Anemia in diabetic kidney disease - underappreciated but still clinically relevant problem

Niedokrwistość w cukrzycowej chorobie nerek - niedoceniany, ale ciągle aktualny problem kliniczny

Introduction
Anemia is the most common disorder of the blood with iron deficiency being the predominant cause. On the other hand, diabetes prevalence is increasing rapidly. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Diabetic kidney disease (DKD) may be present in both types 1 and type 2 diabetes mellitus. Anemia is one of the common feature of chronic kidney disease. The epidemiological data on anemia prevalence are limited. In this review data on epidemiology, pathogenesis, complication and treatment of anemia in diabetic kidney disease are presented.

Epidemiology of anaemia in diabetic kidney disease

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risk of developing diabetic nephropathy and CKD. Also female sex is contributed to higher risk of developing CKD. In diabetic nephropathy risk of anemia is higher compared with the people with non-diabetic kidney disease and it is more severe [14–20]. Diabetic patients often develops anemia while theirs serum creatinine is still within the normal range. According to the study by Al Khury et al. [14] anemia is more prevalent even at the earliest stages of CKD [11,12] not only as in others studies have shown that it is more prevalent at stage 2 and 3 CKD [16]. It has been reported that around 15–25% of people with diabetes have unrecognized previously anemia [15,18–23]. In addition, in a population-based sample of people with diabetes a prevalence of previously unrecognized anemia was 15% [24]. The lower prevalence of diabetes in this study may be due to the fact that previous studies have largely been performed in patients attending hospital diabetes clinics [15–17, 19,20,22, 23,25]. It should be also stressed that the prevalence of anaemia increases in parallel with worsening renal function. Patients with an eGFR < 60 ml/min per 1.73 m² (stages 3, 4 and 5 chronic kidney disease) in this study accounted for 29% which was in line with another UK population-based study (31%) [21].

Screening of anemia in diabetic kidney disease

According to previous studies, a frequent complication of diabetic nephropathy is anemia. Furthermore, the occurrence of anemia is earlier in patients with diabetic renal disease than in non-diabetic with chronic kidney disease [26]. At the beginning we will discuss screening of diabetic nephropathy, which is a clinical syndrome characterized by persistant albuminuria (>300 mg/24 h, or 300 mg/g creatinine), a decline in glomerular filtration rate (GFR), increased arterial blood pressure [27]. Measurement of the albumin:creatinine ratio (usually single early-morning urine sample) allows for diagnosis of DKD. Abnormal values are different 2.5 mg/mmol or more and 3.5 mg/mmol or more in women [27]. KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for Anemia in Chronic Kidney Disease also use WHO criteria for diagnosis, but at the same time pay attention that anemia in CKD, including DKD can indicate of new problem [27]. The appearance or progression of anemia may be a sign of new problem that is causing by blood loss or involve disrupted the red cell production. Typical CKD anemia is normocytic and normochromic with bone marrow of normal cellularity and not differ from anemia of chronic disease. According to KDIGO Guideline anemia connect with CKD is multifactorial and needs wider diagnostics included: complete blood count (CBC), which should include Hgb concentration, red cell indices, white blood cell count and differential, platelet count, absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B12 and folate levels [28]. First treated are detectable causes of anemia such as iron deficiency, vitamin B12 and folate or chronic bleeding [28].

Pathogenesis and differential diagnosis

Anemia in chronic kidney disease is a condition characterised by lower-than-normal concentration of hemoglobin (Hb). The major cause of anemia of CKD is a decrease erythropoietin production due to kidney damage. Erythropoietin stimulates the bone marrow to produce red blood cells, and it increase production by the kidney is a response to low tissue oxygen levels. The pathogenesis of DKD is multifactoral, and therefore identifying the underlying its cause is necessary to initiating the appropriate treatment and help guide management of these patients. There are several possible mechanisms which may contribute to the occurrence of anemia in diabetic patients. Anemia in patients with diabetic kidney disease (DKD) results mainly from insufficient production of erythropoietin with inhibition of erythroid progenitor cells formation and inappropriate response of erythropoietin to decreased concentration of Hb [29,30]. Possible pathophysiological mechanism of erythropoietin hyporesponsiveness are still discussed, but authors suggest chronic inflammation, microvascular damage in the bone marrow, impairment of the tubulointerstitial tissue, an autonomous neuropathy and a variety of other factors [31–33]. Namely, damage to the EPO-producing fibroblasts either through fibrosis or chronic inflammation as well as interstitial pathological changes have been described in diabetic nephropathy and they are more notable in patients with type 2 diabetes [34]. As an alternative, anemia may be developed secondary to autonomic neuropathy which impairs anemia sensing by the erythropoietin-producing cells of the kidney [15]. Lastly, several drugs, predominantly the renin–angioten- sin system inhibitors may decline haemoglobin concentration by 0.2–0.3 g/dl [35–38]. Several mechanisms have been proposed for the anemia inducing effects of inhibitors of the Renin-Angiotensin-Sys- tem. ACE inhibitors decrease the vascular resistance in arteriolar arterioles, enhance the oxygenation in the peritubular region and as a result, induce the signal for erythropoietin synthesis. The tetrapeptide Ac-SDKP (goralalide), a normal inhibitor of the entry of pluripotent stem cells into the S phase, is metabolized by Angiotensin-converting enzyme. Ac-SDKP, in the presence of an ACE inhibitor, can accumulate and thereby decrease erythropoietin synthesis. The decrease the classes of hypotensive drugs may hence induce or worsen symptomatic anemia in patients with kidney disease [35,40,41]. Additionally, there is a growing list of commonly used hypoglycaemic medications implicated as factors underlying anemia. Thi- azolidinedione’s by increasing the plasma volume, may contribute to anemia due to hemodilution [42,43]. The iron deficiency is common cause of anemia in DKD due to numerous factors i.e. reduced intake and impaired intestinal absorption of dietary iron or chronic inflammation. Iron deficiency can be absolute or relative (functional) in nature. Absolute iron deficiency is defined by severely reduced total iron stores in bone marrow resulting in insufficient iron level to produce Hb. In contrast, functional iron deficiency is characterized by sufficient iron stores, but deficient iron availability for incorporation into erythroid precursors during erythropoiesis. It is usually linked with use of erythropoietin-stimulating agents (ESAs) in CKD [42,45]. Other causes including nutritional vitamin deficiencies such as folate and B12 are rare in DKD [37].

Anemia in chronic kidney disease and mentioned deficiencies anemias are included to hyporennerative anemias defined as a reticulocyte count of < 50×10⁹/L. By contrast, regenerative anemias are characterized by a reticulocyte count of > 100×10⁹/L. This classification based on the measurement of reticulocytes indicates whether anaemia is due to a central defect of red blood cells (RBC) production (i.e. aplastic anemia, deficiencies anemias, anemia in chronic diseases) or to accelerated destruction (haemolysis, haemor- rhage). The analysis of the complete blood count (CBC), including Hb concentration, red cell indices, white blood cell count and differential, and platelet count is crucial to indicate severity of anemia, function of bone marrow and to initial differentiation of anemia. The most useful markers to differentiate kind of deficiency are mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values. Folate or vitamin B12 deficiencies may lead to macrocytosis and hyperchromia, whereas iron deficiency (and inherited disorders of Hb formation) may present microcytosis with hypochromia [28] Macrocytosis accompanied by leucocytosis and thrombocytosis can be observed in folate or vitamin B12 deficiencies as well as in other causes of macrocytosis. This is a disorder of hematopoiesis caused by toxins and myelodysplasia. By contrast, the anemia of CKD is normochromic and normocytic with diminished survival of RBCs. It is, in general, morphologically identical with anemia of chronic disease caused by an inflammation-mediated reduction in iron production and utilization. Given that of the white blood cell count and differential or platelet count are not specific of the anemia of CKD and therefore the further investigation of causes should be indicated in that case. [46,47]. To identify iron deficiencies and distinguish between absolute and functional the measurement of serum iron, total iron-binding capacity (TIBC), ferritin, and transferrin saturation (plasma iron concentration di- vided by TIBC x 100) are used commonly. Typically, patients with functional iron deficiency have either normal or elevated serum ferritin concentration (>100 ng/mL)
in non-dialysis dependent patients and >200 ng/mL in hemodialysis dependent patients), but the transferrin saturation is about 20 percent or less. In patients with ESA-induced functional iron deficiency the serum ferritin concentration may be as high as 800 ng/mL or even higher. In patients with absolute iron deficiency we observe decreased transferrin saturation about 20 percent or less, but the serum concentration of ferritin is decreased (<100 ng/mL in non-dialysis dependent patients, <200 ng/mL hemodialysis dependent patients). By comparison, patients with normal renal function and severe iron deficiency anemia typically have a serum ferritin concentration <30 ng/mL [48,49].

Complication of anemia in DKD

Anemia in DKD increases angioanatomy and cardiovascular morbidity and mortality. In case of diabetic kidney disease, anemia develops in its early stage, has higher severity and is related to an increased risk of developing cardiovascular disorders, cerebral stroke and deterioration of renal function. As a result, an increase in the number and duration of hospitalisations as well as mortality rate can be observed [50-53]. Anemia significantly affects life quality, particularly in patients with diabetic kidney disease [54] as well as decreases physical and mental functions. Also, anemia is manifested as malaise, dyspnoea, weakness, appetite and sleep disorders, impairment of cognitive functions and even depressive symptoms. Clinical manifestation of anaemia occurs in advanced stage of renal failure with insufficient blood supply. During the first stage of the disease patients feel no clinical symptoms and adapt to gradual decrease in haemoglobin concentration.

Diabetic anemia in kidney disease deteriorates both the course of the disease and prognosis. Individuals suffering from diabetes, chronic kidney disease and anemia constitute a triad of patients with high rate of mortality and cardiovascular complications [55]. Long-term anemia in diabetic kidney disease is also a factor causing development of chronic renal insufficiency, neuropathy and diabetic foot. The risk of cardiovascular diseases in patients with chronic kidney disease is unrelated to gender, occurs in early stage of renal failure and increases with its progress [56]. Cardiovascular diseases constitute 50% of death causes in patients with end-stage kidney disease. Both cardiovascular mortality and anemia in dialysed individuals is 10-30 fold higher compared to general population and 100-fold higher in persons over 40 years of age with diabetic kidney disease in stage 5 [57]. Hb concentration decrease by 1g/dL leads to increased risk of left ventricular hypertrophy by 6%, increased left ventricular mass index, LVMi, by 7-10g/m2 and increased left ventricular volume index, LVVI, by 8ml/m2 every year [58]. Deteriorating anemia during kidney disease leads to reduction of peripheral resistance, activation of sympathetic system, increased activity of renin-angiotensin-aldosteron system, which affects the release of antidiuretic hormone [59]. This process leads to left ventricular hypertrophy, coronary disease, arrhythmia and sudden cardiac death. 75% of patients starting renal replacement therapy are diagnosed with left ventricular hypertrophy [60]. This disorder leads to reduced ejection fraction and kidney hypoperfusion which is manifested by a decrease in glomerular filtration rate. Haemodynamic changes are then accompanied by neurohormonal changes which also affect renal function. Anemia is related to a constantly increased cardiac output and thus affects large vessels leading to their hypertrophy and reconstruction. Dialyzed patients show increased arterial stiffness and faster atherosclerosis development. Anemia treatment in early stage of renal disease decreases the risk of death in dialysis patients [61] and may prevent heart failure in hemodialysis patients with normal left ventricular volume [62]. Normalization of hemoglobin concentration in case of circulatory insufficiency class I-II by NYHA may increase the risk of developing cardiovascular diseases [63].

Iron therapy in diabetic kidney disease

Early implementation of ESA and iron into anemia treatment allows to keep stable hemoglobin concentration in the maintenance stage of ESA therapy [64]. The decision on treatment commencement ought to be made individually for each patient with respect to hemoglobin concentration and clinical status. Target hemoglobin concentration depends on patient’s age, physical activity, coexisting disorders and response to the treatment [65]. Hemoglobin concentration within 10-12 g/dl in CKD patients is fully sufficient to obtain maximal improvement in the quality of life and to decrease mortality rate [66,67]. Maintaining hemoglobin concentration at 10-12 g/dl in diabetic kidney disease is vital since higher hemoglobin concentrations are related to increased risk of death. Particularly, Hb>13g/dl bears the risk of developing arterial hypertension and thrombosis [28,37,68]. Iron deficiency in patients with chronic kidney disease is a relatively common issue. In early stage of renal failure the major goal of the therapy with iron is to manage iron deficiency, which allows to increase hemoglobin concentration without the necessity to include the erythropoiesis stimulating agent – ESA. Target iron supplementation should be started at ferritin concentration maximally 500 µg/l and TSAT maximally 30% [28]. European guidelines recommend iron supplementation only when iron parameters are indicative of absolute deficiency (TSAT <20% and ferritin < 100 µg/L), while in non-ESA and non-dialyzed patients – at TSAT < 25% and ferritin < 200 µg/L in dialyzed individuals at TSAT <25% and ferritin <300 µg/L [69]. Both oral and intravenous routes of iron supplementation are possible. The choice ought to be made for every patient individually depending on initial iron concentration, response to current treatment, occurrence of undesirable effects of the therapy, possibility of saving vascular access and current blood loss. Also, patient’s comfort as well as the possibility of co-operation are vital. Oral medications fail to provide full biological availability of iron, interact with other medications and thus cause undesirable effects, mainly gastrointestinal ones, leading to difficulties in compliance with oral therapy [69,70]. In case of non-dialyzed patients, the choice of iron administration route commonly depends on clinical status; oral route is most commonly selected for practical reasons. Intravenous route is more effective in dialyzed individuals compared to oral one due to limited iron absorption. Higher effectiveness of intravenous administration than oral route has been shown in several studies aimed at the comparison of the two ways of treatment [71-74]. However, intravenous therapy is related to serious undesirable effects, especially in non-dialyzed patients [75,76]. Frequent administration of intravenous preparations may increase the risk of developing heart diseases, promote bacterial infections and deteriorate diabetes and its complications [77]. However, it was not confirmed in the most recent study on oral vs iv iron treatment in non-dialyzed patients [78]. In FIND-CKD study the incidence of cardiac disorders and infections was similar between groups. At least one ferritin level ≥800 µg/L occurred in 26.6% of high ferritin ferric carboxymaltose patients, with no associated increase in adverse events. No patient with ferritin ≥800 µg/L discontinued the study drug due to adverse events. Estimated glomerular filtration rate remained the stable in all groups [78].

According to ERBP guidelines, both parenteral dialysis and non-dialysis patients can be first treated with oral medications [69]. Typically, 200 mg of ferrous iron in three divisible doses is administered. If iron balance is not obtained within three months of therapy, intravenous administration ought to be implemented at doses of 20-60mg at every hemodialysis or 100-200mg at weekly intervals. Non-dialysis and peritoneal dialysis patients require every-week or 2-week intravenous therapy of iron. Optimal IV iron dose is 25-150mg/week for first 6 months of ESA therapy [69]. During first 3 months of ESA therapy, dialyzed patients require the supplementation of approximately 1000 mg of iron. Special caution ought to be kept when administering iron dextran to persons with diaphragm, and allergic reactions to other intravenous preparations. The individual with over-sensitive response to this iron form show low risk of developing sensitivity to other intravenous iron preparations [79]. The most common undesirable effects of oral iron preparation are gastrointestinal symptoms such as nausea, vomiting, abdominal

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pains, diarrhea and constipation [80]. The assessment of iron balance in patients with stable hemoglobin concentration not treated with ESA should be performed every 2-6 months. In the initial phase of ESA therapy and intravenous iron treatment, the parameters of iron balance ought to be tested every 1-3 months and every 4-6 weeks in case of oral therapy and next, after obtaining target hemoglobin values every 1-2 months. Following the administration of oral iron dose, the iron parameters should be tested after at least a week from the last dose [28,69].

During the therapy, it is not recommended to attempt to obtain TSAT>30% and ferritin > 500 µg/ml in both dialedyzed and non-dialyzed patients. Intravenous iron treatment ought to be withdrawn in the individuals with active systemic infection and in case ferritin concentration is over 800 µg/dl [69].

ESA treatment

The decision on ESA administration requires prior assessment and treatment of all possible and reversible causes of anemia including iron deficiency. Importantly, both benefits of ESA (decreased number of blood transfusion, subsiding of clinical signs of anemia) and the risk of developing adverse effects (arterial hypertension, myocardial infarction, stroke, thrombosis, heart failure) ought to be taken into consideration. Patients with history of arterial hypertension, thromboembolic disease, past cerebral stroke, with active or past cancer are at a high risk of developing side effects. Every decision on applying ESA therapy ought to be made individually depending on the increase in anemia severity, response to previous iron therapy, severity of clinical signs of anemia and possibility to avoid blood transfusion in the future. According to KDIGO guidelines, ESA treatment should be started in patients before dialysis with hemoglobin concentration < 10 g/dl, while in dialyzed patients at Hb 9-10 g/dl. The dose ought to be established the way that minimal hemoglobin concentration is maintained in case of patients reporting considerable improvement in the quality of life with higher hemoglobin concentration, ESA treatment implementation is justified at Hb >10 g/dl [28]. In non-dialyzed individuals, the treatment implementation at hemoglobin of approximately 10-12 g/dl compared to Hb 8.9-9 g/dl decreases the necessity to perform transfusion [81].

Initial dose of the medication depends on the severity of anemia, body mass and clinical picture. During the therapy, modifications of the dose with respect to hemoglobin concentration, speed of changes in its concentrations and current clinical status are necessary. Monthly increase in hemoglobin ought to range between 1 and 2 g/dl and not exceed 2 g/dl. According to ERBP, in case of no necessity to decrease Hb level, it is suggested not to withdraw ESA treatment but only reduce the dose. If hemoglobin concentration increases to 11.5g/dl, the dose ought to be reduced by approximately 25%. If despite dose reduction, the increase in hemoglobin concentration is still observed, the treatment may be withdrawn until hemoglobin starts decreasing and then started again at a dose lower than the previous one by 25%. During the therapy course, hemoglobin concentration should remain on the level of 10-12 g/dl. Reaching hemoglobin concentration over 13g/dl should be avoided [28,69].

Both subcutaneous and intravenous routes of ESA administration are possible depending on properties of particular preparations, their tolerance, stage of advancement of chronic renal failure and patient’s clinical profile. The subcutaneous route is preferred in non-dialyzed patients and the individuals on peritoneal dialysis whereas intravenous route – in hemodialysis patients.

Hemoglobin concentration should be assessed at least once a month at the beginning of the therapy and next, every 3 months in non-dialyzed patients and every month in dialyzed ones. Lack of proper hemoglobin increase during the first month is considered insufficient response to ESA treatment. Therapy ineffectiveness may result from, among others, administration of too small doses of ESA, insufficient iron supply, loss of blood, hyperthyroidism, infection, ineffective dialysis, B12 and folic acid deficiency or malnutrition. Rarely, erythropoietin aplasia caused by the occurrence of anti-erythropoietin antibodies may develop. According to observations, the number of erythropoietin aplasia cases was higher after subcutaneous administration compared to intravenous therapy [82]. It is not recommended to use androgens, vitamins and L-carnitine as a supporting treatment in the course of ESA therapy. A vital element of anemia treatment in dialyzed patients is providing optimal dialysis as optimal conventional dialysis techniques provide visible benefits [B3-6] and should be considered as the rationa-le of treating patients with anemia and the end-stage renal disease. This group of patients shows a high risk of developing protein-energetic deficiencies that may lead to anemia and thus regular monitoring of nutritional status is critical [87,88]. Patients with low BMI more frequently show severe anemia [89,90]. Obese CKD individuals with high BMI show higher hemoglobin concentration and need less ESA (per 1kg of body mass) compared to non-obese individuals [91,92].

Red cell concentrate transfusion as a form of anemia treatment ought to be implemented only in special cases. The criteria of referring patients for transfusion are mainly clinical signs of anemia and not hemoglobin concentration itself. Transfusion is justified in case of patients requiring fast anemia treatment (hemorrhage, unstable coronary disease, scheduled surgical procedures), lack of ESA effectiveness and in patients with high risk of developing complications in ESA therapy. According to ERBP, in hemodynamically stable patients, transfusion may be considered at Hb <7 g/dl, or <8 g/dl in post-operative patients and individuals with cardiovascular disease [69]. Transfusions ought to be avoided in case of renal transplant candidates. Treatment of anemia in post-transplant patients should be conducted as in non-dialyzed patients.

Summary

Despite so high prevalence of anemia in diabetics in the world, data on anemia in diabetic kidney disease are scarce. Diabetic patients often develop anemia while theirs serum creatinine is still within the normal range and anemia is more severe compared with the people with non-diabetic kidney disease. However, anemia in diabetics is relatively often unrecognized, in particular, in outpatient settings. Presence of anemia in diabetic kidney disease increase angioopathy and cardiovascular morbidity and mortality. Regular screening for anemia might help to delay and reduce of other complications associated with diabetes and the cardiovascular system. Treatment includes mainly iron supplementation and erythropoietin stimulating agents.

References:


