Screening for anaemia as part of an annual diabetes review: Is it needed?

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The prevalence and implications of anaemia in people with diabetes have both been gaining increased attention in primary care. For the clinician at the coal face of diabetes care, the ultimate concern is whether haemoglobin counts should be included as part of the routine work-up at 6- or 12-monthly reviews. This is, however, not as straightforward a decision as it might seem at first and is something that I feel requires closer scrutiny.

Evidence from clinical studies

Several studies have been published that shed some light on whether we should be considering haemoglobin screening as a part of people's annual diabetes review. The largest, and therefore the most relevant, study is the TAD (Teesside Anaemia in Diabetes) study (Jones et al, 2010). This investigated the prevalence of anaemia in a prospective, population-based sample stratified by estimated glomerular filtration rate (eGFR). Anaemia was defined using the World Health Organization criteria: <13 and <12 g/dL for men and women, respectively. The study found that previously undiagnosed anaemia was present in 15% of the total study population, 35% of those with an eGFR <60 mL/min/1.73 m^2 and 9% of those with an eGFR >60 mL/min/1.73 m^2. This anaemia was shown to be caused by erythropoietin deficiency or abnormal haematinics, respectively, in 34% and 40% of those with identified anaemia and was unexplained in the remaining 26%. Interestingly, nearly one in 11 people with both diabetes and an eGFR >60 mL/min/1.73 m^2 were anaemic. As a result of this, it was suggested that screening for anaemia should be included in annual diabetes reviews as it frequently remains undetected at present.

The relationship between anaemia and renal disease highlighted by this study requires further discussion. Erythropoietin is a glycoprotein produced predominantly from the peritubular fibroblasts of the renal cortex that plays a key role in the maintenance of red blood cell mass. In people with renal impairment, the loss of erythropoietin secretion is considered to be the key factor leading to anaemia. However, there are other causes of anaemia in people with renal disease, including shortened red blood cell life-span, impaired erythropoiesis secondary to toxic metabolites or increased bleeding because of defective platelet function (Bosman et al, 2001). Interestingly, one other cause of anaemia in people with diabetes could be the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which are both known to lower the concentration of haemoglobin (Astor et al, 2002; Mohanram et al, 2008).

Anaemia worsens as renal function diminishes, and anaemia itself is associated with a more rapid decline in renal function (Jones et al, 2010). Furthermore, of particular pertinence to people with diabetes is the fact that anaemia should be considered to be a modifiable cardiovascular risk factor, which probably occurs through a strong association with left ventricular hypertrophy.

The particular relevance of the TAD study is that current UK recommendations for anaemia in chronic kidney disease (CKD) suggest that only people with CKD stages 3, 4 or 5 should be screened (NICE, 2006). Moreover, CKD is common in people with diabetes, occurring in approximately one-third of them (Middleton et al, 2006). The authors of the TAD study, therefore, suggest that the screening threshold for anaemia as a complication of CKD should be reviewed, and perhaps lowered, especially

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for people with diabetes. This is because current clinical surveillance in the UK would not detect the 9% of people, suggested by this study, who have both diabetes and anaemia, and an eGFR >60 ml/min/1.73 m^2.

Another much smaller study demonstrated that anaemia occurs earlier in people with diabetic kidney disease compared with those with non-diabetic renal disease, and again highlighted that this anaemia is often underdiagnosed (Bosman et al, 2001). In this study, 27 people with type 1 diabetes with persistent proteinuria, serum creatinine <180 µmol/L and retinopathy were compared with 26 people who did not have diabetes but who had glomerulonephritis and persistent proteinuria. They found that 13 of the 27 people with diabetic nephropathy had anaemia as a result of erythropoietin deficiency. None of the people with glomerulonephritis were anaemic. As such the investigators reported that anaemia associated with erythropoietin deficiency can occur earlier in people with diabetic nephropathy, and that it is unlikely to occur in people with non-diabetic renal disease of a similar severity.

However, these two studies are "one-off" observational studies and not ongoing prospective investigations powered to conclusively prove the worth of annual screening. I feel that it would, therefore, take a leap of faith to base the adoption of annual haemoglobin measurement for the entire population with diabetes on these studies. This is especially true since there is no evidence proving the value of screening for anaemia on an annual basis that stands up to scrutiny by the Wilson and Jungner criteria (1968), which still remain the gold-standard definition for robust screening programmes.

Are there other reasons to consider annual screening for anaemia?

Another reason for measuring haemoglobin routinely is to provide assurance of the accuracy of HbA_{1c} measurement. HbA_{1c} is an Amadori product, which is formed via an intermediary Schiff base. This glycation involves the formation of a covalent bond between the terminal amino acid of the protein (haemoglobin) and a sugar, first producing the Schiff base and subsequently the Amadori product in a stepwise manner. This means that anything that influences haemoglobin levels will also affect HbA_{1c}. The consequence of this is that people with anaemia will typically have falsely low HbA_{1c} levels, thus underestimating actual glycaemic control. The reverse is true for people with polycythaemia. This also explains the rationale for the caveats to the use of HbA_{1c} for diagnosing diabetes, such as not using it during pregnancy or in people with haemaglobinopathies (e.g. sickle cell disease or thalassaemia).

To screen or not to screen?

Having considered all of this evidence, what position should we take? In my view, the case for the widespread measurement of haemoglobin levels in people with diabetes does not yet exist, as there is currently no evidence proving the worth of routine annual screening. In addition, at a time when costs are of paramount importance and there is an increasing need to prove the value of our actions, I would urge caution about what would currently be considered as the indiscriminate assessment of haemoglobin. Furthermore, some people will undoubtedly require further investigation following the screening and this will have cost implications as well as, more importantly, being associated with a risk of morbidity and mortality. Last but not least, the management of diabetes is already complex, with many issues to cover during consultations, including a number of tests that we already have to perform, and I would not advise adopting any unnecessary further tests that would increase this complexity.

Nevertheless, I would highlight that screening people with CKD stages 3–5 is included in NICE guidelines and that an individualised approach to selecting other people for haemoglobin testing, based upon their clinical characteristics, would be appropriate. I would suggest that a similar individualised approach to screening for thyroid disease in people with diabetes should also be adopted. However, the decision is ultimately your own, and only you can choose what approach to take. ■

Astor BC, Muntner P, Levin A et al (2002) Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Arch Int Med* **162**: 1401–9

Bosman DR, Winkler AS, Marsden JT et al (2001) Anaemia with erythropoietin deficiency in early diabetic nephropathy. *Diabetes Care* **24**: 495–9

Jones SC, Smith D, Nag S et al (2010) Prevalence and nature of anaemia in a prospective, population based sample of people with diabetes: Teeside anaemia in Diabetes (TAD) study. *Diabet Med* **27**: 655–9

Middleton RJ, Foley RN, Hegarty J et al (2006) The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant* **21**: 88–92

Mohanram A, Zhang Z, Shahinfar S et al (2008) The effect of losartan on hemaglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes. *Kidney Int* **73**: 630–6

NICE (2006) *Anaemia management in people with chronic kidney disease* (CG114). NICE, London. Available at: www.nice.org.uk/cg114 (accessed 27.05.2013)

Wilson JM, Jungner G (1968) *Principles and practice of screening for disease*. WHO, Geneva, Switzerland. Available at: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf (accessed 27.05.2014)