The purpose of the present study was to determine the early pathologic changes in glucose transport and inflammation by characterizing alterations in proteins that play key roles in innate immunological responses and the inflammation pathway in an equine model of naturally occurring compensated insulin resistance (IR). Visceral and subcutaneous adipose tissue (AT) and skeletal muscle (SM) biopsies were collected from horses, which were classified as insulin-sensitive (IS) or compensated IR based on the results of an insulin-modified frequently sampled intravenous glucose tolerance test. Protein expression of insulin receptor substrate one (IRS-1), Toll-like Receptor 4 (TLR-4) and tumor necrosis factor alpha (TNF-α) were measured by Western blotting in visceral and subcutaneous adipose depots and skeletal muscle. Calsequestrian protein was used as a loading control. To better characterize the relationship between inflammation, IR and impaired glucose transporter trafficking, the inflammatory pathway phosphatase, suppressor of cytokine signaling three (SOCS-3), was quantified. IR was associated with a significantly increased total SOCS-3 in SM and omental AT, and TNF-α content in omental AT without a significant change in content in the other adipose sites. In addition, IRS-1 was increased in SM and nuchal ligament AT, but was not considered significant. A positive correlation between TLR-4 content and SOCS-3 was found. The data suggests that increased TLR-4 and SOCS-3 content of AT and SM were identified as biomarkers and fundamental pathogenic factors in IR. In addition, we show that SOCS-3 is a novel link between inflammation and glucose transport in insulin sensitive tissues.