Type 2 diabetes mellitus (T2DM) is a common complication of obesity; however, how obesity or high-fat diet (HFD) feeding contributes to development of systemic insulin resistance and ultimately T2DM is complex and not well understood. Our recent findings have revealed that IgG Fc domain is hyposialylated upon HFD feeding in mice, and that the hyposialylated IgG induces insulin resistance through activation of FcγRIIB in endothelium. We have made a parallel observation in human IgG isolated from T2DM patients. In the upcoming talk, I will summarize the newly-discovered mechanisms that are operative both in obese mice and in T2DM in humans.