Anemia of Chronic Disease in Saudi Arabia

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Abstract

Background: Anemia of chronic disease (ACD) means that autoimmune disorders in which the body’s immune system attacks joints and/or organ or other chronic diseases that lasts more than 3 months cause low blood cell levels. ACD occurs in patients with active immune or inflammatory response in their current conditions that leads to a decreased intake of iron at different locations but not to patients who are specifically anemic with their diseases or treatments such as certain malignancies and the use of cytotoxic medications.

Aim: The aim of this paper is to review the prevalence of ACD in Saudi Arabia, highlight pathogenesis, diagnosis and management of ACD in Saudi Arabia.

Conclusion: Understanding of ACD and its management among public Saudi population especially in patients with one or more chronic disease is important to control ACD prevalence in Saudi Arabia. Health education sessions and training courses for physicians and chronic disease patients should be conducted to increase health awareness about this growing problem.

Keywords: Anemia of Chronic Diseases; ACD; ACD in Saudi Arabia; Diagnosis of ACD

Introduction

Anemia is defined non-sufficient level concentration of hemoglobin in blood which affects indivial physiological need [1]. Anemia of chronic disease (ACD) means that autoimmune disorders in which the body’s immune system attacks joints and/or organ or other chronic diseases that lasts more than 3 months cause low blood cell levels [2]. It is the second most widespread cause of anemia, after iron defi-

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Anemia occurs in patients with active immune or inflammatory response in their current conditions that leads to a decreased intake of iron at different locations but not to patients who are specifically anemic with their diseases or treatments such as certain malignancies and the use of cytotoxic medications [4].

It is typically seen as mild to moderate anemia in patients diagnosed with other conditions of chronic disease. ACD can be seen in various disease conditions like malignancies, chronic infections, heart failure and obesity [5,6]. According to previous studies: most Saudi elderly men experienced at least one chronic illness. The number of chronic diseases increased across the categories of growing age and BMI. Cigarette smoking, age and BMI has been associated substantially with chronic diseases. Saudi Health Interview Survey reported prevalence of hypertension and diabetes among those aged 65 and older 65% and 50% respectively [7].

Symptoms of ACD are similar to IDA including pale face, fatigue, shortness of breath, tachycardia, dizziness and headache [8]. Laboratory diagnosis include blood film morphology, serum ferritin and hepcidin [9].

Management of ACD is important to help patient getting healthier and prevent further complications by improving oxygen-carrying capacity of blood and detect and treat the underlying cause [10]. There’s no specific pharmacological treatment for this type of anemia, but doctors focus on fixing the underlying condition. If symptoms become severe, a blood transfusion or injection of erythropoietin might help stimulate red cell production and ease fatigue [11].

The aim of this paper is to review the prevalence of ACD in Saudi Arabia, highlight pathogenesis, diagnosis and management of ACD in Saudi Arabia.

Prevalence of chronic disease in Saudi Arabia

Prevalence of chronic diseases among Saudi population is generally estimated to be high than reported in other countries; but available data are from studies that have sampled the adult population and reported findings of age-stratified diseases [12].

The most recent report about cardiovascular risk factors among the Saudi population presented a prevalence of 31.4% for hypertension [13]. Prevalence of DM in adults in KSA is 23.7% [14]. 4% obesity was reported in rural areas. Conversely, obesity is reported to be 10% in the Western regions and 14% in the Jizan (12%), Riyadh (22%) and Hail (34%) due to the consumption of fast food and a sedentary lifestyle [15]. The caloric intake from the period between 1990 and 1992 in Saudi Arabia has been increased from 3120 Kcal/person/day to 2850 to 2008 [16].

Regarding malignant diseases; incidence and deaths of cancer in Saudi Arabia during the period between 1990 and 2016 have dramatically increased [17].

Anemia of chronic disease and iron deficiency anemia

Even as anemia is not due to a reduced intake or elevated need for iron in many biological systems, people with acute and chronic illnesses, bacterial infestations, infectious disorders, neoplastic disorders, injuries and major diseases are not associated with anemia [18].

ACD is a normochromic microcytic anemia, presumed to be attributable to the host defense response, which has been formed in such a way as to suppress the inflammatory cytokines interleukin 6 (IL-6), interleukin-1 (IL-1) of the iron-5-007 bacteria [19,20].

Iron limitation, compromised response to erythropoietin, and decreased half-life of red blood cells are the main pathological mechanisms that underlie ACD [3]. Despite the adequate preservation of iron and the presence of iron in the bone marrow, ACD is characterized by anemia and hyperemia [21]. Anemia occurs as a result of reduced recovery of iron from food and supplies rather than insufficient nutritional consumption. A number of animal and human studies have shown that inflammation leads to hypoferremia, lower iron

bioavailability, and eventually ACD, by increasing IL-6-mediated hepcidin production, which would reduce Fpn expression in intestinal enterocytes and body iron stores [22]. Elevated serum and urinary hepcidin levels have been observed in several conditions associated with the ACD including multiple myeloma and chronic kidney disease [23,24]. ACD may be misdiagnosed as ID or IDA. Ferritin levels can be normal or even higher among persons with ACD [25,26]. If ACD and ID/IDA co-exist, ferritin levels can remain elevated secondary to the inflammatory mechanism and may be misleading as to the actual amount of cellular iron [27]. Serum coupling ferritin can help to diagnose if underlying inflammation exists and help to explain elevated serum when measuring another acute phase reactant, such as CRP ferritin, beyond the underlying ID [28].

Pathogenesis of ACD

Anemia is a disorder in which blood contains fewer red blood cells than normal blood cells. Red blood cells can also contain less hemoglobin than normal blood cells. Hemoglobin is an iron-rich protein that helps the red blood cells carries oxygen to the rest of the body from the lungs. Your body requires oxygen to function properly [29,30]. With less red blood cells or reduced hemoglobin, the body may not get enough oxygen [31]. This is a significant finding in ACD that pathogenic pathways differ [32].

Bone marrow infiltration

Cancer-related anemia develops by three specific mechanisms. First mechanism is reduced red cell growth either through tumor invasion, cytotoxic drug impact, suboptimal diet or cytokine-based inhibition. Second mechanism elevated red cell failure (hemolysis or hemorrhage) and third mechanism is miscellaneous etiologies [33]. In most cases these mechanisms have large overlaps; however, the main mechanism is inflammation caused by cancer [34].

Marrow penetration of malignant cells, leading to physical obstruction and destruction of the micro-environment of the bone marrow tends to occur over time in most cancers. However, extreme anemia is found in certain malignancies in the absence of a marrow invasion or loss of essential nutrients [35].

Celecoxib, a cyclo-oxygenase-2 enzyme, has also been shown to overcome ACD-associated anemia and cachexia. Growth differentiation factor 15 (GDF-15) is an enzyme of leucocyte integrin and a member of the transforming growth factor-β superfamily [36]. This novel molecule has been shown to have an inverse association with serum hepcidin levels in cancer patients with ESA-resistant anemia. Elevation of GDF-15 results in depression of hepcidin levels [37]. This was proposed as a significant trigger for anemia in cancer-driven inflammation since the serum level of GDF-15 is primarily correlated with the level of anemia in cancer patients.

Reduced erythropoiesis

It was hypothesized that IL-6 be the most important cytokine mediating the pathogenesis of ACD. It is a potent TNF-5-007 inhibitor and induces transcription of ferritin leading to improved preservation and deposition of iron in the reticuloendothelial cells [38]. Previous findings suggested the existence of other pathway-inducing anemia in critically sick animal species where TNF inhibition did not preclude anemia from developing [39]. IL-6 inhibits erythropoiesis by inhibiting the accumulation and accumulation of copper. It controls the expression of the SLC4a1 gene in late erythroid precursors and thus enhances hemoglobin synthesis [40]. The mitochondrial mass and function also declines in budding erythroid progenitors. It causes enhanced hepatic synthesis of the hepcidin protein in the acute process. IL-6 tends to induce anemia by other mechanisms that are not dependent on hepcidin, thereby indicating either direct inhibition of erythropoiesis or the presence of other mechanisms that have yet to be identified [41].

Diagnosis and laboratory findings

Diagnosis of ACD can be reasonably easy for a patient with a current diagnosis of chronic inflammatory or malignant disease. Exclusion of iron deficiency anemia (IDA) is important in the work of patients with ACD, as the conditions sometimes coexist; certain patients

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with ACD have FID status and can respond to intravenous iron supplementation even though they have body iron stores are ‘adequate’. Serum iron levels and transferrin saturation are decreased in patients with ACD, and transferrin levels are increased in IDA but normal or decreased in ACD [40].

Hepcidin can be assayed using mass spectrometry or immunoassay, with several assays now commercially available. It is a small peptide hormone that functions as both the homeostatic regulator of systemic iron metabolism and the host defense and inflammatory mediator, and is detectable in human urine, plasma, and serum [42]. It is known that circulating iron and iron stores are found in the liver, which is the main site of hepcidin production and secretion [41].

Generation in adipose tissue, heart, placenta, and kidneys is not likely to be controlled by body iron status, but more likely by inflammation (IL-6 mediated) [43]. Infection increase hepcidin and consequent hypoferremia reduce the bioavailability of dietary and cellular iron leads to slow microbial growth. In contrast, when body iron levels are decreased or presence of anaemia or hypoxia the expression of hepcidin is minimal, allowing increased absorption of dietary iron and mobilization from body stores through active Fpn transporters. Researchers indicated that hepcidin concentrations in iron-replete women are inversely associated with iron absorption from nutritional and food-based non-heme iron sources [44].

Morphology of red cell shows hypochromic and microcytic RBCs. Blood film can provide details on the underlying cause of ACD: thrombocytosis in cases of chronic hemorrhage, toxic granules in neutrophils in extreme sepsis, hyper-segmented neutrophils in mixed nutritional deficiency or folate/B12 deficiency in malignant conditions [45].

Assay of serum transferrin receptor (sTfR) has been proposed as a tool for distinguishing ACD from IDA, as levels do not vary from steady state in the former, but are increased in the latter. Serum iron levels and transferrin saturation are decreased in patients with ACD, and transferrin levels are increased in IDA but normal or decreased in ACD [46].

Management of ACD

If end organ damage is imminent and cardiac prevention mechanisms may be overactive, adverse consequences can arise, emergency treatment avoids a weak prognosis of anemia in most diseases. Emergency care prevents the bad prognostic result for anemia in most illnesses [47]. Anemia has been observed to convene a poorer forecast in patients with CKD, cancers, and congestive cardiac failure. Hemoglobin levels of ≤ 8 g/dL in CKD patients on hemodialysis are linked with a double rise in risk of mortality relative to patients who had hemoglobin levels of 10 - 11 g/dL. Patients who had hemoglobin concentrations of 10 - 11 g/dL increased survival and enhanced treatment results [48].

Iron therapy

Iron therapy could not be particularly effective in ACD given that the pathogenesis involved requires a general lack of abundance and total lack of iron to red cell precursors. In addition, some micro-organisms and tumor cells use extra iron for cell proliferation [49]. Iron has an inhibitory effect on the immune system through repression of IFN-Δ-mediated pathways. However, parenteral iron can be used in cases of low oral intake or slow absorption, has a strong bioavailability in its reduced form and should be avoided only in confirmed cases of malabsorption [50].

Iron can be administered parentally, intravenously or intramuscularly. Intravenous iron is typically administered as a loading dose and provided as iron dextran in a gradual infusion. The main side effect is a serious anaphylactic response, often life-threatening, requiring an emergency department nearby [51]. The importance of oral or parenteral iron is known in patients with inflamed intestinal disease and ESA CCD Which may be based on the idea that certain degrees of iron deficiency can exist in ACD patients; it also provides a better outcome for rheoarthritis and CKD through the inhibitory action of iron on TNF-5-007 [50].

Erythropoiesis-stimulating agents

Erythropoietin promotes the proliferation of erythroid precursor marrow-forming erythroid complex via its action on bone morpho-
genetic protein (BMP-SMAD) and JAK-STAT5 pathway BMP is part of the transforming family of growth factor β that binds and transforms
signals to serine-threonine kinase receptors through SMAD. and a consequent drop in absorption of iron [52]. Erythropoietic agents have
been approved for use in ACD due to cancer or anticancer chemotherapy, as well as in patients with CKD and HIV infection, including
blocking the anti-proliferation activity of pro-inflammatory cytokines and promoting iron intake and haem biosynthesis in erythroid pre-
cursors [53]. The negative effects of erythropoietin should be examined and should include elevated blood pressure, cerebral convulsions,
thromboembolic complications, iron toxicity and influenza-like syndrome Influenza [54].

Blood transfusion

Transfused blood remains a precious resource and also carries risks of transfusion-transmitted infection, alloimmunisation and hae-
mosiderosis. In particular for people with serious heart defect when hemoglobin level less than 6.5 g/dL), blood transfusion remains a
significant shortsighteous treatment choice. Repeated use of red cell transfusion has been associated with elevated mortality, primarily
due to excess of iron and immune activation of HLA antigens in patients that could potentially be transplanted [55]..

Conclusion

Understanding of ACD and its management among public Saudi population especially in patients with one or more chronic disease is
important to control ACD prevalence in Saudi Arabia. Health education sessions and training courses for physicians and chronic disease
patients should be conducted to increase health awareness about this growing problem. We also recommend large scale and more de-
tailed national researches about ACD in patients with ACD.

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