

Metabolic effects of TNF

The metabolic effects of TNF are highly reproducible in rodent models, but the effects of TNF neutralization in human patients have had inconsistent results.

Finding	References
TNF levels correlate with obesity, insulin resistance, and other adverse phenotypes in humans	1-20
Genetic loss of TNF function improves glucose homeostasis in animal models of obesity and insulin resistance	21-25
Antibody-mediated TNF blockade improves glucose homeostasis in animal models of obesity and insulin resistance	26-32
Genetic loss of TNFR1 and/or TNFR2 mediates insulin sensitivity or other metabolic pathologies	33-37
Mice lacking both TNFR1 and TNFR2 fed high fat diet have impaired insulin sensitivity	38
TNF production in macrophages contributes to systemic glucose dysmetabolism	25,39
TNF infusion causes insulin resistance in humans	40-42
TNF neutralization improves glucose homeostasis or reduces diabetes risk in human patients	43-47
TNF neutralization does not improve glucose homeostasis in human patients	48-51
Meta-analysis of TNF neutralization studies demonstrating improved glucose homeostasis	52,53

- 1 Kern, P. A. *et al.* The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest* **95**, 2111-2119, doi:10.1172/JCI117899 (1995).
- 2 Arner, P. Obesity and insulin resistance in Swedish subjects. *Diabet Med* **13**, S85-86 (1996).
- 3 Zinman, B., Hanley, A. J., Harris, S. B., Kwan, J. & Fantus, I. G. Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. *J Clin Endocrinol Metab* **84**, 272-278, doi:10.1210/jcem.84.1.5405 (1999).

- 4 Park, H. S., Park, J. Y. & Yu, R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Prac* **69**, 29-35, doi:10.1016/j.diabres.2004.11.007 (2005).
- 5 Peti, A. *et al.* Relationship of adipokines and non-esterified fatty acid to the insulin resistance in non-diabetic individuals. *J Endocrinol Invest* **34**, 21-25, doi:10.3275/7025 10.1007/BF03346690 (2011).
- 6 Haus, J. M. *et al.* Plasma ceramides are elevated in obese subjects with type 2 diabetes and correlate with the severity of insulin resistance. *Diabetes* **58**, 337-343, doi:10.2337/db08-1228 (2009).
- 7 Hyun, Y. J. *et al.* Atherogenicity of LDL and unfavorable adipokine profile in metabolically obese, normal-weight woman. *Obesity* **16**, 784-789, doi:10.1038/oby.2007.127 (2008).
- 8 Chedraui, P. *et al.* Nitric oxide and pro-inflammatory cytokine serum levels in postmenopausal women with the metabolic syndrome. *Gyn Endocrinol* **28**, 787-791, doi:10.3109/09513590.2012.671395 (2012).
- 9 DeLoach, S., Huan, Y., Keith, S. W., Martinez Cantarin, M. P. & Falkner, B. Relationship of blood pressure and obesity with inflammatory cytokines among African Americans. *Ther Adv Cardiovasc Dis* **5**, 149-157, doi:10.1177/1753944711408757 (2011).
- 10 Majumdar, I. & Mastrandrea, L. D. Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome. *Endocrine* **41**, 442-449, doi:10.1007/s12020-011-9589-4 (2012).
- 11 Swaroop, J. J., Rajarajeswari, D. & Naidu, J. N. Association of TNF-alpha with insulin resistance in type 2 diabetes mellitus. *Indian J Med Res* **135**, 127-130 (2012).
- 12 Nilsson, J., Jovinge, S., Niemann, A., Reneland, R. & Lithell, H. Relation between plasma tumor necrosis factor-alpha and insulin sensitivity in elderly men with non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol* **18**, 1199-1202 (1998).
- 13 Mishima, Y. *et al.* Relationship between serum tumor necrosis factor-alpha and insulin resistance in obese men with Type 2 diabetes mellitus. *Diabetes Res Clin Prac* **52**, 119-123 (2001).
- 14 Koster, A. *et al.* Body fat distribution and inflammation among obese older adults with and without metabolic syndrome. *Obesity* **18**, 2354-2361, doi:10.1038/oby.2010.86 (2010).
- 15 Katsuki, A. *et al.* Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* **83**, 859-862, doi:10.1210/jcem.83.3.4618 (1998).
- 16 Tsukui, S. *et al.* Moderate-intensity regular exercise decreases serum tumor necrosis factor-alpha and HbA1c levels in healthy women. *Int J Obes Relat Metab Disord* **24**, 1207-1211 (2000).
- 17 Ziccardi, P. *et al.* Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* **105**, 804-809 (2002).
- 18 Bruun, J. M., Pedersen, S. B., Kristensen, K. & Richelsen, B. Opposite regulation of interleukin-8 and tumor necrosis factor-alpha by weight loss. *Obes Res* **10**, 499-506, doi:10.1038/oby.2002.68 (2002).

- 19 Lechleitner, M., Herold, M., Dzien-Bischinger, C., Hoppichler, F. & Dzien, A. Tumour necrosis factor-alpha plasma levels in elderly patients with Type 2 diabetes mellitus-observations over 2 years. *Diabet Med* **19**, 949-953 (2002).
- 20 Popko, K. *et al.* Proinflammatory cytokines Il-6 and TNF-alpha and the development of inflammation in obese subjects. *Eur J Med Res* **15 Suppl 2**, 120-122 (2010).
- 21 Uysal, K. T., Wiesbrock, S. M., Marino, M. W. & Hotamisligil, G. S. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* **389**, 610-614, doi:10.1038/39335 (1997).
- 22 Ventre, J. *et al.* Targeted disruption of the tumor necrosis factor-alpha gene: metabolic consequences in obese and nonobese mice. *Diabetes* **46**, 1526-1531 (1997).
- 23 Bouter, B., Geary, N., Langhans, W. & Asarian, L. Diet-genotype interactions in the early development of obesity and insulin resistance in mice with a genetic deficiency in tumor necrosis factor-alpha. *Metab Clin Exper* **59**, 1065-1073, doi:10.1016/j.metabol.2009.11.003 (2010).
- 24 Salles, J. *et al.* TNFalpha gene knockout differentially affects lipid deposition in liver and skeletal muscle of high-fat-diet mice. *J Nutrit Biochem* **23**, 1685-1693, doi:10.1016/j.jnutbio.2011.12.001 (2012).
- 25 Aouadi, M. *et al.* Gene silencing in adipose tissue macrophages regulates whole-body metabolism in obese mice. *Proc Natl Acad Sci USA* **110**, 8278-8283, doi:10.1073/pnas.1300492110 (2013).
- 26 Li, Z. *et al.* Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. *Hepatology* **37**, 343-350, doi:10.1053/jhep.2003.50048 (2003).
- 27 Araujo, E. P. *et al.* Infliximab restores glucose homeostasis in an animal model of diet-induced obesity and diabetes. *Endocrinology* **148**, 5991-5997, doi:10.1210/en.2007-0132 (2007).
- 28 Borst, S. E. & Bagby, G. J. Neutralization of tumor necrosis factor reverses age-induced impairment of insulin responsiveness in skeletal muscle of Sprague-Dawley rats. *Metab Clin Exper* **51**, 1061-1064 (2002).
- 29 Borst, S. E., Lee, Y., Conover, C. F., Shek, E. W. & Bagby, G. J. Neutralization of tumor necrosis factor-alpha reverses insulin resistance in skeletal muscle but not adipose tissue. *Am J Phys Endocrinol Metab* **287**, E934-938, doi:10.1152/ajpendo.00054.2004 (2004).
- 30 Ishikawa, K. *et al.* Subcutaneous fat modulates insulin sensitivity in mice by regulating TNF-alpha expression in visceral fat. *Horm Metab Res* **38**, 631-638, doi:10.1055/s-2006-954580 (2006).
- 31 Shimizu, I. *et al.* Semaphorin3E-induced inflammation contributes to insulin resistance in dietary obesity. *Cell Metab* **18**, 491-504, doi:10.1016/j.cmet.2013.09.001 (2013).
- 32 Hadad, N. *et al.* Induction of cytosolic phospholipase a2alpha is required for adipose neutrophil infiltration and hepatic insulin resistance early in the course of high-fat feeding. *Diabetes* **62**, 3053-3063, doi:10.2337/db12-1300 (2013).
- 33 Uysal, K. T., Wiesbrock, S. M. & Hotamisligil, G. S. Functional analysis of tumor necrosis factor (TNF) receptors in TNF-alpha-mediated insulin resistance in genetic obesity. *Endocrinology* **139**, 4832-4838, doi:10.1210/endo.139.12.6337 (1998).

- 34 Steinberg, G. R. *et al.* Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of AMP-kinase signaling. *Cell Metab* **4**, 465-474, doi:10.1016/j.cmet.2006.11.005 (2006).
- 35 Liang, H. *et al.* Blockade of tumor necrosis factor (TNF) receptor type 1-mediated TNF-alpha signaling protected Wistar rats from diet-induced obesity and insulin resistance. *Endocrinology* **149**, 2943-2951, doi:10.1210/en.2007-0978 (2008).
- 36 Romanatto, T. *et al.* Deletion of tumor necrosis factor-alpha receptor 1 (TNFR1) protects against diet-induced obesity by means of increased thermogenesis. *J Biol Chem* **284**, 36213-36222, doi:10.1074/jbc.M109.030874 (2009).
- 37 Yamato, M. *et al.* High-fat diet-induced obesity and insulin resistance were ameliorated via enhanced fecal bile acid excretion in tumor necrosis factor-alpha receptor knockout mice. *Mol Cell Biochem* **359**, 161-167, doi:10.1007/s11010-011-1010-3 (2012).
- 38 Schreyer, S. A., Chua, S. C., Jr. & LeBoeuf, R. C. Obesity and diabetes in TNF-alpha receptor-deficient mice. *J Clin Invest* **102**, 402-411, doi:10.1172/JCI2849 (1998).
- 39 De Taeye, B. M. *et al.* Macrophage TNF-alpha contributes to insulin resistance and hepatic steatosis in diet-induced obesity. *Am J Phys Endocrinol Metab* **293**, E713-725, doi:10.1152/ajpendo.00194.2007 (2007).
- 40 Nielsen, S. T. *et al.* Tumour necrosis factor-alpha infusion produced insulin resistance but no change in the incretin effect in healthy volunteers. *Diabetes Metab Res Rev* **29**, 655-663, doi:10.1002/dmrr.2441 (2013).
- 41 Plomgaard, P. *et al.* Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes* **54**, 2939-2945 (2005).
- 42 Krogh-Madsen, R., Plomgaard, P., Moller, K., Mittendorfer, B. & Pedersen, B. K. Influence of TNF-alpha and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. *Am J Phys Endocrinol Metab* **291**, E108-114, doi:10.1152/ajpendo.00471.2005 (2006).
- 43 Antohe, J. L. *et al.* Diabetes mellitus risk in rheumatoid arthritis: reduced incidence with anti-tumor necrosis factor alpha therapy. *Arthritis Care Res* **64**, 215-221, doi:10.1002/acr.20657 (2012).
- 44 Kiortsis, D. N., Mavridis, A. K., Vasakos, S., Nikas, S. N. & Drosos, A. A. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* **64**, 765-766, doi:10.1136/ard.2004.026534 (2005).
- 45 Stanley, T. L. *et al.* TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *J Clin Endocrinol Metab* **96**, E146-150, doi:10.1210/jc.2010-1170 (2011).
- 46 Pina, T. *et al.* Anti-TNF-alpha therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* **29**, 1325-1330, doi:10.1111/jdv.12814 (2015).
- 47 Miranda-Filloy, J. A. *et al.* TNF-alpha antagonist therapy improves insulin sensitivity in non-diabetic ankylosing spondylitis patients. *Clin Exp Rheumatol* **30**, 850-855 (2012).

- 48 Dominguez, H. *et al.* Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. *J Vasc Res* **42**, 517-525, doi:10.1159/000088261 (2005).
- 49 Ferraz-Amaro, I. *et al.* Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Horm Met Res* **43**, 801-808, doi:10.1055/s-0031-1287783 (2011).
- 50 Paquot, N., Castillo, M. J., Lefebvre, P. J. & Scheen, A. J. No increased insulin sensitivity after a single intravenous administration of a recombinant human tumor necrosis factor receptor: Fc fusion protein in obese insulin-resistant patients. *J Clin Endocrinol Metab* **85**, 1316-1319, doi:10.1210/jcem.85.3.6417 (2000).
- 51 Ofei, F., Hurel, S., Newkirk, J., Sopwith, M. & Taylor, R. Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* **45**, 881-885 (1996).
- 52 Burska, A. N., Sakthiswary, R. & Sattar, N. Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *PLoS One* **10**, e0128889, doi:10.1371/journal.pone.0128889 (2015).
- 53 Solomon, D. H. *et al.* Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* **305**, 2525-2531, doi:10.1001/jama.2011.878 (2011).