranges of random plasma glucose and glycosylated haemoglobin were 70–140 mg/dl and 4.6–5.6%, respectively. Significant values are shown in bold.

polydipsia (25.0%), fatigue (28.6%) and body weight loss (14.3%), were individually uncommon, although 60.7% of patients in the Fissure group presented with at least one of these symptoms. All 30 patients with newly diagnosed diabetes were referred for consultation and follow-up at the endocrinology clinic. After blood sugar control, preputial fissures improved in 23 of the 28 patients in whom circumcision was not elected. Five of these 28 patients chose to have a circumcision, and the pathology of the prepuce was consistent with chronic inflammation and congestion.

DISCUSSION

Diabetes is usually asymptomatic in the early stage (14). Although classic hyperglycaemic symptoms and signs may be present in up to 89% of undiagnosed persons, we are unaware of any published data that is entirely specific for diagnosis of DM (12). In the present study, the incidence of diabetes in patients with undiagnosed diabetes with a combination of acquired phimosis and preputial fissures was 100%; this compares to a 7.1% incidence of diabetes in patients with acquired phimosis but no preputial fissures.

Accumulation of advanced glycosylated end-products in the foreskin tends to impair production of collagen and extracellular organization; this may progress to decreased skin elasticity, dehydration, increased hydroxyproline content and superoxide dismutase activity and impaired sebaceous gland function (15, 16). Stiff, inelastic foreskin, which is repeatedly retracted for urination and/or sexual intercourse, may fissure and cause further scarification, worsening the fibrotic process.

As the renal threshold of glucose excretion in healthy subjects is 180–200 mg/dl, it is important to analyse HbA1C whenever routine urinalysis reveals glucosuria (17).

Importantly, diabetes tends to be diagnosed most often in men over the age of 45 years (18). By the age of 45 years many diabetic men have probably had the condition for years and may already have experienced some end organ damage by the time of diagnosis. In our study cohort 60.7% of patients were under 45 years of age. Diagnosis of type 2 DM at this younger age makes early treatment possible and, over time, may lead to improved patient outcomes and reduced long-term costs (7).

Balanoposthitis and phimosis are common dermatological and urological disorders, and are usually managed symptomatically without considering a possible association with diabetes. Poor metabolic control may result in recurrent balanoposthitis and impede wound healing in general. Several studies have indicated that the overall rate of wound infection might be up to 10 times higher in patients with diabetes than in those without diabetes (19). Diagnosing DM in these men might not only reduce operative complications, but also prompt appropriate diabetic management and reduce the rate of recurrent balanoposthitis and long-term complications. It is therefore important to diagnose DM as well as to start intensive control of blood sugar before circumcision.

There are some limitations to this study. First, the number of men presenting with phimosis with fissuring is relatively small, as reflected by our acquisition of only 28 cases over a 4-year period. Secondly, the associations between the degree of preputial fissures and HbA1C

levels are unknown. Thirdly, questions remain about a lack of molecular data on the underlying mechanisms of tissue effect. However, to our knowledge, this is one of the more specific clinical signs of diabetes in young patients. Further studies on the role of diabetes in patients with phimosis and preputial fissures are warranted.

In conclusion, these results suggest that phimosis with preputial fissures is a specific sign of undiagnosed DM in young men. Patients presenting with phimosis and fissures should undergo blood testing for diabetes. Early diagnosis may help to prevent recurrent balanoposthitis and operative complications, and enable early management of diabetes, thus reducing long-term morbidity and expense.

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The authors declare no conflicts of interest.

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