Case Report

Long-term outcome of renal glucosuria type 0: the original patient and his natural history

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Introduction

Primary renal glucosuria (OMIM 233100) is defined by an increased urinary glucose excretion in a patient with a normal blood glucose concentration in whom all other filtered substrates are handled completely normally by the proximal tubules. Mild renal glucosuria is a relatively common condition that was first studied at the beginning of the last century [1], but it was not until 1987 that a study on a patient with virtual absence of renal tubular glucose reabsorption was published. This condition has been termed type 0 renal glucosuria [2]. Here we report on the long-term history of this patient whose underlying genetic defect has recently been identified [3,4].

Case

Patient P.M., a male of German descent, was born in Romania. His parents are distantly related; the maternal grandfather and the paternal great-grandfather were twins. Eczema developed when he was 1 year old. Glucosuria was first detected in the patient at the age of 11 years, as he had suffered from persistent nocturnal enuresis, polyuria, polydipsia and episodes of polyphagia. Extensive laboratory examinations at the age of 15 years revealed a daily glucose excretion in the range of 109–141 g (606–780 mmol) with normal blood glucose levels. His physical examination and a detailed analysis of other renal function tests were entirely normal. In particular, other renal tubular function parameters investigated, such as the clearance for sodium, potassium, chloride and phosphate, and the tubular reabsorption for free amino acids, were within normal limits. Finally, tubular proteinuria and enzynuria were not detected. Clearance determinations repeatedly showed virtual absence of net tubular glucose reabsorption (Table 1) and thus, this patient was the first to be described in the literature as having 'renal glucosuria type 0' [2].

We reinvestigated this patient 20 years after his first presentation at an age of 31 years. Meanwhile, the basic molecular defect of the patient’s condition has been identified. He was found to be homozygous for a 5 bp deletion (973–7 del ATGTT) within exon 8 of the recently characterized SGLT2 gene [3,4]. Both parents had very mild but constant glucosuria and were heterozygous for the 5 bp deletion. This mutation predicts a frame shift, a premature stop of translation, and a truncated, non-functional SGLT2 protein [4].

On re-evaluation, the past medical history was unremarkable. Although the patient continued to suffer from endogeneous eczema, he was in good clinical condition and his physical examination was otherwise normal. He had had a marked constitutional delay of statural growth and puberty, but he reached a final body height of 175 cm (Figure 1). His weight was 74 kg and he had a blood pressure of 125/85 mmHg. On a regular daily fluid intake of 3–5 l and at blood glucose levels within the normal range, the patient continued to have a urinary glucose excretion that was highly elevated [38.7 g/l (215 mmol/l)]. Further laboratory analyses gave normal plasma concentrations for sodium (135 mmol/l), potassium (4.4 mmol/l), chloride (102 mmol/l), calcium (2.31 mmol/l), phosphate (1.21 mmol/l), bound urea nitrogen (5.2 mmol/l) and creatinine (57 μmol/l). Hypokalaemia or hyponatraemia were never detected. Analyses of spot urine samples showed a potassium concentration of 36 mmol/l, sodium was 146 mmol/l, bound urea nitrogen 1.43 mmol/l and creatinine 3.5 mmol/l. The calcium/creatinine ratio was slightly elevated (1.07 mmol/mmol creatinine, normal: <0.57). Maximal tubular phosphate-reabsorption according to Brodehl et al. [5] was normal (1.09 mmol/l, normal: >1.0). His creatinine clearance at the last follow-up was normal (135 ml/min/1.73 m² accord-
Renal glucosuria type 0

Table 1. Laboratory findings in patient P.M.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Urine glucose (g/l)</th>
<th>Plasma glucose (mg/dl)</th>
<th>Urine creatinine (mmol/l)</th>
<th>Plasma creatinine (mmol/l)</th>
<th>( C_{\text{in}} ) (ml/min/1.73 m²)</th>
<th>( C_{\text{crea}} )</th>
<th>( C_{\text{crea}}' )</th>
<th>( C_{\text{glc}} ) (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.3</td>
<td>77.2</td>
<td>429</td>
<td>75</td>
<td>4.2</td>
<td>5.1</td>
<td>39</td>
<td>153, 148</td>
<td>218</td>
</tr>
<tr>
<td>18.1</td>
<td>55.4</td>
<td>309</td>
<td>86</td>
<td>4.8</td>
<td>3.8</td>
<td>36</td>
<td>n.d.</td>
<td>231</td>
</tr>
<tr>
<td>31.0</td>
<td>38.7</td>
<td>215</td>
<td>77</td>
<td>4.3</td>
<td>3.5</td>
<td>57</td>
<td>n.d.</td>
<td>155</td>
</tr>
</tbody>
</table>

\( C_{\text{in}} \) = inulin clearance; \( C_{\text{crea}} \) = endogenous creatinine clearance; \( C_{\text{crea}}' \) = creatinine clearance according to Schwartz et al. [10]; \( C_{\text{glc}} \) = endogenous glucose clearance; n.d., not determined.

Fig. 1. Statural growth of P.M. in comparison to normal German males. Dots represent measured height at a certain age and the diamond represents the patient’s bone age for the respective height. (Note that the patient’s height given in reference 2 should be corrected.)

Table 1. Laboratory findings in patient P.M.

Discussion

Type 0 glucosuria is defined by the complete absence of renal tubular glucose reabsorption and it is the most severe variant of primary renal glucosuria. It has been shown recently that renal glucosuria type 0 results from non-functioning mutations within the \( SGLT2 \) gene [4]. This gene codes for one of the ‘active’ glucose transporters within the apical membrane of epithelial cells of the proximal tubulus. The fact that a loss of function of this transporter results in no residual glucose reabsorption demonstrates the pivotal role of \( SGLT2 \) in renal glucose handling. The results of molecular genetic investigations in this family confirm an idea already formulated in the original report. The suspicion ‘that the propositus might be homozygous and the parents (with mild glucosuria)... heterozygous for the mutant gene’ [2] has proved to be correct. Thus, renal glucosuria due to \( SGLT2 \) defects indeed shows characteristics of a co-dominant trait with variable penetrance [4], as shown in 21 families with 21 different mutations. In contrast, Van den Heuvel et al. [7] concluded that in one patient renal glucosuria was attributable to an autosomal recessive trait.

A urinary glucose excretion similar to renal glucosuria type 0 can be found in only a few conditions; among them are diabetes mellitus and the Fanconi–Bickel syndrome (FBS). The pathophysiological mechanisms and the long-term outcome in the latter two diseases, however, differ from renal glucosuria type 0. Glucosuria in diabetes mellitus results from a markedly increased tubular glucose load that is above the normal tubular transport maximum for glucose. FBS is caused by an impaired function of the GLUT2 protein that normally facilitates glucose efflux at the basolateral membrane of tubular cells. This defect leads to an accumulation of free glucose and glycogen within the proximal tubular cell. Due to a mechanism not yet fully understood, this results in a generalised proximal tubulus dysfunction (the de Toni–Debré–Fanconi syndrome) with disproportionally severe glucosuria [8,9].

It is well known that with diabetes mellitus nephrological complications correlate well with the degree of metabolic control and with glucosuria and that, ultimately, glomerulosclerosis and renal failure may develop. Although rare, patients with FBS may also develop renal damage similar to diabetic nephropathy [10]. From the long-term follow-up of our patient, we conclude that glucosuria per se is not a causative factor for the development of renal changes. Even after more than 30 years of persistent glucosuria, there were no signs of hyperfiltration syndrome or of microalbuminuria in this patient. The only functional change in the kidneys in renal glucosuria type 0 was polyuria.

Primary renal glucosuria has been considered a ‘non-disease’ with an excellent prognosis. This is also
acknowledged by the fact that ‘benign glucosuria’ has been used as a synonym in many textbooks [11], but until now no long-term observations have been reported. Only very rarely has a propensity to hypovolaemia and hypoglycaemia been discussed in such patients. Our case report demonstrates that even extreme glucose loss which is characteristic for the type 0 variant of renal glucosuria has a favourable prognosis. We can only speculate whether glucose loss may result in a chronic caloric deficit and secondary hormonal changes which could be responsible for the markedly delayed growth and pubertal development observed in our patient, but to answer this question, studies in a larger patient group will be necessary. We conclude that chronic nephrologic complications do not have to be anticipated in patients with renal glucosuria.

Conflict of interest statement. None declared.

References


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