Abstract Rheumatoid arthritis (RA) is a sexually dimorphic, autoimmune inflammatory disorder affecting the joints. Joint disability in RA results primarily from loss of matrix components (collagen and glycosoaminoglycan) in the cartilage and synovium. This study was carried out to understand the effect of physiological levels of testosterone, estrogen, and progesterone on oxidative stress-induced changes in matrix composition in rat synovium in arthritis. Arthritis induction in castrated and ovariectomized rats resulted in enhanced oxidative stress and this was assessed by lipid peroxidation levels and depletion of antioxidants. This, in turn, led to significantly ($p < 0.01$) increased levels of TNF-a and matrix metalloproteinase-2 (MMP-2), subsequently resulting in loss of collagen, elastin, and glycosoaminoglycan (GAG) and disorganization of reticulin as evidenced by biochemical quantitation and also by staining for collagen, reticulin, and elastin. Treatment with physiological doses of dihydrotestosterone (25 mg topically) and estrogen (5 µg/0.1 ml subcutaneously) restored the antioxidant levels significantly ($p < 0.05$) and reduced the levels of TNF-a and MMP-2, with estrogen exhibiting a higher potency. This, in turn, attenuated the damage to reticulin organization as well as the loss of collagen and GAG in the articular tissues. However, elastin loss could not be attenuated by either treatment. Progesterone (2 mg/0.1 ml subcutaneously) was not shown to have any significance in disease modification, and on the contrary, it inhibited the protective effects of estrogen. However, progesterone contributed to increased collagen levels in the tissues.