////Title: A Personalised Mathematical Model for Anaemia in Patients with Chronic Kidney Disease

////Stand-first:

Individuals with chronic kidney disease commonly also suffer from renal anaemia. Renal anaemia, a condition in which individuals lack enough red blood cells to adequately supply oxygen to the tissue, can have many underlying causes. Treatment is based on hormones that stimulate the production of red blood cells but this has varying outcomes and it is difficult to estimate the effects treatment will have on a specific patient. Dr Doris H. Fuertinger [fyor-ting-gur], at Fresenius [fre-sen-oos] Medical Care Deutschland is using a mathematical model to predict the causes of renal anaemia and to guide treatment for individual patients.

////Body text:

Chronic kidney disease is a long-term condition in which the kidneys do not function as they should. A common occurrence in patients that suffer from chronic kidney disease is that they also suffer from anaemia. Anaemia arises when there is a reduction in the total amount of red blood cells, the cells responsible for transporting oxygen around the body. Additionally, anaemia can be caused by a decrease in haemoglobin [HEE-muh-GLOH-bin], the protein found on red blood cells that is responsible for carrying oxygen. Individuals diagnosed with renal anaemia often have poorer clinical outcomes.

In 2014, 84% of patients with chronic kidney disease in the USA were treated for anaemia using erythropoiesis [EH-rih-THROH-poy-ee-sis] stimulating agents, otherwise known as ESA. These drugs increase the production of red blood cells. However, anaemia that occurs in chronic disease kidney patients is often difficult to treat. This is because it often takes a very severe form in this patient population and it is difficult to estimate how individual patients respond to the drug, partially because there is a long delay between administering ESA and the time it takes effect. Also, the response to the treatment can be described as nonlinear, whereby the increase in red blood cells is not proportional to treatment that is administered. Consequently, haemoglobin levels do not reach the desired amount or fluctuate widely. This has made it difficult for scientists and clinicians to predict how individuals will respond to ESA therapy.

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Erythropoiesis stimulating agents drive erythropoiesis, the process which produces red blood cells. This process is stimulated by decreased oxygen levels detected by the kidneys. The kidneys then secrete a hormone, erythropoietin [EH-rih-THROH-poy-eh-tin], which drives erythropoiesis in the bone marrow, the site where red blood cell production occurs. However, in individuals with chronic kidney disease, this process is disturbed. Erythropoiesis is regulated by multiple complex systems that make it difficult to predict the effects that drugs such as ESA will have. To try to address this issue, computer simulations and mathematical models have been used to improve understanding of how erythropoiesis is regulated and its responsiveness to treatment.

Although previous models have provided insight into how erythropoiesis operates, not all models are detailed, and none have been designed to predict response to treatment with ESA on an individual level. A model produced by Dr Doris H. Fuertinger and her colleagues seeks to overcome these shortcomings.

Dr Fuertinger's team produced an age structured model, whereby all stages a cell must pass through to become a red blood cell are considered. Red blood cells begin as a stem cell, a cell that can differentiate into any cell type. The cells then progressively differentiate into a red blood cell. The researchers also accounted for a process known as neocytolysis [NEE-oh-SIT-oh-LIE-sis]. Neocytolysis occurs when there is only a low amount of the hormone erythropoietin. This results in the selective destruction of young red blood cells, also known as neocytes. Neocytolysis has been shown to contribute to anaemia in individuals with chronic kidney disease.

Collectively, this information was used to produce mathematical equations to estimate parameters, including the lifespan of red blood cells, the half-life of ESA, erythropoietin production and effects of the ESA, on the proliferation of red cell progenitor cells. This was achieved using haemoglobin measurements taken during dialysis and patient data obtained over 150 days from 60 patients with chronic kidney disease treated with ESA. Dialysis is a procedure that is used to clean the blood and remove excess fluid in the body when the kidneys are not working as they should be.

Dr Fuertinger and her team used their model to successfully estimate the haemoglobin levels of individual patients for up to 21 weeks, despite some individuals requiring blood transfusions and having significant blood loss. The recruited patients were ethnically diverse with different clinical symptoms. The model could be used to identify reasons for non-responsiveness to ESA treatment for patients, such as short lifespan of red blood cells and low erythropoietin production. This would help identify underlying causes of anaemia in chronic kidney disease patients that have been previously difficult to quantify. Critically, these details can inform decisions on how to best treat patients using a personalised approach.

Importantly, the model is based on data that are easy to collect – patient gender, weight, and height, as well as their haemoglobin levels and ESA treatment information from the past 5 months. All of this information can be acquired without the need for invasive procedures and is routinely completed in dialysis clinics.

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In follow up work, Dr Fuertinger and her colleagues predicted haemoglobin levels and patterns in a larger dialysis patient population. They are in the process of comparing data from virtual and real patients in a large patient cohort to test how well the model performs. It is hoped that the model can predict individual haemoglobin levels for different ESAs and provide further insight into the underlying cause of anaemia in patients with chronic kidney disease. The next step is to use the model to assess and recommend fully personalised ESA treatments. For that purpose, the model will be regularly adapted to represent changes in the individual patient data over time. Through this work, the model is evolving into an important diagnostic and clinical tool.

This SciPod is a summary of the paper 'Prediction of haemoglobin levels in individual hemodialysis patients by means of a mathematical model of erythropoesis', from the open access journal PLOS ONE: https://doi.org/10.1371/journal.pone.0195918

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