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Haemoglobin as a marker of fibrosis in early diabetic kidney disease

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Diabetes prevalence reaches 8% of the global population, and this number is projected to increase over the coming years. Approximately 40% of patients with diabetes will develop chronic kidney disease (CKD), and diabetes is still the leading cause of end-stage renal disease (ESRD) worldwide. By definition, diabetic kidney disease (DKD) designates any type of CKD during diabetes. Early identification of rapid progressors is particularly important to adjust the treatments and follow-up, and to adequately inform our patients. To date, clinical practice relies mostly on urinary albumin/creatinine ratio and creatinine-based equations to both define and classify DKD. However, creatinine-based estimated glomerular filtration rate (eGFR) equations are influenced by non-renal determinants and sometimes lack accuracy. Also, they do not reflect early tubulointerstitial damage, since creatinine elevation occurs after the loss of more than half of kidney mass [1]. Other biomarkers than serum creatinine can be used, for example, cystatin C, which is not influenced by muscle mass and shows a better outcome prediction, but its routine use is still limited and it fails to detect early DKD [2]. Beta-2-microglobulin has also been proposed, and could better reflect tubular function, but is also influenced by other diseases [3]. In diabetic populations, studies about inflammatory biomarkers such as soluble tumour necrosis factor receptors or interleukin-18, or tubular markers such as lipocalin (NGAL) or KIM1, have shown promising results, but their use in daily clinical practice is limited [4]. Of course, albuminuria is to date the best marker of renal risk. However, up to 40% of DKD patients can demonstrate substantial loss of renal function in the absence of albuminuria [5].

To assess the individual risk of ESRD in CKD, some scoring systems have been developed. The kidney failure risk equation addresses mostly more advanced renal disease and the 5-year risk of dialysis. Specifically, in DKD, several prognosis factors have been described for renal function loss, such as age, sex, body mass index, eGFR, albuminuria, microvascular complications, glycated haemoglobin, vitamin D and blood pressure control [4]. Smaller prospective studies have previously tested haemoglobin in DKD progression prediction in Types 1 and 2 diabetes, with some hints that it could add to the prediction independently of eGFR. In a prospective observational study following 227 Type 2 diabetes patients, baseline haemoglobin was predictive of DKD progression, as defined by doubling of serum creatinine or ESRD [6]. In another prospective study focusing on 174 patients with Type 1 diabetes, higher haemoglobin levels correlated with lower ESRD rate [7], and similar results were found in a smaller study with Type 1 diabetes from Morocco [8].

Anaemia is a well-known complication of DKD. DKD differs from CKD in anaemia prevalence, with an earlier decline of haemoglobin levels [9]. Anaemia in CKD and DKD is multifactorial—related to inflammation, relative iron deficiency and mostly defective renal erythropoietin (EPO) production [10] (Figure 1). Defective EPO production is probably multifactorial but may be caused by a phenotype change of peritubular renal fibroblasts [renal EPO-producing cells (REP cells)], which transdifferentiate into myofibroblasts and partly lose their ability to produce EPO [11], explaining some association with kidney fibrosis. However, myofibroblasts have a remaining capacity to produce EPO during severe anaemia, and it seems that other regulatory pathways are at play. As EPO production is regulated by the hypoxia-inducible factor 2 (HIF-2α), some observations suggest that there may be an insufficient HIF activation during CKD [12], and HIF stabilizers are now commercialized for renal anaemia treatment. In DKD specifically, one study showed that HIF activation was only transient during early stages of DKD in a rat model [13]. Glucose levels could also hinder the HIF-mediated response to hypoxia and may modify kidney metabolism, itself related to kidney fibrosis [14]. The origin of anaemia in DKD is therefore complex, but is likely due to a global metabolic and cellular change in tubulointerstitial cells, explaining a link between anaemia and kidney structural lesions.

The study by Yamanouchi *et al.* [15] is based on a national Japanese cohort of biopsy-proven DKD and focuses on 242 patients with early-stage DKD, selecting patients with an eGFR >60 mL/min/1.73 m^2. The study describes the association between haemoglobin levels and renal histological lesions in this population, mostly interstitial fibrosis. Although as expected, eGFR displayed the highest association with interstitial fibrosis, haemoglobin ranked a close second. Importantly,

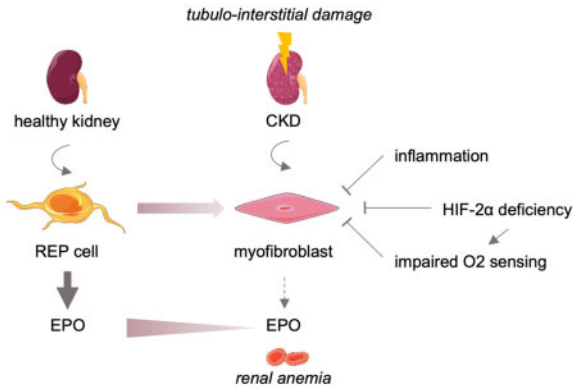

FIGURE 1: Potential link between tubulo-interstitial damage and renal anaemia. Physiologically, REP cells adapt their production to the systemic needs. During CKD, REP cells transdifferentiate into myofibroblasts, losing partly their ability to produce EPO. Inflammation, HIF-2α deficiency and impaired oxygen sensing participate in this process, aggravating further the EPO deficiency.

haemoglobin was shown to predict a worse evolution defined as ESRD or creatinine doubling, in an additive manner to eGFR and albuminuria. Using a multivariable Cox regression model, the risk of DKD progression was improved by the addition of haemoglobin to known risk factors.

The major strength of the study relies on the inclusion of DKD patients at early stages of the disease, with the realization of a kidney biopsy. In these early stages, it is very difficult to estimate the risk of progression, and histology is very rarely available. The correlation between haemoglobin levels and interstitial fibrosis may be explained given the pathophysiology of renal anaemia, but its strength is important and supports the previously developed pathophysiological hypothesis on anaemia in CKD. Haemoglobin is usually obtained in every routine laboratory performed in DKD patients and is a cheap marker to identify patients with early interstitial fibrosis. The study also confirms an important role of anaemia in risk identification in this population, as suggested by previous studies. Adding anaemia to risk equations could be implemented easily in clinical practice and could increase the sensitivity of identification of high-risk patients, and also enable nephroprotective treatment to be introduced and the follow-up to be adapted. Finally, an important population is probably the population of non-albuminuric DKD. In these specific patients, the value of an identification marker of early structural lesions would even be greater than in the albuminuric population, to detect tubulo-interstitial fibrosis at an early stage and to identify patients at most risk of progression. In the present study, haemoglobin levels also appeared discriminant in this subgroup, although the number of patients was low.

Many questions nevertheless remain unanswered. The population of the study is very homogeneous, which may preclude generalization to other clinical settings. As the authors recognize, gender bias may be a problem here, and the accuracy of haemoglobin as predictive was lower in women. In some widely used clinical risk scores, albumin, phosphate, calcium, glycated haemoglobin, blood pressure and bicarbonate were also additive to eGFR and albuminuria for prognosis. The value of haemoglobin in comparison with these other factors also deserves more studies. Similarly, as inflammation is often a cause of anaemia, the inclusion of CRP would have been interesting.

Nevertheless, this study highlights a new and easy-to-use laboratory value for risk identification in early DKD. Loss of haemoglobin may be an early marker of fibrosis and a prognostic tool independent of eGFR and albuminuria in this population. This needs to be replicated in other settings, but certainly underlines some important pathophysiological aspects of the anaemia of DKD, and a new prognostic tool that could easily be developed for routine clinical use.

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CONFLICT OF INTEREST STATEMENT

None declared.

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