

## **Coexistence and clinical implications of anemia and depression in the elderly population**

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### **Summary**

Anemia and depression are common in the elderly and they are important medical, social and economic problems for the world. Both disorders are associated with a lower quality of life, multimorbidity and a higher risk of death. The connections between anemia and depression have been reported, but the mechanism and clinical consequences of their coexistence are not fully understood. Several links can be found between anemia and depression in the elderly: common etiological factors, low socioeconomic status of patients, poor education and less physical activity. Both conditions are associated with the occurrence of the same pathological changes: age-related (especially with the presence of inflammation, oxidative stress, degenerative changes in organs and tissues), nutritional deficiencies (iron, vitamin B12, folic acid) and hormonal disorders (especially thyroid gland disorders, sex hormone deficiencies). Anemia and depression are not sufficiently diagnosed in the elderly and, as a result, are often left untreated. The diagnosis and treatments of these conditions in the elderly differ from those in other age groups. The study provides an overview of the literature regarding the coexistence of anemia and depression in elderly patients and clinical recommendations.

**Key words:** anemia, depression, aging

### **Introduction**

Anemia and depression are significant health problems among elderly people around the world. Anemia is diagnosed in about 17% of people aged  $\geq 65$ , more often in hospitals (40%) and nursing homes (47%) [1]. According to WHO data, more than 20% of adults aged  $\geq 60$  suffer from mental or neurological disorders (excluding headache disorders). The most common mental and neurological disorders in this age group are dementia and depression, which affect approximately 5% and 7% of the world's older population, respectively [2]. Both anemia and depression are associated with multi-morbidity and a higher risk of death in the elderly [3, 4] and worsen the quality of life [5, 6].

Despite both anemia and depression being documented as having a negative impact on the health of elderly patients, they still do not get enough attention. The symptoms of anemia, especially mild (hemoglobin – Hb  $\geq 10$  g/dL) and also depression in elderly patients may be overlooked and considered a natural part of the aging process. This may result in delays in diagnosis. The presence of numerous other health problems which are considered to be more life- and health-threatening means that slight Hb drops in a geriatric patient go unnoticed. Furthermore, as anemia and depression share a number of certain common symptoms, there are cases of only one of these disorders being diagnosed and treated, despite the presence of both.

All the factors mentioned above justify the need for special attention that should be paid to the elderly regarding their likelihood of suffering from depression or anemia. The aim of the study is to characterize anemia and depression in elderly patients and to discuss the correlations, common etiology, clinical implications and recommendations on treating both disorders.

### **Coexistence of anemia and depression**

Although the mechanism of the co-occurrence of depressive symptoms and anemia has not been fully explained, this association has been confirmed [7]. The InCHIANTI study found that elderly patients with depression had a higher risk of anemia; anemia was present in 15% of the participants with depression and in 8% of the participants without depression. Additionally, the risk of anemia was higher depending on the severity of the depression [8]. An analysis of 1,616 patients aged  $\geq 60$  showed that anemia is a risk factor for depression [9]. In another study, poorer performance in both cognitive function and in physical strength tests in anemic patients was reported (these were also predictors of depressive symptoms) [10]. A recently published study found that anemia and its severity is a risk factor of depression, and this association can be modified by cognitive performance [11]. In this international study, elderly patients with anemia and poorer cognitive function had almost five times higher risk of depression during a four-year observation period compared to the people with good cognitive functions. The authors suggest that treatment of anemia may, to some extent, prevent depression. A study on oncological patients with anemia confirmed this thesis [12]. The improvement of Hb in patients with anemia during chemotherapy has shown to reduce the symptoms of depression, anxiety, and fatigue, and hence to improve patients' quality of life.

A number of etiological factors common to both anemia and depression can be found. These include the following: aging processes of the body (especially with the presence of inflammation and oxidative stress and degenerative changes in organs and tissues), vitamin deficiencies, iron deficiency, eating disorders, alcohol abuse, and hormonal disorders. The development and course of both disorders are influenced by multi-morbidity and polypharmacy in the elderly (Fig. 1). Other shared risk factors are: chronic pain, low education, socioeconomic factors, and decreased physical activity [13, 14].

The aging processes of the organism contribute to the development of anemia and depression. The prevalence of anemia in the elderly population increases with age [3].

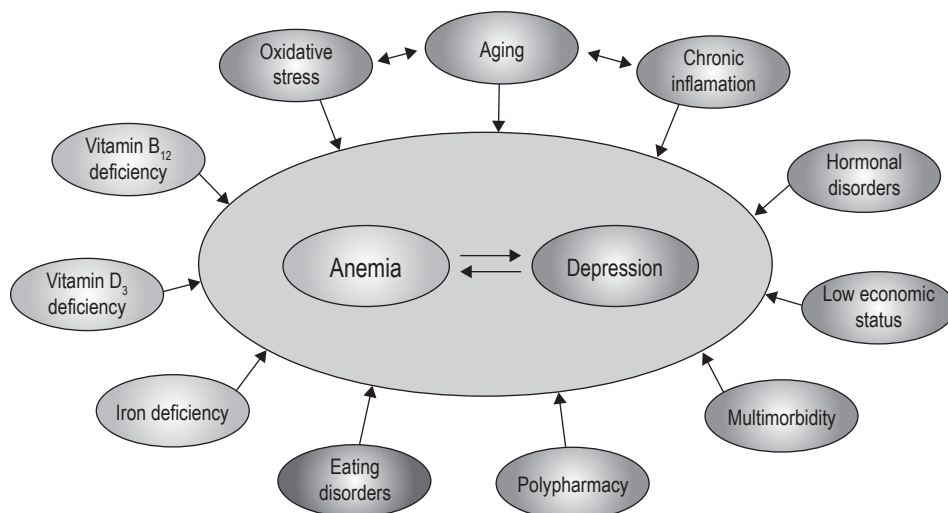


Fig. 1. Associations between anemia and depression Aging of the organism, inflammation, oxidative stress in the development of anemia and depression

The etiology of this phenomenon is complex and not fully understood; the deterioration of renal function as well as changes in the bone marrow structure and functions are very important factors, but not the only ones [15]. An increase in the concentration of pro-inflammatory factors, especially interleukin 6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-18, IL-1 receptor antagonist and an increase in CRP (C-reactive protein) and fibrinogen levels are observed more commonly with age [16]. IL-6 stimulates the synthesis of hepcidin – a regulator of iron metabolism and a mediator of inflammatory processes. Other pro-inflammatory cytokines (especially IL-1, TNF- $\alpha$ , interferon  $\gamma$ ) inhibit the proliferation of the red blood cell progenitor cells. Notably high parameters of inflammation are associated with the presence of anemia of chronic disease (ACD), a common type of anemia in the elderly [3, 17]. Another important factor in the process of aging is the oxidative stress. An increase of oxygen free radicals leads to damage of cell membranes, proteins and DNA and in consequence the lifetime of the red blood cells is shortened [18].

Oxidative stress and inflammation also contribute to the development of depression, schizophrenia, and bipolar disorders [19]. Patients with depression have shown increased levels of circulating pro-inflammatory molecules such as IL-6, IL-8, IL-1 $\beta$ , TNF- $\alpha$ , monocyte chemoattractant protein 1 (MCP1), CRP, etc. High levels of IL-8, IL-6 and TNF have been shown to be potential biomarkers of depressive disorders in the elderly [20]. The increase in pro-inflammatory factors leads to an increase in tryptophan metabolism and, consequently, to the development of anemia and depression in cancer patients [21]. Vascular and neurodegenerative factors also play an important role in the pathogenesis of depression in the elderly [22].

### **Hormonal disorders and anemia, depression**

Patients with thyroid gland disorders are predisposed to anemia and depression. Hypothyroidism or hyperthyroidism can lead to anemia; however, the mechanisms of this phenomenon have not been comprehensively studied [23]. Hypothyroidism sometimes manifests through neuropsychiatric symptoms. In subclinical hypothyroidism, depressive symptoms and cognitive deficits are mild but very common. In clinical hypothyroidism, the severity of cognitive and depressive disorders is sometimes significant [24].

A decrease in the secretion of insulin-like growth factor 1 (IGF-1) or sex hormones, is one of the causes of lowered Hb levels in elderly patients [23]. Sex hormone deficiencies, especially testosterone, are also factors in the development of depression in both women and men [25, 26].

The levels of cortisol are similar in the elderly and middle-aged groups. However, in the case of elderly people with depressive disorders, these levels are elevated and increase with age. Disorders in the hypothalamic-pituitary-adrenal (HPA) axis are a possible cause of that. From this perspective, a depressive disorder is a chronic hypercortisolemia [27]. Depression is also accompanied by excessive activation of the sympathetic nervous system [28]. These changes can negatively affect the functioning of bone marrow [29].

### **Iron and vitamin deficiencies in anemia and depression**

Malnutrition contributes to anemia [30] and depression [31]. Iron deficiency may result in anemia, cognitive impairment, decreased physical activity, and depression [32, 33]. The 2005 Health Survey for England study on 1,875 people aged  $\geq 65$  reported significant associations between lower Hb levels and higher serum transferrin receptor levels and a higher number of depressive symptoms [32]. Iron plays an important role in the oxygenation of the brain and therefore in the proper functioning of neurotransmitters, which may have impact on the development of mood disorders. An example is tyrosine – an amino acid used to produce dopamine, in processes possible only in the presence of iron [32, 33].

Vitamin B12 and folic acid deficiency may be the cause of anemia, dementia or depression, and the risk increases with age [34]. The association of depressive disorders and vitamin B12 deficiency anemia has been confirmed in a study conducted on 700 patients aged  $\geq 65$  [35]. Patients with vitamin B12 deficiency were two times more likely to develop depressive disorders compared to the control group. Furthermore, decreased levels of vitamin B12 have been observed to be a negative effect on the treatment of depression [36]; but vitamin B12 deficiency may result in a potentially reversible form of dementia in which depressive symptoms are common.

The elderly are at risk of vitamin D3 deficiency [37]. This deficiency is associated with a higher incidence of anemia, especially ACD. Vitamin D3 is a regulator of the hepcidin-ferroportin axis and influences the levels of pro-inflammatory cytokines

[38]. Vitamin D3 is also involved in the processes of neuromodulation (it regulates the secretion of a brain neurotrophic protein – BDNF), neuroprotection and neuroplasticity. The link between vitamin D3 deficiency and the occurrence of depressive symptoms has been well documented [37].

### Polypharmacy in anemia and depression

Polypharmacy is common in the elderly and is a possible risk factor in the occurrence of various types of anemia. Iron deficiency anemia may be the result of some commonly used drugs: proton pump inhibitors and H2 receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants. There have been reported incidences of anemia resulting from drug-induced immune hemolysis, most commonly caused by: cephalosporin antibiotics, beta-lactamase inhibitors, chemotherapy drugs (e.g., carboplatin, oxaliplatin) and methyl dopa [39]. Some drugs may lead to macrocytic anemia from deficiencies: vitamin B12 (proton pump inhibitors, H2 receptor blockers or biguanides) or folate acid (phenytoin, sulfasalazine, methotrexate, trimethoprim) [40].

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) potentially increase the risk of bleeding, and thus lead to anemia. The mechanism behind this phenomenon may be related to platelet dysfunction as well as the increase of gastric acid secretion caused by the drugs [41]. On the other hand, antidepressants may lower the risk of anemia by reducing the stress on the sympathetic nervous system, reducing inflammation and therefore increasing erythropoiesis [42].

### Diagnostics of anemia and depression in the elderly

Anemia is a condition in which hemoglobin levels, red blood cell counts or hematocrit are below the reference values defined for the population, depending on gender and age. In most studies on the elderly, anemia is defined according to the WHO criteria as Hb <12 g/dL for women and <13 g/dL for men [43]. While anemia is relatively simple to detect, a much more complex diagnostic process is required to determine the type and etiology, often by the exclusion of multiple disorders (Table 1).

Table 1. Diagnostic procedures for anemia in the elderly

Diagnostic procedures	Indications
Physical examination and medical history including lifestyle (diet, use of alcohol) comorbidities, medications and supplementation	Old age
Primary evaluation: full blood count, blood smear, reticulocyte count, ferritin, TSAT, bilirubin, vitamin B12, folic acid, CRP, ESR	Anemia

*table continued on the next page*

Hemolytic screen: LDH, DAT, haptoglobin, urine for hemosiderin	Raised reticulocyte count, raised unconjugated bilirubin, blood smear with polychromasia or spherocytes or agglutination
Additional test after hematological consultation: extended assessment of iron homeostasis (sTfR, sTfR/log sF) or hemolysis	Diagnostic difficulties
Bone marrow examination	Additional blood count abnormalities (duo-, pancytopenia); suspected clonal hematologic disease
Primary identification of underlying disorders: creatinine, eGFR, ALT, AST, TSH, urine tests	Old age
Infection or autoimmune disease screen	Clinical symptoms or previous test results
Gastroscopy, colonoscopy	Iron deficiency anemia; clinical symptoms indicating neoplasticity or bleeding
Imaging tests: ultrasound of the abdomen or thyroid gland, X-ray imaging, CT – chest or abdomen or pelvis	Clinical symptoms indicating neoplasm or other disorders
Other tests: vitamin D3 serum levels, Beck's self-esteem scale	Old age
Other specialist consultations: gynecological, urological, laryngological, etc.	Clinical symptoms or previous test results

ALT – alanine aminotransferase; AST – aspartate aminotransferase; DAT – direct agglutination test; eGFR – estimated glomerular filtration rate; ESR – erythrocyte sedimentation rate; sF-ferritin; sTfR – soluble transferrin receptor; TSAT – transferrin saturation, TSH – thyroid-stimulating hormone

The diagnostic scheme of depressive disorders consists of taking a medical history (from the patient and his relatives), a clinical examination and a verification of the initial diagnosis through available scales (Table 2). The final criteria for the diagnosis of depressive disorders are defined in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition) [44]. The currently used criteria in Poland is ICD-10, but the ICD-11 classification will soon be introduced [45]. The main symptoms of depression are mood decline, anhedonia and fatigue. Additional symptoms include: decreased appetite, sleeping disorders, suicidal tendencies, pessimistic attitude, low self-esteem, feeling of guilt, decreased concentration and attention, etc. As an in-depth discussion of depression diagnosis is beyond the scope of this paper, please see the paper of other authors [46]. Certain symptoms such as cognitive deficits or apathy are present in depression, but also in dementia and anemia. Therefore, the differentiation between these disorders poses difficulties. Especially in cases of severe depressive episodes determining the primary cause of symptoms is a challenge [47].

Table 2. **Diagnostic procedures for depressive disorders in the elderly**

Diagnostic procedures	Indications
Initial evaluation: neurological or psychiatric medical history	Old age
Depression diagnosis: assessment of current symptoms (interview with the patient and his relatives), Beck's self-esteem scale, Geriatric Depression Scale (GDS)	Presence of depressive symptoms
Cognitive function assessment: Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Montreal Cognitive Assessment (MoCA)	Old age, clinical symptoms
Other tests: physical examination; laboratory tests: full blood count, glucose, AST, ALT, creatinine, eGFR, calcium, TSH, vitamin B12, folic acid, vitamin D3, lipidogram, urine test; electrocardiogram	Old age and depressive symptoms
Neuroimaging: CT, MRI of the brain	The first episode of depression, pharmacologically-resistant depression; cognitive impairment; neurological symptoms

ALT – alanine aminotransferase; AST – aspartate aminotransferase; CT – computerized tomography; eGFR – estimated glomerular filtration rate; MRI – magnetic resonance imaging; TSH – thyroid-stimulating hormone

### Treatment of anemia and depression among the elderly

In the treatment of anemia and depression among elderly patients, similarly as in the treatment of other disorders at this age, we must take into account the presence of many comorbidities as well as polypharmacy, changes in pharmacokinetics and pharmacodynamics of drugs. The mainstay of anemia treatment is to define and to treat the underlying cause. A description of the treatment of various types of anemia is not the purpose of this study and has been presented earlier [17, 39, 48].

Pharmacotherapy and psychotherapy are used in the treatment of depression in older adults [49]. While choosing a drug, a history of good response to treatment, the number of side effects, and the pharmacological interactions should be taken into account. The main groups of drugs used include: SSRIs (especially sertraline, citalopram, and escitalopram), SNRIs (venlafaxine and duloxetine), norepinephrine reuptake inhibitors (reboxetine), tricyclic antidepressants (e.g., amitriptyline), and others (mirtazapine, bupropion, vortioxetine, agomelatine). Among the elderly, any treatment should start by implementing lower doses, which may next be modified to achieve optimal efficacy. Newer guidelines recommend both SSRIs and SNRIs as



first-line drugs [50]. In case of intolerance to these groups of drugs an alternative may be mirtazapine, whose side effect is an increased appetite, which can be desirable. Treatment is to be monitored by a biweekly assessment and dose adjustments according to clinical observations. In case of no response, or after 4-8 weeks with only a partial response, a change of the antidepressant may be considered. A period of up to 8-10 weeks may be required to determine the correct treatment (drug and dosage of antidepressants). No response to treatment is possible in approximately 30% of patients. The following recommendations in such cases are: (1) treatment with the maximum dose of the current drug; (2) switching to another drug of the same pharmacological class; (3) switching to a drug from a different pharmacological group; (4) combination of two drugs from different pharmacological classes; (5) adding other non-antidepressant drugs (e.g., antiepileptic).

In the elderly particular emphasis should be put on certain, possible side effects and interactions of antidepressants. Hyponatremia (especially after SSRI, SNRI, mirtazapine) is quite common in this age group [51]. The risk factors for antidepressant-induced hyponatremia include initial phase of therapy, older age, low baseline serum sodium level, low body weight, female gender, presence of comorbidities (i.e., cardiovascular diseases, diabetes mellitus, hypothyroidism, chronic obstructive pulmonary disease, malignancies), polypharmacotherapy (i.e., diuretics, cytochrome P450 inhibitors), and a past history of hyponatremia [49]. SSRIs cause gastrointestinal side effects, including loss of appetite; citalopram increases the risk of QT prolongation. SNRI drugs lead to an increase in blood pressure [52]. The use of a serotonergic agent is linked to the risk of serotonin syndrome, whose symptoms include: inducible or spontaneous clonus, ocular clonus, tremor, agitation, hyperreflexia, hypertonia, hyperthermia, diaphoresis, diarrhea, anxiety, and in severe cases – disturbances of consciousness. The course of serotonin syndrome in the elderly can be oligo-symptomatic or atypical [53, 54]. Antidepressants (especially SSRIs) increase the risk of bleeding, which is already high at an older age. The concomitant use of NSAIDs, corticosteroids, anticoagulants and antiplatelet drugs further increase the risk. Antidepressant discontinuation syndrome may take place following the interaction, reduction or discontinuation of SSRIs and SNRIs. Tricyclic antidepressants can cause cholinergic symptoms, cognitive decline, and lead to postural hypotension [52].

According to the recommendations of the National Institute for Health and Care Excellence [49] – psychotherapy, especially cognitive-behavioral and interpersonal therapy, is recommended at every stage of treatment. Among the elderly, however, this method has its limitations due to the rigidity of cognitive schemas and the limited possibility of personal change.

### **Conclusions and recommendations**

Undoubtedly, depressive disorders and anemia in the elderly affect one another. The topic is very interesting and requires further research. However, even with our current, limited knowledge simple recommendations can be formulated for everyday clinical practice.



Anemia and depression management in the elderly:

1. In the elderly particular attention should be paid to the co-occurrence of depression and anemia to treat both disorders. Basic methods can be used to verify the clinical diagnosis: a blood count test to exclude anemia and simple scales to confirm depression (Beck's self-assessment scale and GDS).
2. In old age blood screening is recommended at least twice a year and always in the case of changes in health or well-being. The presence of even a single symptom suggesting depression should be a direct recommendation for further diagnosis.
3. Both anemia and depression are disorders, not the diseases themselves; therefore, it is necessary to look for their etiology. Several causes of anemia and depression often occur simultaneously in the elderly.
4. SSRI or SNRI antidepressants should be considered as the first choice treatment in the elderly. The starting doses of antidepressants in this age group should be lower than standard. It is also recommended to incorporate psychotherapy and to provide community support at each stage in the treatment of depression. Therefore, psychotherapy should not be the only method used.
5. It is advised to supplement vitamin D3 in accordance with the current recommendations for the elderly. The exclusion of thyroid pathologies is advisable in both anemia and depression.

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