Anemia and Diabetes Mellitus

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Diabetes Mellitus (DM) is considered a major public health problem. Its frequency is increasing worldwide, particularly in the Western world and estimations suggest that 1 in 3 adults in the US is likely to suffer from diabetes in 2050. About 25% of diabetic patients is assumed to have anemia. The risk in diabetics to develop anemia is estimated to be 2-3 times higher than the general population, when comparing patients with similar glomerular filtration rate (eGFR) and iron levels. It has been observed that prolonged duration of DM may increase the incidence of anemia in diabetics\(^1,2\). The etiology of anemia in diabetics is a complex, multi-factorial and often unrecognized issue (table)\(^3,4\).

<table>
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<tr>
<th>Table. Possible causes of anemia in diabetics.</th>
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<tbody>
<tr>
<td>1 Chronic blood loss</td>
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<td>2 Iron deficiency</td>
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<td>3 (B_{12}) or folate deficiency</td>
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<td>4 Relative erythropoietin deficiency (EPO)</td>
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<td>5 EPO resistance associated with chronic infection or inflammation</td>
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<td>6 Autonomic neuropathy</td>
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<td>7 Converting enzyme inhibitors (ACEis) or angiotensin II receptor inhibitors (ARBs)</td>
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<td>8 Nephrotic syndrome</td>
</tr>
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<td>9 Increased catabolism of HIF complex, associated with hyperglycemia</td>
</tr>
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<td>10 Decreased red blood cell survival time</td>
</tr>
<tr>
<td>11 Hypothyroidism</td>
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</tbody>
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In diabetics with an eGFR less than 60 ml/min, anemia is observed in 29%, while in diabetics with an eGFR higher than 60 ml/min only in 9%\(^5\). Hepcidin, a peptide hormone released by the liver, seems to be the key regulator of iron homeostasis and could be possibly used as an index of anemia, iron status and inflammation, as well as a therapeutic target. It inhibits ferroportin, a protein responsible for the intestinal absorption of iron, leading to a consequent reduction of iron’s absorption. Additionally, hepcidin increases the difficulty for iron to be released from its storages in...
macrophages and hepatocytes (leading to functional iron deficiency). In CKD — due to decreased clearance of hepcidin through kidneys — its levels are increased and this partly explains the iron deficiency in diabetic patients with CKD. In addition the effect of antidiabetic drugs on circulating hepcidin has not been explored so far; it is only established that metformin treatment is not associated with reductions in hepcidin, but hypocaloric diet could be involved in it.

Glycosylated hemoglobin (HbA1C), which is an irreversible nonenzymatic process that depends on the glucose concentration in red blood cells, is used as an important diagnostic index to assess glycemia and has low intraindividual variability. The association between anemia and concentrations of HbA1C has received limited attention. HbA1C constitutes the measurement of the non-enzymatic glycosylation of the beta-chain of the Hb molecule, whose levels are affected by a variety of genetic, hematologic and disease-related factors. The most important factors are coexistence of hemoglobinopathies, coexistence of various anemias and disorders related to acceleration of the regeneration rate of the red blood cells. Every situation that contributes to increased erythrocyte turnover (anemia of chronic disease, hemolytic anemias, anemia after acute blood loss), results in falsely low HbA1C.

In contrast, iron deficiency anemia may lead to a false increase in HbA1C, causing changes to the shape of Hb molecule promoting glycation of the terminal valine or by lowering the erythrocyte turnover, thus allowing more time for glycation of Hb. The haematologic status should therefore always be taken into account for a correct interpretation of the HbA1C result. According to the guidelines of the National Academy of Clinical Biochemistry, it is recommended for all samples of HbA1C to be re-measured by the laboratory, when values lower than the reference interval (<4%) are detected. Should they be confirmed, the clinician is advised to check for a variation of the patients Hb (hemoglobinopathy) or an indication of increased red cell destruction. It should be strongly noted that HbA1C should only be used for glycaemia assessment in the absence of anemia. The recurrent measurement of Hb, iron, and HbA1C is vital to correctly assess the glycaemia status in order to avoid misclassification between diabetes and prediabetes. People with anemia who appear on the border of the diagnostic threshold of diabetes may require the use of another diagnostic method, such as fructosamine or glycated albumin (excluding situations where protein metabolism is amended). Furthermore, red blood cell transfusion can complicate the interpretation of HbA1c values in diabetic patients, because it introduces haemoglobin molecules exposed to glucose concentrations that may have been different from the glucose concentrations in the diabetic transfusion recipient. The ADA recommendation is to measure HbA1c in all hospitalized diabetic patients who have not had an HbA1c measurement taken within the previous 60 days, and the American Joint Commission has adopted this recommendation as a standard for inpatient diabetes care.

Treatment of anemia in DM lacks clear targets and specific therapy is not well defined. Recent studies on the correction of anemia in diabetic patients (ACORD, CREATE, CHOIR, TREAT), in contrast to the clinical practice so far, showed that therapeutic interventions concerning anemia with EPO administration or intravenous iron, should be attempted at an early stage of DM and not only at the CKD phase. However, both erythropoietin analogs (epoetin-A and darbepoetin) and iron are not without side effects. At high doses, EPO is implicated in hypertension, thrombotic and cardiovascular events and in inducing the growth of various neoplasms. Hypertension occurs 2-16 weeks after starting treatment and does not depend on the Ht increase, but on the increase of intracellular calcium, which both inhibit the vasodilating action of nitric oxide (NO) and cause direct vasoconstriction in arterioles. EPO effect on hemostasis is mediated by a quantitative increase and consequent improvement of platelet function, in addition to a reduction in proteins C and S. Moreover, iron administered in a high dosage may cause hemosiderosis and increase the sensitivity of the body to infections. Target hemoglobin concentration is now lower and a trial of iron therapy alone is advised before decision for EPO administration, which is recommended in diabetic anemic patients, only when CKD co-exists, in order to achieve Hb levels between 10,0-12,0 g/dl, but not higher. Of course, the benefit from the early treatment of anemia in diabetics should be considered versus the cost of the treatment for the patient and the health system.
Up until now it is well established that HbA1c levels can be affected by conditions such as anemia. There are very few population-based studies, with small sample size examining the differences in the prevalence of diabetes and prediabetes according to categories of anemia versus normal Hb. Additional studies with larger numbers of participants with anemia would be helpful in examining the impact of anemia and its correction on measurements of HbA1c.

References