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The Pathophysiology of Anemia of CKD

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Here's Dr. Steven Fishbane.

Dr. Fishbane:
Hi, I'm Dr. Steven Fishbane from Northwell Health at Hofstra University, working out of Great Neck, New York, and I'm pleased to be speaking to you about the pathophysiology of anemia of Chronic Kidney Disease.

These are my disclosures.

When we think about anemia in patients with CKD, it's very important that we remember this is absolutely a multifactorial process. [Babitt; Babitt; Kalantar-Zadeh; Babitt] How do we get from chronic kidney disease to anemia? We know the very important role that inflammation plays in our patients. [Babitt] It increases liver production of hepcidin, which plays a critical role in anemia. [Babitt] Hepcidin is the primary regulator of iron and iron status within the body, but it can also hurt the ability to produce red blood cells. [Babitt]

Starting on the left side of the screen, we see that hepcidin blocks availability of iron and absorption of iron from the intestines release of iron is already in the body in storage tissues. [Ganz and Nemeth] And the net effect is that patients who have kidney disease end up with reduced availability of iron, and this contributes importantly to the anemia of kidney disease. And it does so because iron affects erythropoiesis, the production of new erythrocytes, or red blood cells. [Ganz and Nemeth; Babitt]

Now on the right-hand side of the screen, the primary cause of anemia and kidney disease is limited amounts of erythropoietin. [Kalantar-Zadeh; Panwar] We talked about iron which reduces erythropoietin production [Atkinson], but even red cells that have been formed are going to be limited in their lifespan because of the presence of inflammation. [Babitt] We can even see that inflammation also limits the production of erythroid precursors within the bone marrow. [Li]

Blood and iron [Babitt], nutritional factors [Atkinson], secondary hyperparathyroidism [Chutia], the presence of uremic toxins [Babitt] medications whether the patients are adherent with medications [KDIGO] all of these have an effect and can impact the anemia of chronic kidney disease.

With CKD there is a gradual reduction in the cells in the kidney, the renal erythropoietin-producing cells. And as these cells located in the tubular interstitial compartment, are gradually reduced in numbers. [Atkinson]

20 years ago, I would've said that the entire mechanism for anemia of kidney disease was this– decreased kidney tissue, reduced REP cells, and less erythropoietin production. [Fishbane] When the kidneys respond to anemia they're actually sensing less oxygen but there's less oxygen being used locally in the kidneys and therefore, the anemia which is affecting the whole body is the same anemia that makes the patient feel tired, feel cold is actually not picked up normally by the kidneys in patients with chronic kidney disease. They don't see the imbalance in oxygen and that contributes to reduced erythropoietin production. And it's one of the important issues that hasn't been able to be effectively treated simply by giving erythropoietin. So together, we understand that there's a reduction in serum iron, a reduction in erythropoietin and these then lead to the anemia of chronic kidney disease by reducing red cell production or erythropoiesis. [Wenger; Mathias]

Iron and hepcidin play critical roles in anemia of chronic kidney disease. We saw that elevated hepcidin results from inflammation. It is also a result of reduced renal clearance. So, when you have reduced kidney function, hepcidin is going to become elevated in the bloodstream, and that again is going to limit the absorption of iron from the intestines and overall iron availability for production of new red blood cells. [Portoles; Haase] There is a secondary effect and that's that erythroblasts produce less erythroferrone and that also is going to affect iron availability so erythropoiesis will be limited and all of these factors contribute. [Portoles] Atkinson]

Now the HIF pathway. So HIF or, hypoxia-inducible factor, this pathway is critically important. It's the key oxygen-sensing pathway in the body in all of our cells. [Koury 2015] The cells in our body right now are all going through the process of sensing, sensing for enough oxygen to function normally. [Koury 2015] And within the cell, under normal oxygen conditions, or normoxia, HIF-alpha is produced, and produced continuously, if there's enough oxygen present, then HIF-alpha is gradually tagged and its signaled to be degraded. Certain enzymes, the prolyl hydroxylases, will then break down HIF-alpha. So with normal oxygen present, HIF-alpha is continually produced, but continually broken down so that it doesn't exert any signal. This way the cells of your body look for the presence of adequate oxygen. And that could be hypoxia, it could be anemia, but in those situations where there is not enough oxygen the cell will react differently. [Locatelli]

So in contrast, when hypoxia is present, something very different happens. HIF-alpha is still produced continually, but now you don't get the hydroxylation of HIF-alpha by the prolyl hydroxylases. When HIF-alpha is able to remain stable because of hypoxia, it's now able to enter the nucleus of the cell, where it binds to its sister compound, HIF-beta, and they will bind to key genes in the nucleus of the cell that will protect against hypoxia. The HRE or hypoxia response elements within the nucleus turns on a whole variety of cells that are critical for protection against hypoxia. In CKD, damage to the kidneys can lead to decreased oxygen consumption, and you get reduction in the activation of the HIF pathways. [Locatelli]

In healthy kidneys, when hypoxia is present, you get production of the HIF pathway, so erythropoietin is produced and new red cells develop constantly to make up for hypoxia. [Wenger] But in chronic kidney disease its different. The process is impaired, and it's an important aspect in the multifactorial causes of anemia. [Locatelli] Because of the dysregulation in HIF activation, the effect is less signaling, less erythropoietin production, you don't have the erythropoiesis you need to make red cells, to take care of the anemia, and to get oxygen delivery to compensate for anemia or other causes of hypoxia. [Locatelli]

So with HIF stimulation under normal conditions, what you get is a coordinated erythropoietic response. Throughout the body, all of the organs that are key here will work together under the influence of HIF pathway stimulation, and it not just for erythropoietin but other key iron compounds and other substances as well, like suppression of hepcidin, and you get an increase in iron availability, and coordinated production of red cells that leads to adequate and efficient erythropoiesis. [Wenger, Koury 2015]

So in summary, the anemia of chronic kidney disease, we've learned, is a multifactorial disease. [Babitt; Babitt; Kalantar-Zadeh; Babitt] The HIF pathway plays an important role in the physiologic response to hypoxia. It's activated in the renal erythropoietin-producing cells in the kidneys in response to anemia. But we've seen that the HIF pathway influences a wide range of hypoxia-sensitive proteins that stimulate erythropoietin, regulate erythropoiesis, iron, iron metabolism, and all aspects of mobilization and utilization. [Koury 2015]

I'd like to thank you very much for listening. I hope you found this presentation to be helpful for the practice and management of anemia in patients with chronic kidney disease.

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