

News Releases

Decreased red blood cell clearance appears to predict development and worsening of serious diseases

Understanding mechanism behind previously observed biomarker could improve disease diagnosis, prognosis

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Massachusetts General Hospital (MGH) investigators have found the probable mechanism underlying a previously described biomarker associated with the risk of developing serious diseases ranging from cancer to cardiovascular disease and the risk of serious complications. In a paper published in the *American Journal of Hematology*, the research team reports finding that higher levels of a measure routinely taken as part of the complete blood count – the extent of variation in the size of red blood cells – is caused by reduced clearance of aging cells from the bloodstream. Hundreds of studies since 2007 have found that elevations in this measure – called RDW for RBC (red blood cell) distribution width – predicted the development, progression and risk of death from many conditions.

“It appears that the human body slightly slows down the production and destruction of red blood cells in just about every major disease,” says John Higgins, MD, [MGH Center for Systems Biology](#) and [Department of Pathology](#), senior author of the report. “If we can accurately measure the production or destruction rates, we might be able to identify many of these diseases in their earlier stages when they are most treatable. Existing measures of the production rate are far too imprecise to detect these subtle changes, but this paper shows how the destruction rate can be estimated using existing blood count data and a mathematical model.”

Healthy adults generate red blood cells at a rate of more than two million per second, and the cells circulate in the bloodstream for 100 to 120 days, during which their size decreases by around 30 percent. Aged red blood cells are then cleared at about the same rate of two million per second. Prior to the reports associating an elevated RDW with increased risk for many diseases, that measure had only been used to help distinguish between different forms of anemia. In their effort to understand the correlation between RDW and disease prognosis, the MGH team analyzed raw data from more than 60,000 randomly selected blood samples from the hospital’s clinical laboratories, using a mathematical model developed by Higgins and a colleague to replicate how red blood cell populations behave differently in health and in disease.

Using this model to measure the extent to which red blood cells in different phases of their life cycle contribute to increased RDW they found that the variance in size was strongly determined by mild increases in the numbers of the smallest and oldest cells. Since the

determined by mild increases in the numbers of the smallest and oldest cells. Since the most important mechanism controlling the number of the oldest cells is the rate at which they are cleared from the blood stream, the research team made several predictions, which were validated by applying their model to clinical data from the MGH blood samples and to data from several published studies:

- increased RDW was associated with delayed red blood cell clearance,
- increased RDW was associated with increased average age of red blood cells,
- delayed red blood cell clearance was as strongly associated with overall risk of death as was increased RDW,
- delayed red blood cell clearance was associated with the presence of early signs of hidden diseases associated with increased RDW,
- patients with delayed red blood cell clearance had a greater risk of developing signs of those diseases in the future than did those with a typical clearance rate,
- in healthy patients the rate of red blood cell clearance varied less than did any other traditional blood-count characteristic.

Higgins notes that there are many potential clinical applications of these findings, which need to be validated by future studies. “Finding a reduced clearance rate in an apparently healthy person would likely mean that an underlying disease process was developing – such as the early stages of iron deficiency, kidney disease, colon cancer or congestive heart failure – and would warrant further diagnostic evaluation. Based on this analysis of routine blood tests, a primary care physician could immediately consider appropriate follow-up diagnostic testing, instead of waiting for other signs and symptoms to appear as the condition progresses. In a patient with established disease, a reduced clearance rate could mean progression of disease or treatment failure, and imminent complications could be avoided or reduced by adjusting treatment right away or at least by more frequent monitoring.

“In addition to confirming our findings in prospective studies that would follow a group of patients over time, we hope to identify the diseases for which an early warning provided by delayed clearance would lead to the most significant improvements in patient outcomes,” he continues. “We’d also like to understand more about the processes controlling red blood cell clearance and are actively developing similar models for populations of white blood cells and platelets.”

Higgins is an assistant professor of Systems Biology at Harvard Medical School. The co-authors of the *American Journal of Hematology* paper are lead author Harsh Patel and Hasmukh Patel, both of the MGH Center for Systems Biology and Department of Pathology. The study was supported by National Institute for Diabetes and Kidney Disease grant K08DK083242, National Institutes of Health Director’s New Innovators Award DP2DK098087 and Abbott Hematology.

Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than \$760 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, reproductive biology, systems biology, transplantation biology and photomedicine.

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