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Female sex hormone clue to fighting serious immune disease

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The results of a study presented today at the European League Against Rheumatism Annual Congress (EULAR 2016) showed for the first time a beneficial effect of oestrogens in experimental models of skin fibrosis that are representative of the disease process in systemic sclerosis (SSc). These findings may explain the increased incidence of SSc in women after the menopause, the greater severity of SSc in men, and importantly open up the possibility of developing potential hormone therapies for this difficult-to-treat condition.

SSc (also known as scleroderma) is an autoimmune disease affecting multiple organs, which predominantly affects women (with a female-to-male ratio of up to 9:1). Skin thickening is a defining feature of SSc, with excessive production of proteins such as collagen by fibroblasts resulting in skin thickening.

Skin involvement may be mainly confined to the face and extremities; however, in some SSc patients, disease progression is very rapid, with skin thickening extending beyond the extremities, and earlier, more widespread fibrosis involving the internal organs. The extent of skin involvement in SSc correlates inversely with survival and is considered a valuable marker of overall disease severity.3 Currently, no therapy with an acceptable toxicity profile has proven to be effective in the treatment of SSc skin disease.

"Because of the clear sex bias in SSc, we decided to assess if blocking the action of oestrogens, (female hormones that decrease in menopause)

plays a role in the development or vulnerability to this disease," explained Dr Jerome Avouac of the Paris Descartes University, Cochin Hospital, Paris, France.

The effect of oestrogen inhibition was evaluated in mouse models of skin fibrosis using two techniques. Firstly, in a population of mice in whom gene inactivation had knocked out the key receptor that responds to oestrogens, and secondly using tamoxifen which is a hormone therapy that blocks the action of oestrogen. Results showed that oestrogen inhibition consistently and significantly exacerbated the process of skin fibrosis.

In a second experiment, skin fibroblasts from SSc patients were stimulated with the cytokine that activates skin fibrosis (TGF-β) and then incubated with different concentrations of 17-?-oestradiol (a form of oestrogen) and/or tamoxifen to inhibit oestrogen. Measurements of the release of collagen from the fibroblasts, differentiation of these fibroblasts into myofibroblasts, and evidence of activation of the TGF-β pathway all confirmed that oestrogens significantly slow down fibrosis.

"Having confirmed that oestrogens indeed play a role in protecting against skin fibrosis in experimental models representative of SSc, the next step will be to begin investigating the potential role of hormone therapies as a treatment of SSc skin disease," Dr Avouac concluded.

Provided by European League Against Rheumatism