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Interleukin-6 Levels below a Certain Threshold have Molecular Repercussions

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Commentary

In end-stage renal illness, cardiovascular disease is the primary cause of morbidity and death: approximately 50% of patients die from cardiovascular disease, and cardiovascular mortality is 15–30 times greater than in the age-adjusted general population. In addition to typical Framingham risk factors, a variety of non-traditional variables, including as inflammation, vascular calcification, and LVH, are known to have a role in the progression of cardiovascular disease in end-stage renal illness (left ventricular hypertrophy).

Increased circulating levels of CRP (C-reactive protein) and IL (interleukin)-6, both considered strong predictors of poor outcome in particular, have reported that the relative risk associated with each 1 pg/ml increase in IL-6 concentration was increased by 4.4% in ESRD patients, primarily due to the poor biocompatibility of Renal Replacement Therapy. By regulating cell growth, gene activation, proliferation, survival, and differentiation, IL-6 triggers a wide range of cellular and physiological responses, including the immune response, inflammation, haematopoiesis, and oncogenesis.

IL-6 communicates through a receptor that is made up of two subunits: a ligand-specific subunit [gp80 (glycoprotein 80) or IL-6R (IL-6 receptor)] and a receptor component that is shared with other cytokines in the IL-6 family, gp130 (glycoprotein 130). When IL-6 binds to its receptor, it triggers a cascade of events in the cell, including the activation of JAKs (Janus kinases) and Ras-mediated signalling. The Signal Transducer and Activator of Transcription factors, notably STAT3, are phosphorylated and activated by activated JAKs.

STAT3 that has been phosphorylated forms a dimer and translocate into the nucleus, where it activates the transcription of genes that contain STAT3-response elements. In liver cells, IL-6 is a significant inducer of acute-phase protein production. Lower plasma concentrations of fetuin-A and greater amounts of hepcidin are characteristic acute-phase protein patterns in ESRD. Low circulating levels of fetuin-A have been linked to vascular calcification in ESRD patients. Fetuin-A, which is generated by hepatocytes and suppressed by IL-6, is a key systemic inhibitor of calcification in humans.

Low levels of this glycoprotein were linked to higher levels of CRP and a higher risk of cardiovascular death. Hepcidin is a circulating peptide hormone that is mostly generated in the liver and has recently been hypothesised as a factor that regulates iron homoeostasis via its interaction with ferroportin, the primary iron export protein. Hepcidin attaches to ferroportin molecules and stimulates their internalisation and destruction, resulting in a reduction in iron release.

Inflammation increases the synthesis of hepcidin, which is a significant mediator of anaemia in chronic illnesses. Naemia, in turn, plays a critical role in the onset and development of LVH. In both dialysis patients and the general population, LVH has long been recognised as a significant and independent risk factor for mortality and cardiovascular events. Although the quality of RRT has improved significantly in recent years, cardiovascular mortality remains high despite the reduction in inflammation. The idea of microinflammation in ESRD still has to be evaluated more precisely.

It's unclear, for example, what level of IL-6 is required and sufficient to cause a micro-inflammatory disease, or how it may be more precisely described. In ESRD patients without inflammatory clinical episodes, a mean level of 4.4 pg/ml IL-6 was found with considerable intra-individual variation. In another research, dialysis patients with neither inflammation nor malnutrition had levels between 1.6 and 2.5 pg/ml. These figures range significantly from those reported in healthy people, who have circulation levels of about 1.0 pg/ml or less.

This suggests that even minor increases in circulating IL-6 levels may contribute to an increased risk of CVD. It found that even minor increases in IL-6 levels (1.81 versus 1.46 pg/ ml) were linked to an elevated risk of future myocardial infarction in seemingly healthy people.

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