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RETHINKING GLYCEMIC THRESHOLDS: DIABETIC KIDNEY DISEASE IN THE ABSENCE OF OVERT DIABETES

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ABSTRACT

Diabetic kidney disease is traditionally regarded as a complication of chronic hyperglycaemia associated with diabetes. However, the relationship between glycaemic thresholds and the development of diabetic kidney disease is increasingly questioned. We present a case of a 69-year-old woman with progressive renal dysfunction and biopsy findings suggestive of diabetic kidney disease, despite repeatedly normal glycosylated haemoglobin (haemoglobin A1c) and without a clinical diagnosis of diabetes or pre-diabetes. This case highlights the limitations of current haemoglobin A1c thresholds and raises the question of whether diabetic kidney disease can truly develop in the absence of diabetes. Stricter glycaemic criteria may help identify at-risk patients earlier and prevent renal complications.

KEYWORDS

CKD management, diabetic kidney disease, diabetic nephropathy, diabetes, endocrinology

LEARNING POINTS

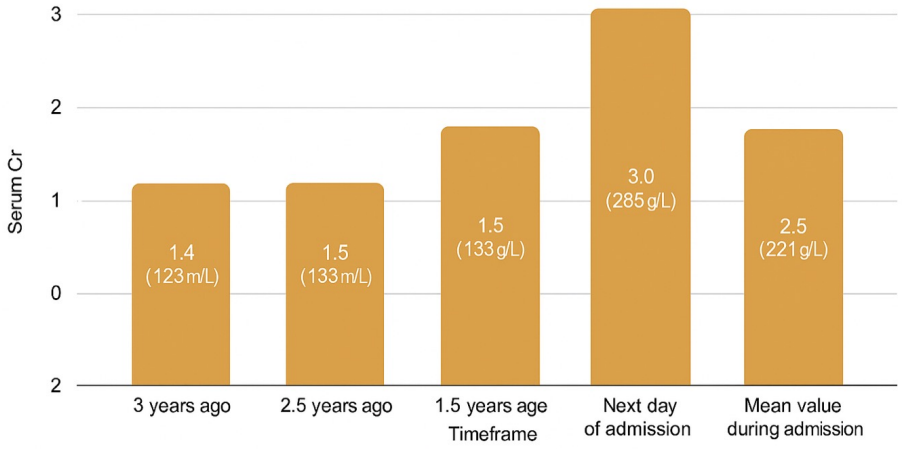
- Diabetic kidney disease can occur without overt diabetes or pre-diabetes, challenging current diagnostic methods.
- Reliance on haemoglobin A1c alone may miss at-risk individuals, and stricter glycaemic thresholds may be warranted.
- The diagnosis of diabetic kidney disease in normoglycemic patients challenges disease definitions and pathogenesis.

INTRODUCTION/BACKGROUND

Diabetic kidney disease (DKD) is a known complication of chronic poorly controlled hyperglycaemia in diabetics. Presently, diagnostic protocols employ established glycaemic thresholds, such as haemoglobin A1c, to ascertain at-risk individuals. However, emerging evidence suggests DKD may develop without overt diabetes or pre-diabetes, challenging traditional assumptions about disease pathogenesis and

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Abbreviations: Cr, creatinine.

Figure 1. Graphical demonstration of renal function expressed in serum creatinine values over the past 3 years to current period express in mg/dl.

diagnostic criteria [1]. This article presents a case in which biopsy-proven DKD occurred in a patient with repeatedly normal hemoglobin A1c and glucose levels, highlighting the limitation of current glycaemic thresholds, and a need for an individualized approach to identify high risk individuals [2].

CASE DESCRIPTION

A 69-year-old woman was evaluated in the inpatient setting for progressive renal dysfunction after routine laboratory testing revealed a serum creatinine of 269 µmol/l and blood urea nitrogen of 30.7 mmol/l. She reported intentional weight loss of 7.7 kg and increased urinary frequency, but denied polydipsia, polyuria, or other symptoms suggestive of diabetes. Her past medical history included gastroesophageal reflux disease on a proton pump inhibitor and a remote history of smoking. She denied alcohol consumption, engaged in moderate exercise, primarily walking for 20-30 minutes, approximately 5 days per week. She has no history of acute or chronic blood loss anaemia, no personal history of blood transfusions, or chronic liver disease.

On examination, her blood pressure was 111/59 mmHg, and her body mass index was 21.2 kg/m^2. Physical examination revealed an anxious but non-distressed patient with clear bilateral lung sounds and normal cardiac auscultation without murmurs. No pedal oedema was present. Laboratory findings included mild hyperglycaemia (7.8 mmol/l) on admission, hypokalaemia (2.8 mmol/l), and normocytic anaemia (haemoglobin 110 g/l). Importantly, her haemoglobin A1c was 38 mmol/mol (5.6 mg%) on two separate occasions, 3 months apart. Fasting plasma glucose was 5.2 mmol/l, and postprandial glucose measured during hospitalization was 6.7 mmol/l, both within normal limits. Continuous glucose monitoring was not performed, but no random glucose values exceeded 7.8 mmol/l during her admission. Urinalysis revealed trace proteinuria, and the urine albumin-to-creatinine ratio was 23 mg/mmol. A comprehensive list of the laboratory values is shown in *Table 1*. Given her history of decreased oral intake, low blood pressure, and relevant lab findings, prerenal acute kidney injury was suspected. Admitted for evaluation and management, telemetry monitoring was initiated. Intravenous (IV) 0.9% normal saline at 100 ml/h was started for 24 hours. A renal ultrasound was scheduled, with the patient nil per oral (NPO) from midnight. Nausea and pain control were provided as needed.

On the second hospital day, the patient remained clinically stable but reported no significant improvement in symptoms. She was euvolemic on examination, though her blood pressure had decreased to 90/60 mmHg; however, she reported that her baseline blood pressure was in that range. Given her persistent hypotension, midodrine 0.5 mg three times daily was initiated for blood pressure support, and strict intake and output monitoring were continued. Renal ultrasound revealed medical renal disease with a left kidney measuring 8.1 cm. The right kidney was not well visualized. If renal function failed to improve, a non-contrast computed tomography (CT) scan of the abdomen and pelvis was planned to better assess the right kidney.

Subsequent laboratory workup revealed persistent renal dysfunction with a creatinine level of 238.7 µmol/l (2.7 mg/l), which trended downward and stabilized around 221 µmol/l (2.5 mg/dl). Additional findings included phosphorus of 1.07 mmol/l (3.3 mg/dl), and parathyroid hormone (PTH) of 116 pg/ml. Given the incomplete visualization of the right kidney on ultrasound, a non-contrast CT abdomen and pelvis was performed, revealing a left kidney measuring 10.1 cm and a right kidney measuring 8 cm, consistent with underlying chronic kidney disease (CKD).

A comprehensive review of the patient's medical records revealed a gradual deterioration in kidney function over a 3-year period. Creatinine levels, which were 123.8 µmol/l (1.4 mg/dl) 3 years prior, 132.6 µmol/l (1.5 mg/dl) 2.5 years prior, and 141.4 µmol/l (1.6 mg/dl) 1.5 years prior, had progressively increased to 265.2 µmol/l (3 mg/dl) upon admission. Considering the patient's stable creatinine levels after fluid restriction and clinical improvement, the nephrology team recommended outpatient follow-up. *Fig. 1* show the trend of renal function in terms of serum creatinine from the patient's records.

To investigate the cause of the patient's renal disease, an immunologic workup was conducted. Serologies, such as antinuclear antibody (ANA), glomerular basement membrane (GBM) antibody, rheumatoid factor, myeloperoxidase

Lab parameter	Value (SI Units)	Value (US units)
White blood cell count	6.1 ×10⁹/l	6.1 ×10³/µl
Haemoglobin	110 g/l	11 g/dl
Platelet count	287 ×10⁹/l	287 ×10³/µl
Sodium	137 mmol/l	137 mmol/l
Potassium	3 mmol/l	3 mmol/l
Chloride	91 mmol/l	91 mmol/l
Bicarbonate	37 mmol/l	37 mmol/l
Blood urea nitrogen	23.9 mmol/l	67 mg/dl
Creatinine	269 µmol/l	3.05 mg/dl
Calcium	2.02 mmol/l	8.1 mg/dl
Protein (total)	60 g/l	6 g/dl
Bilirubin (total)	5.1 µmol/l	0.3 mg/dl
Alkaline phosphatase	79 U/l	79 U/l
Alanine transaminase	17 U/l	17 U/l
Aspartate transaminase	21 U/l	21 U/l
Magnesium	0.86 mmol/l	2.1 mg/dl
Phosphorus	1.55 mmol/l	4.8 mg/dl
Arterial blood gas (pH)	7.38	7.38
PCO_2	6.64 kPa	49.8 mmHg
PO_2	15.9 kPa	119 mmHg
Cholesterol (total)	4.5 mmol/l	174 mg/dl
Triglycerides	1.44 mmol/l	127 mg/dl
High density lipoproteins	2.20 mmol/l	85 mg/dl
Urine colour	Yellow	Yellow
Urine pH	5.5	5.5
Urine specific gravity	1.02	1.02
Urine appearance	Clear	Clear
Urine Protein	0.4 g/l	40 mg/dl
Urine albumin present/absent	present	present
Urine microalbumin/ creatinine ratio	23 mg/mmol	204 µg/mg
Urine glucose	negative	negative
Urine red blood cells/hpf	0	0
Urine WBC/hpf	0	0
Urine casts	none	none
Urine bacteria/hpf	0	0
Urine east/hpf	0	0
Urine nitrites	negative	negative
Urine leukocyte esterase	negative	negative

Table 1. Laboratory tests done at time of presentation.

(MPO) antibody, and proteinase 3 (PR3) antibody, were all negative. Additionally, complement levels were within the normal range (C3: 76 mg/dl, C4: 31 mg/dl). Hepatitis serologies were also negative. A repeat urinalysis revealed trace proteinuria, but otherwise unremarkable. Considering the asymmetric kidney sizes and the unexplained renal dysfunction accompanied by proteinuria despite two sets of normal haemoglobin A1c of 38 mmol/mol (5.6 mg%) – the second one being repeated outpatient in 5 weeks (from initial presentation), a left renal biopsy was performed after shared decision-making with the patient. Renal biopsy revealed arterial hyalinosis, interstitial fibrosis, and tubular atrophy, while preserving the luminal structure. Scanning electron microscopy demonstrated minor podocyte injury changes, consistent with diabetic nephropathy, but without the presence of Kimmelstiel-Wilson nodules.

These findings suggested the diagnosis of diabetic kidney disease (DKD) in the absence of overt diabetes. Consequently, the patient was initiated on empagliflozin for the management of DKD and had outpatient follow-up.

DISCUSSION

This case presents a diagnostic conundrum: can DKD develop in the absence of diabetes or pre-diabetes? The patient's haemoglobin A1c was 38 mmol/mol (5.6 mg%) on two occasions, below the established thresholds for both pre-diabetes (39–47 mmol/mol or 5.7-6.4 mg%) and diabetes (≥48 mmol/mol ≥6.5 mg%). Fasting and postprandial glucose levels were consistently normal, and there was no clinical evidence of hyperglycaemia. While mild hyperglycaemia was noted on admission, this was not persistent and could be attributed to acute illness. Thus, by current diagnostic criteria, the patient did not have diabetes or pre-diabetes.

The reliance on haemoglobin A1c as the primary marker for diagnosing diabetes and its complications is widespread, but not without limitations. Haemoglobin A1c reflects average glycemia over the preceding 2–3 months and may miss intermittent hyperglycaemic spikes or postprandial excursions[3]. However, in this case, repeated haemoglobin A1c and glucose measurements did not suggest undiagnosed dysglycaemia. Furthermore, CKD can sometimes lower haemoglobin A1c due to reduced red cell lifespan, but this typically becomes significant only at advanced stages, and there was no evidence of haemolysis or other confounders in this patient[4].

The central question, therefore, is whether our current glycaemic thresholds are too high, potentially missing individuals at risk for microvascular complications such as DKD. Recent studies have shown that even individuals with pre-diabetes (haemoglobin A1c 39–47 mmol/mol or 5.7 to 6.4 mg%) may develop early kidney dysfunction, suggesting that renal injury may begin at lower glycaemic levels than currently recognized[2]. However, our patient's haemoglobin A1c remained below even these revised thresholds, raising the possibility that the pathogenesis of DKD may not be exclusively glycemia-dependent, or that

current cutoffs are overly lenient. The ADVANCE study suggests that below haemoglobin A1c levels of 48 mmol/mol (or 6.5 mg%), there was no significant change in the risks for the development of kidney complications[3]. However, other research indicates that the risk for reduced kidney function can linearly increase with rising haemoglobin A1c levels, with a turning point at haemoglobin A1c of 47 mmol/mol (or 6.4 mg%)[2]. This discrepancy highlights the ongoing debate about appropriate glycaemic thresholds for predicting renal complications.

It is also important to note that DKD is not the only renal disease that can affect patients with diabetes. Studies have shown that non-diabetic renal disease can occur in patients with diabetes, with prevalence rates ranging from 35.3 to 52.9% in biopsied patients[5]. While our patient did not have diabetes by current definitions, the histopathological findings were consistent with DKD, raising questions about the relationship between glycaemic status and renal pathology.

Alternatively, the histological findings of "diabetic nephropathy" in normoglycemic patients may reflect overlapping mechanisms, such as insulin resistance, hypertension, or metabolic syndrome, which can produce similar renal lesions[1]. However, this patient was not obese, and her blood pressure was in the normal range. The absence of other causes after an extensive workup further supports the diagnosis of DKD. Recent research has identified new molecular pathways, including those related to insulin resistance and epigenetic changes, that may contribute to DKD even in the absence of overt hyperglycaemia[1].

Another important consideration is the growing recognition of nonalbuminuric DKD pathways. Studies have demonstrated that many patients with diabetes can follow a nonalbuminuric pathway to renal function loss[7]. Our patient had only trace proteinuria, suggesting that traditional markers of DKD may not always be present, further complicating the diagnostic process.

Therapeutically, SGLT2 inhibitors are increasingly recognized as beneficial for both diabetic and non-diabetic CKD, offering renoprotection beyond glycaemic control[8,9]. Real-world evidence confirms their beneficial effect on the decline of glomerular filtration, even in the absence of albuminuria[8]. This supports our decision to initiate empagliflozin in this patient, despite her not meeting criteria for diabetes.

This case underscores the need to re-examine the adequacy of current haemoglobin A1c thresholds for diagnosing diabetes and its complications. It is possible that individuals with "high-normal" glycemia may be at risk for DKD, or that renal injury can occur via non-glycaemic pathways that mimic diabetic nephropathy histologically. Either way, the concept that one can have a complication of a disease they do not have is inherently problematic, and calls into question the sufficiency of our diagnostic criteria.

Laboratory reference ranges are typically established using data from large populations of presumed healthy individuals, defining what is considered "normal" for the general population[10,11]. However, these ranges are statistical constructs that may not account for individual variability due to genetics, comorbidities, or unique physiological states[10]. As a result, values falling within the reference range may not necessarily be optimal or "normal" for every individual, just as values outside the range do not always indicate pathology. This subjectivity in defining normality underscores the limitation of applying population-based reference intervals to individual patients and highlights the need for personalized interpretation of laboratory results[11].

CONCLUSIONS

This case highlights the limitations of current glycaemic thresholds in identifying patients at risk for DKD. Despite repeatedly normal haemoglobin A1c and glucose levels, our patient developed biopsy-proven DKD, challenging the notion that DKD cannot occur without diabetes. We suggest that current haemoglobin A1c cutoffs may be too lenient, and that stricter or more nuanced criteria are needed to identify at-risk individuals. Further research is required to clarify the relationship between glycemia and DKD, and to determine whether lowering diagnostic thresholds could improve early detection and prevention of renal complications.

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