What is 14-3-3η?

14-3-3η (eta) is normally a ubiquitous intracellular protein with critical life-sustaining functions. In RA, it is pathologically expressed in the extracellular space, through an exosomal-mediated process, where it can be measured in blood by a standard ELISA test in a clinical laboratory. 14-3-3η’s extracellular presence mechanistically drives up the expression of inflammatory factors such as TNFα, IL-6, MCP-1 as well as joint damage factors such as MMP1/3 and RANKL. Stimulation of cells, in vitro, with increasing concentrations of 14-3-3η leads to a dose-dependent increase in inflammatory and joint damage factors. These effects are induced by 14-3-3η’s selective activation of key intracellular pathways.

Clinical Data

The 14-3-3η protein is a biomarker for RA. It is produced by joints and it plays a biologic role in the joint erosion process. Blood levels are elevated in patients with RA, but not in other diseases including psoriasis, osteoporosis, gout, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, Crohn’s disease, primary Sjögren syndrome, scleroderma, and multiple sclerosis. Patients with Erosive Psoriatic Arthritis may be positive. A positive test indicates that the patient should be considered for referral to a rheumatologist, prior to the onset of significant joint damage. A positive JOINTstat™ test early in disease also marks high joint damage risk, and therefore, along with other clinical indicators, would signal to a rheumatologist how aggressively to manage the patient. Studies to date have shown that 14-3-3η:

- When positive (>0.19 ng/ml), provides a 5-50 times greater likelihood of having RA versus non-RA.
- Is positive in patients with joint pain who develop RA within 5 years of symptom onset.
- At high levels (>0.80 ug/L) is an indicator of RA that will lead to more joint damage over 3 years.
- At lower levels (<0.40 ug/L or negative in RA diagnosed patients) is an indicator of a higher likelihood of response to RA therapy.
- Decreasing levels with treatment or over time indicate a better disease outcome.
- Overall, RA patients who are negative or who have low levels (<0.40 ug/L) have a more favourable outcome.

One in three RA patients are missed by the sensitivity measures of RF or anti-CCP; 14-3-3η improves diagnostic sensitivity to 81%, 96% of healthy individuals are negative for 14-3-3η. JOINTstat™ (14-3-3η) testing improves early RA diagnosis, which along with prompt referral and appropriate treatment can significantly improve patient outcomes.

Clinical Availability

- In the United States, 14-3-3η testing has been available through Quest Diagnostics either as a stand-alone test or with RF and anti-CCP in an RA diagnostic panel called IdentRA™ since October 2013.
- In Canada, LifeLabs Medical Laboratory Services has launched 14-3-3η as JOINTstat™, which has been available since December 2014. In BC, healthcare providers must indicate JOINTstat™ under the section “Other tests” of the standard requisition form. In the rest of Canada, JOINTstat™ requires a separate requisition form.
- The 14-3-3η test is Health Canada approved, CE marked for clinical use in Europe and is FDA CLIA regulated in the US.

References


3. van Schaardenburg D, Maksymowych WP, Boers M, Turk S, Marotta A. 14-3-3η is an independent predictor of radiographic changes in early RA and higher titres inform a higher likelihood of joint damage progression. Ann Rheum Dis 2014; 73(Suppl2):THU0244.

4. van Schaardenburg D, Maksymowych WP, Marotta A. Lower Levels of 14-3-3η Predict DMARD Associated DAS Remission at 1 Year Follow Up. Ann Rheum Dis 2014; 73(Supp2).


