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Hypothesis

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Tumor Necrosis Factor Inhibitors May Improve Glycemic Control in Patients Rheumatoid Arthritis and Concomitant Type 2 Diabetes Mellitus

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Insulin resistance is a key feature of obesity, metabolic syndrome, and Type 2 Diabetes Mellitus (T2DM). Inflammation and insulin resistance are closely linked with each other. I. Tumor necrosis factor-α (TNF-α) has been found to impair the insulin sensitivity and promote insulin resistance through multiple actions on the insulin sensitive tissues. Inflammatory cytokines such as TNF, Interleukin (IL)-6, IL-1 and IL-8 may inhibit insulin signaling.[1] Hotamisligil et al[2] did the pioneering work in 1993 confirming the link between TNF-α and insulin resistance in mice. Animal studies have confirmed that the TNF-α interferes with phosphorylation cascades of the insulin receptor beta subunit and insulin receptor substrate-1, thereby altering the transmembrane signaling that is essential for insulin action in various insulin sensitive tissues.[3-5] Also TNF-α causes depletion of GLUT 4, the insulin sensitive glucose transporter in adipocytes and muscles.[2,6,7] A intravenous administration of a recombinant TNF-α receptor antibody resulted in improvement in insulin sensitivity[2] and dramatic reductions in plasma insulin, glucose, and non-esterified fatty acid levels[5] in obese, as compared with lean rats.

These findings suggested that TNF-α inhibitors (TNFi) could be used for the treatment of T2DM. But initial two human clinical trials of anti TNF-α antibodies for treatment T2DM failed to show statistically significant improvement in insulin sensitivity.[8,9] These studies however had few limitations; they had short duration of treatment, small number of patients and were underpowered.

Short-term treatment with etanercept over 4 weeks was associated with beneficial effect on reduction of the inflammatory markers, but no improvement in vascular or metabolic insulin sensitivity in 20 adult patients with T2DM in an open labeled study.[10] In 2011, a prospective study of 40 patients of metabolic syndrome without diabetes, prolonged therapy with etanercept for 6 months clearly showed improved fasting glucose, increased the ratio of high molecular weight to total adiponectin, and decreased soluble intercellular adhesion molecule-1 (sICAM-1) . In another study TNF-α antagonism with etanercept was associated with reduction in glucose level and increase in the proportion of high molecular weight adiponectin in obese patient's metabolic syndrome.[11]

Rheumatoid Arthritis (RA) is autoimmune inflammatory disease involving joints and extra-particular tissues. T2DM patients are at increased risk of developing RA. A large nationwide population based case control study showed elevated risk of RA in female Taiwanese patients with T2DM.[12] Similarly, patients with RA are also at increased risk of developing diabetes.[13] There is a direct correlation between the degree of impaired glucose handling and the severity of the inflammatory activity in patients with RA. Dessein and colleagues[14] reported an increased prevalence of insulin resistance as assessed by the Homeostasis Model Assessment

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of Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) in patients with inflammatory arthritis, including RA, spondyloarthritis, and undifferentiated inflammatory arthritis, as compared to in healthy controls. In this study, insulin resistance was associated with several markers of inflammation, including TNF-α, interleukin (IL)-6, Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), and measures of disease activity and damage. Moreover, in this series of patients with RA insulin resistance was associated with coronary calcifications as well. These results point towards the role of insulin resistance and inflammation in the pathogenesis of coronary atherosclerosis in RA.[15] Circulating TNF-α is also an important mediator of endothelial dysfunction and has been implicated in increased cardiovascular risk in patients with RA.[16,17]

TNF-α is the major cytokine involved in the immunopathogenesis of RA. Excellent response to TNFi therapy has changed the paradigm of treatment of RA worldwide. As TNFi therapy gained wider acceptance for various rheumatic and other inflammatory diseases, researchers have observed significant improvement in insulin resistance in psoriasis, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis patients treated with TNFi particularly infliximab and etanercept.[18-20] Effects were more pronounced in patients with high baseline insulin resistance.[21] There have been case series where patients with Crowns disease and T2DM who were treated with infliximab, showed improved fasting glucose and insulin sensitivity.[22] Also complete control of diabetes leading to withdrawal of insulin therapy while on infliximab and relapse of diabetes after discontinuation of infliximab has been reported.[23]

TNFi have been found to decrease the risk of development of T2DM in patients with RA. In a large observational study consisting of 13,905 patients with RA treated with different DMARDS from 1996 to 2008, adjusted risk of incident DM was lower for individuals starting a TNFi or hydroxychloroquine compared with initiation of other nonbiologic DMARDs. In another study, involving 1,587 patients with RA, only 16 of 522 (incidence rate 8.6 per 1000 person-years) as opposed to 75 among 1065 patients (incidence rate 17.2 per 1000 person years) developed new onset T2DM (p=0.048) after adjusting for age, sex, race, BMI, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), erythrocyte sedimentation rate (ESR), and use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, hydroxychloroquine, and methotrexate. The study concluded that TNFi use was associated with a 51% reduction in risk of developing T2DM.[24] In a retrospective study, 8 patients with diabetes and either RA or Crowns disease treated with etanerecept or infliximab over 10 years were compared with controls matched for the diagnoses. Patients treated with TNFi had statistically significant improvement in fasting glucose, HBA1C and fasting triglyceride levels as compared to controls.[25]

Theoretically, patients with RA who also have concomitant T2DM are more likely to have difficult to control diabetes by virtue of increased insulin resistance caused by elevated TNF-α levels. Anti-TNF therapy should lead to improved insulin resistance and improved diabetes control. There is no large study available to evaluate the effect of TNF inhibitor therapy on the control of the concomitant diabetes in patients with rheumatic diseases. We hypothesize that patients with RA and concomitant T2DM who are on TNFi have better controlled diabetes as compared to those who are on conventional DMARDS. We also hypothesize that patients with RA and DM on TNFi have lower risk of cardiovascular disease as compared to those on traditional DMARDS by virtue of control of inflammatory activity in both DM and RA. We look forward for prospective studies in this interesting area of research.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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