

## **Tumor Necrosis Factor Alpha: Role in the Development of Obesity and Diabetes Mellitus**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author ZMS managed the literature searches and wrote the first draft of the manuscript. Author TSS edited and approved the first manuscript. Author LST managed the literature searches and corrected English version. All authors read and approved the final manuscript*

### **Article Information**

DOI: 10.9734/AJBGMB/2020/v4i330108

#### Editor(s):

(1) Dr. Theocharis Koufakis, Aristotle University, Greece.

#### Reviewers:

(1) R. S. Chauhan, GB Pant University, India.

(2) Divya Pingili, Osmania University, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/58560>

**Review Article**

**Received 29 April 2020**

**Accepted 05 July 2020**

**Published 20 July 2020**

### **ABSTRACT**

Obesity and Diabetes Mellitus (DM) are defined as worldwide pandemics by the World health organization due to their economic burden and widespread. Although a huge amount of research is being done in the field of obesity and DM today, many questions remain unsolved. Tissue inflammation is the main factor in the development of both obesity and DM, leading towards irreversible changes in the tissue and formation of specific complications. One of the widespread cytokines, tumor necrosis factor alpha (TNF- $\alpha$ ), was shown to be involved with inflammation in the development of metabolic disorders and neurodegenerative diseases. Even though the role of TNF- $\alpha$  in the pathogenesis of these two diseases remains unclear, new ways of treating and preventing diseases based on TNF- $\alpha$  antagonism attracted the attention of scientists. In this review, TNF- $\alpha$  and its receptors' structures and properties are explored, and their role in disease development, including obesity and type 2 DM (DM2) will be discussed by viewing data from literature.

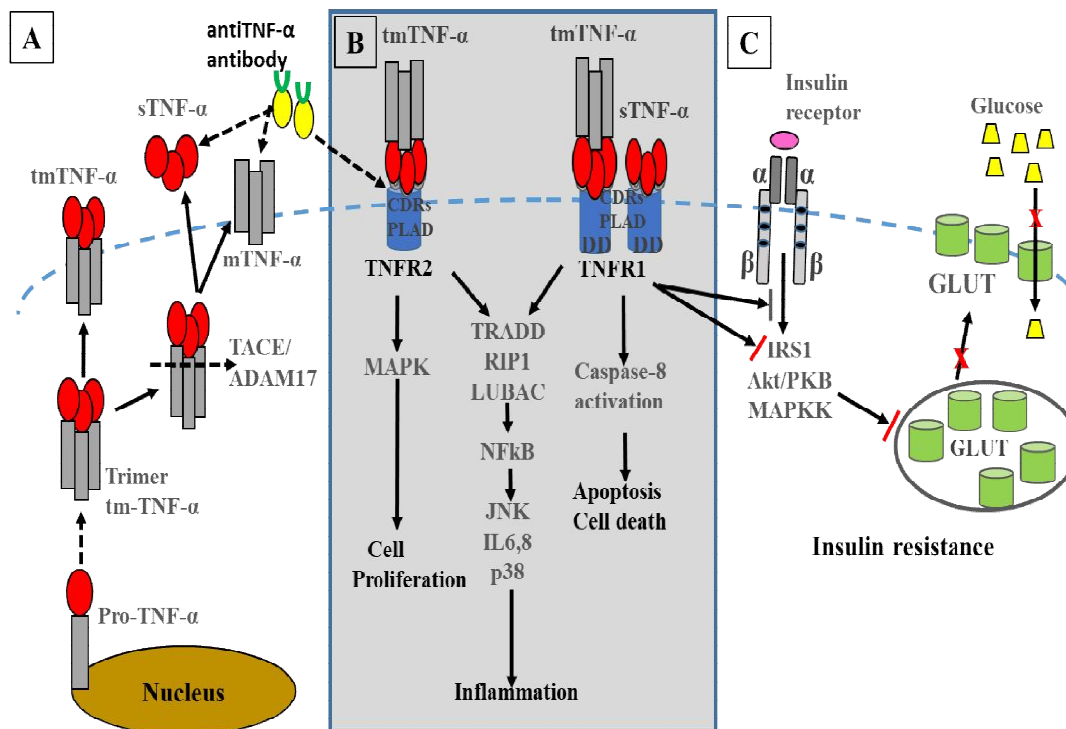
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**Keywords:** Tumor necrosis factor alpha; TNF receptors; TNF- $\alpha$  inhibitors; obesity; diabetes.

## 1. INTRODUCTION

Obesity and Diabetes Mellitus (DM) are two worldwide pandemics, which consume a big amount of the medical and social budget, and affect nearly one tenths of the population [1]. Although the number of people diagnosed with DM is around 425 million, according to data from epidemiological studies, only one third of people with type 2 DM (DM2) have been diagnosed, while the other two thirds don't even know that they have this disease [2-5]. It is well known that obesity is the future of DM2 and is viewed as the initial step of the disease. Due to similar biochemical abnormalities and clinical features, obesity, diabetes, ischemic heart disease, hypertension, and polycystic ovarian syndrome

are defined as metabolic syndromes [6,7]. Finding new effective ways of treating and preventing these diseases remains a priority in the health care system, as well as among the life sciences. Although adipocytokines, including the tumor necrosis factor alpha (TNF- $\alpha$ ), were shown to be involved in the pathogenesis of both obesity and DM2 [2, 3,5,8-11], treatment based on TNF- $\alpha$  antagonism is presented in a few studies, [12-16] but cannot fully explain the mechanisms of their efficacy. In this review we would like to characterize TNF- $\alpha$ , describe its mechanism of action, its binding characteristics with its specific receptors, and describe how TNF- $\alpha$  can be involved in the pathogenesis of diseases, specifically obesity and DM2.



**Fig. 1. TNF-  $\alpha$  structure and forms (A), binding with its receptors (B) effects on insulin signaling (C)**

*Panel A – TNF- $\alpha$  synthesizes from nucleus as a pro-TNF- $\alpha$ , then forms trimers (tm-TNF- $\alpha$ ), which can be cleaved by TACE (ADAM17) to soluble sTNF- $\alpha$  and membrane bound part mTNF- $\alpha$ ; AntiTNF- $\alpha$  antibody can bind with tmTNF- $\alpha$ , mTNF- $\alpha$  and sTNF- $\alpha$  and inhibits its effects;*

*Panel B – TNF receptors type 1 (TNFR1) and type 2 (TNFR2) binds both sTNF- $\alpha$  and tm-TNF- $\alpha$ ;*

*Panel C – TNF- $\alpha$  affects insulin signaling pathway through IRS1 and MAPK*

## 2. TNF-A STRUCTURE, FRACTIONS AND FUNCTION

There are widely expressed transmembrane TNF superfamily proteins such as cytokines, lymphotoxins, and receptor ligands that contain a specific homology domain and commonly have a three-dimensional structure [17,18]. The first discovered protein in this family is TNF- $\alpha$  [18,19]. This protein is associated with acute inflammation and was first cloned in 1986 [18,19]. TNF- $\alpha$  is a transmembrane cell signaling protein that contains a specific homology domain which can be cleaved into circulation and is involved in producing systemic inflammation, especially in the acute phase reaction [20,21]. TNF- $\alpha$  is mainly located in the immune and neuronal cell membranes [22,23]. As shown by many authors, TNF- $\alpha$  is produced by active macrophages, CD4+ lymphocytes, natural killers cells, mast cells, eosinophils, and neuronal cells, and is involved in systemic inflammation [18,19,22, 23].

TNF- $\alpha$  is initially produced as a monomer 26kDa membrane protein (pro-TNF- $\alpha$ ) which combines in trimers and becomes a mature TNF- $\alpha$ , tm-TNF- $\alpha$  (Fig. 1, Panel A). The tm-TNF- $\alpha$  can act independently or can be cleaved by the TNF- $\alpha$  converting enzyme (TACE/ADAM17) to a membrane bound protein (mTNF- $\alpha$ ) and soluble 51 kDa protein (sTNF- $\alpha$ ) [23,24]. These molecules from the TNFs family are usually secreted from the cell membrane into circulation, functioning as cytokines triggering inflammation and apoptosis [13,24].

TNFs as integral membrane proteins participate in signal transduction and regulate many cell functions, in which sometimes their effects may be controversial [24]. For example, TNF- $\alpha$  is a powerful physiological inducer of apoptosis [19, 23]. At the same time, cytokines are endogen pyrogens, involved in fever, inflammation, cell apoptosis, cachexia, depression of tumor development, and inhibition of viral gene replication [24].

Based on data from literature in the Fig. 1 we tried to explain schematically appearance of TNF- $\alpha$  molecule isoforms (panel A), their binding with receptors, signaling, crosstalk (panel B), and how TNF- $\alpha$  may affect insulin signaling and cause insulin resistance (panel C).

## 3. TNF-A RECEPTORS

TNF- $\alpha$  usually realises its effects through specific receptors. Structurally TNF receptors are composed from extracellular and intracellular domains (Fig. 1, panel B). An extracellular domain contains four cysteine-rich motifs (CDRs) which are important for ligand binding and molecule assembly, known as the pre-ligand binding assembly domain (PLAD), which is necessary for further downstream signaling [25-27].

Two types of receptors were found for TNF- $\alpha$ : TNF- $\alpha$  receptor type 1 (TNFR1), referred to as p60, and TNF- $\alpha$  receptor type 2 (TNFR2), referred to as p80 [17,26]. These two receptors are also distinguished by their expression. TNFR1 is an ubiquitously expressed protein in all tissues. Whereas TNFR2 is mostly expressed in immune and endothelial cells [23,25,26]. TNF- $\alpha$  can provide its effects through its type 1 and type 2 receptors simultaneously or separately [14,28]. However, stimulation of both receptors provides signaling for inflammatory factors and gene transcription, probably through the nuclear factor kappa beta (NF- $\kappa$ B) and the AP2 protein [14,23, 29].

TNFR1 can bind and act by both sTNF- $\alpha$  and tm-TNF- $\alpha$  (Fig. 1, panel B), whereas TNFR2 can be induced only by tm-TNF- $\alpha$ . Interestingly, TNFR2 was found to be capable of activating apoptosis even without the death domain (DD) [17,27]. When TNF- $\alpha$  binds to its receptor, it usually interacts through the specific DD with the other DD that contains proteins such as the TNFR1 associated death domain protein TRADD or TNF receptor associated factor 2 TRAF2. This mobilizes apoptosis, suppressing signalling complexes such as the protein receptor interacting protein kinase 1 or RIP1, linear ubiquitin chain assembly complex LUBAC [8,17,24]. Moreover, this complex can also induce different signaling pathways such as NF- $\kappa$ B and trigger inflammatory transcription genes such as IL-6, IL-8, p38, c-junk N-terminal kinase (JNK), and TNFs [8,17,30]. The next property of TNF- $\alpha$  signal transduction is the assembly of receptor DD with the Fas associated adapter protein towards procaspase 8, which then will be inhibited by RIP1 and RIP3 [31,32].

TNFR2, unlike TNFR1, does not contain the DD domain and provides signaling towards NF $\kappa$ B, inhibits apoptosis, and signals to Phosphoinositol-3 kinase (PI3K) protein kinase B

(PKB)/Akt and Mitogen activated protein kinase (MAPK) pathways, leading to protein transcription, synthesis and cell proliferation [24, 33-35].

Interestingly, the presence of both receptors is necessary for apoptosis signaling. Whereas, in the absence of TNFR1, but not TNFR2, the apoptosis signalling of TNF- $\alpha$  was fully suppressed [14,28,29].

However, the intracellular domain of TNFR2, unlike TNFR1, contains 80 amino acid residues associated with cell apoptosis and is called the death domain (DD) because it activates caspases and is associated with cell death [17, 27].

Thus, the multifaceted effects of TNF- $\alpha$  can be explained by differences in its signalling through the TNFR1 and TNFR2 receptor properties, which permit the development of new treatments and therefore prevention of diseases [24,36,37] [19,33].

#### 4. SOLUBLE FRACTION OF TNFRS

TNF- $\alpha$ 's both receptors i.e. TNFR1 and TNFR2 are found on the cell membrane as well as in the circulation as soluble fractions sTNFR1 and sTNFR2 [23,38]. Some authors have shown the formation of soluble TNFR1 and TNFR2 by shedding their external domains by TACE (Fig. 1, panel B), as well as by exocytosis and migration towards the intracellular space and appearing in the circulation as soluble receptor forms [38,39]. The activity of TACE was also found in the blood serum [40,41]. In healthy volunteers, there were appearances of sTNFR1 and sTNFR2 in the circulation after a TNF- $\alpha$  injection [42].

The soluble fraction receptors in the blood stream are seen as an early predictor of disease and can be used in diagnostics [40]. For example, if soluble TNFRs and TACE are found, this can be used to predict that it is from small alterations to Alzheimer's disease [40,43]. High levels of soluble TNFRs and increased TACE activity in the blood serum were found in Alzheimer's disease [40], Parkinson's disease [44], and in patients with multiple sclerosis, and were shown to remain high throughout the diseases [45].

Interestingly, mTNF- $\alpha$  can bind with sTNFRs to produce a reversible signal in the cell (Fig. 1, panel B). This can be regulated by Transforming

Growth Factor beta (TGF- $\beta$ ), that is responsible for cell proliferation and differentiation and also by p38MAPK, which regulates gene transcription, metabolism and cell proliferation [41]. Moreover, TNFR1 at low concentrations of TNF- $\alpha$  can bind with sTNFR1 to form a ligand to imitate TNF- $\alpha$  action, and produce a reverse signal [41]. Authors showed activation of extracellular kinase Erk1/2 and cellular growth of connecting axons of sympathetic neurones from the upper neck node due to reverse TNF- $\alpha$  signaling [41,46]. According to the material mentioned above, we can propose that the action of TNF- $\alpha$  inhibitors may depend on reverse signaling [41,46]. The authors also suggested to take this phenomena into account when interpreting the results of experiments [46].

#### 5. INHIBITION OF TNF-A EFFECTS

Nowadays the pharmacological inhibitors of TNF- $\alpha$  and its receptors are developed (Fig. 1, Panel A) and used in experiments as well as in clinical practice [46-49]. Pharmacological TNF- $\alpha$  inhibitors Infliximab (Remicade), Adalimumab (Humira), Certolizumab (Cimzia) and Golimumab (Simponi) are antibodies designed to TNF- $\alpha$ , whereas Etanercept (Enbrel) are antibodies designed to TNFRs [50-52]. Interestingly, the activation of sphingomyelinase in sphingomyelin hydrolysis leads to the formation of ceramides, galactosylceramides, and sulphatides in neurodegenerative brain diseases [46,49]. However, treatment with the antihistaminic agent dimebon – 3,6-dimethyl-9-(2-methyl-pyridyle-5)-ethyl-1,2,3,4-tetrahydrocarboline dihydrochloride simultaneously with a blockade of H1 receptors were shown to suppress the activity of TNF- $\alpha$ , resulting in the prevention of Alzheimer's disease [53,54]. Treatment with Dimebon showed protected sphingomyelin and lipid destruction on the surface of neuronal cells of mice in the experiment and also prevented Alzheimer's disease [54]. Other authors have shown the neuroprotective effect of TNFR1 that occurred by activation of the neuronal growth factor (NGF) necessary for neuronal cell growth. TNFR2 unlike TNFR1 promotes expression of intracellular adhesion molecules type 1 ICAM1 and stimulates neuronal inflammation and neurodegeneration [10,54]. However, authors there mentioned the possibility of cross interaction between both receptor signaling pathways. Other authors indicate that TNF-beta lymphotoxin alpha can also bind with both TNF- $\alpha$  receptors and is probably involved in the pathogenesis of brain ischemia [30]. As shown,

interactions between TNFR2 and the D-receptor of IL-17 leads to the activation of NF- $\kappa$ B in experiments on cells from the kidney's proximal tubules [37].

The complexity of multicomponent signaling pathways define the controversial effects of TNF- $\alpha$ , TNFR1, and TNFR2, and complicates the development of a new therapy based on TNF- $\alpha$  antagonism. Specifically, more evidence is needed for explaining the mechanism of TNF- $\alpha$  and its receptors involved in systemic inflammation [24].

## 6. ROLE OF THE TNF-A IN DISEASE DEVELOPMENT

As noted above, the major effects of TNF- $\alpha$  involved in the development of diseases such as rheumatoid arthritis, and other neurodegenerative, vascular and metabolic diseases, were shown by many authors. The major effects of TNF- $\alpha$  and the major diseases where TNF- $\alpha$  is involved in their pathogenesis is presented in Fig. 2.

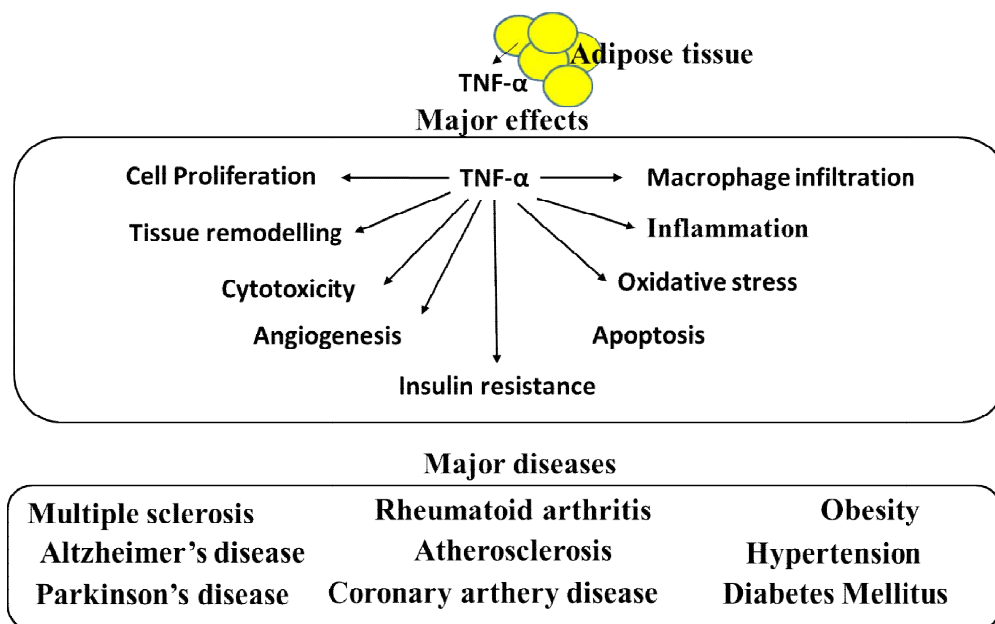
Studies have shown that inhibition of TNFR1 signaling through suppression of inflammation has decreased neurodegenerative changes in the brain and prevents Alzheimer's disease. However, inhibition of TNFR2 signaling has shown to be beneficial in the prevention of Parkinson's disease and multiple sclerosis [52,55]. The effects of suppressing TNF- $\alpha$  derived inflammation markers were shown in experiments with rheumatoid arthritis, psoriatic arthritis, and coeliac disease [24,55-57]. Results showed where suppression of TNF- $\alpha$  in mice leads to axon remyelination due to the lower expression of neurofilament H, which is responsible for axon injury [58,59].

The beneficial effect of these mechanisms in the prevention of disease were shown in clinical studies with the inhibition of effects of TNF- $\alpha$  signaling by Etanercept, Adalimumab, and Infliximab [50,52,60,61]. Unfortunately, there are few studies done regarding TNF- $\alpha$  inhibition therapy and due to their wide side effects, there are limitations for their usage [51,62-64].

It is well known that ischemia and stroke cause neuronal cell hypoxia and death. In response to ischemia, most neuronal, glial, and astrocyte cells increase their TNF- $\alpha$  secretion capability [65,66], which has a two-sided effect, such as

impairing as well as protecting. Treatment with Etanercept, which is an anti-TNFR2 antibody presented a Fc-fusion fragment of Immunoglobulin G (IgG), showing beneficial effects in the regression of ischemia and inflammation [67]. Whereas other authors showed impaired neuron sensitivity to ischemia and increasing neuronal inflammation after that treatment [68]. Interestingly, TNF- $\alpha$  pre-treatment showed neuroprotection at the ischemia site [68]. These kinds of controversial results are probably related to the type of TNFRs involved in signalling [69]. Moreover, authors were shown increased expression of TNFR1 in the early stages of stroke during the first 6 hours, whereas TNFR2 expression was detected 24 hours after an ischemic stroke [67]. These differences in TNFRs expression proposed results of posttranslational regulation of the receptors expression, probably by NF- $\kappa$ B [70].

In some studies it was shown that the ischemia site was wider in mice with the TNFR1 gene suppressed in comparison to mice with the TNFR2 gene suppressed or to their normal expression [71,72]. These results permit authors to conclude that TNFR1 is involved in preconditioning and resisting ischemia [73]. Moreover, it was shown that higher expression of TNFR1 was found to be responsible in the regulation of different neuroprotective mediators such as vascular and endothelial growth factors, VEGF and EGF [74]. Mice with TNFR1 gene suppression and human TNFR2 gene over expression were shown to have increasing TNFR2 signaling with the stimulation of an anti-inflammatory response in the brain endothelium resulting in inflammatory ischemia [75]. Thus, the neuroprotective effects of TNFR1 and the neurodegenerative inflammatory effects of TNFR2 were shown [24, 74]. Unexpected results from other authors show that there is a decrease in neurodegeneration after suppression of the TNFR1 gene by retinal ischemia-perfusion and an increase of neurodegeneration after TNFR2 gene suppression in mice [76]. Their results suggest that signaling through TNFR1 increases neuronal damage and signaling through TNFR2 was neuroprotective [77]. Similar results were shown in mice experiments with brain ischemia after lipopolysaccharide treatment [78]. Authors found that signaling through TNFR1-JNK are responsible for neuroinflammation and neurovascular damage [78].



**Fig. 2. Major effect of TNF-  $\alpha$  and major disease where TNF-  $\alpha$  is involved in their pathogenesis**

As shown in the literature, the role of TNFRs in the development of neurodegeneration and neuroinflammation was controversial and depended on the type of ischemia, its duration, and character, and could not explain the process of alterations and neuron damage in Alzheimer's or Parkinson's diseases where TNFR1 and TNFR2 signaling were shown as unstable and variable effects of TNF- $\alpha$  [76,79].

Interestingly, small conductance calcium-activated potassium channels type 2 ( $K_{Ca}$ )<sub>2</sub> and ( $K_{Ca}$ )<sub>2.2</sub> were viewed as a following step in signal transduction through TNFR2 [70,80]. Authors explained that channel overstimulation lead to neuroprotection and decrease of their neuroexcitation. These channels were found to be responsible for plasticity of CA1 cells in the hippocampus and for cognition and memory [81].

In another study shown, stimulation of PI3K/PKB/Akt signaling by TNFR2 in primary astrocytes induced gene expression of neuropeptides, including the leukemia inhibition factor LIF gene [10]. The leukemia factor presented a neurotrophic cytokine produced by astrocytes [10]. Increasing this cytokine level showed that during oligodendrocytes maturation, protected primary neurons from excitotoxicity i.e. cell damage after overexcitation [82,83]. They also protected axons from acute inflammation [83].

Another following signaling product of TNF- $\alpha$  is a CXCL12, cytokine C-X-C motive 12, that was found to be involved in the proliferation and differentiation of oligodendrocyte precursor cells. This was found to affect brain function in areas such as cognition and memory [84,85].

Recent studies have shown that TNFR2 signaling in microglia was related to the activation of anti-inflammatory pathways, such as increasing IL-10 [86]. Many authors supported the opinion that signaling through TNFR1 especially increased factors promoting neurodegeneration, whereas TNFR2 signaling specifically increased neuroprotection [24].

The effectivity and preference of TNFR inhibition in disease pathogenesis, specifically diabetes mellitus, remains unclear and continues to be studied intensively.

## **7. OBESITY, INSULIN RESISTANCE AND TNF-A**

Obesity is described as an increase of fat masses that leads to augmentation of adipocytokines as well as TNF- $\alpha$  secretion [87]. As were shown by recent studies, obesity also results in the loss of regulation and balance between energy intake and expenditure by the hypothalamus [14,87].

TNF- $\alpha$  gene deletion in mice protected them from diet-induced obesity due to increasing heat production [14,87]. TNF- $\alpha$  has shown to play a role in adipose tissue modification, promoting white adipocytes to turn beige (beigeing) in response to augmentation of uncoupled protein type 1 and type 3 (UCP1 and UCP3) gene expressions and showed how TNF- $\alpha$  could be involved in the pathogenesis of obesity and diabetes. The hormone of white adipose tissue, leptin, is a major regulator of body weight in the hypothalamus [88]. Interestingly, in mice with TNFR1 suppression, the resistance to leptin was not observed. While Janus kinase 2 (JAK2), signal transducer and activator transcription 3 (STAT3), and Forehead box protein O 1 (FOXO1) gene expression under leptin over stimulation remained normal in TNFR1 knockout mice [14]. Whereas in wild type mice with diet induced obesity and resistance to leptin, the signal transduction through JAK2/STAT3/FOXO1 pathways were affected [88].

Interestingly, in mice on high-fat high-carbohydrate diets, obesity and type 2 DM were prevented by TNF- $\alpha$  suppression with infliximab, leaving mice insulin sensitive [89,90]. Moreover, they showed improving glycemia levels under the TNF- $\alpha$  suppression as a result of Insulin Receptor Substrate 1 and 2 (IRS1 and IRS2) and Akt phosphorylation, and also showed increasing levels of glucose uptake by muscle, liver and hypothalamus due to better insulin signaling [89]. However, the genetic blockade of TNFR2 did not show any changes in insulin sensitivity [14,89]. Similar decreases in body weight, fat masses, and size of adipocytes were shown by suppression of the Tole-like receptor type 4 (TLR4) gene [31,91-93]. Thus, as was mentioned above, TNF- $\alpha$  can affect insulin sensitivity through TNFR1 and TNFR2. Inhibition of TNF- $\alpha$  by Anti-TNF- $\alpha$  or anti-TFRs antibodies showed better results for glycemia and insulin sensitivity (Fig. 1, Panel C).

Interestingly, suppression of TNFR1 and TNFR2 separately promoted the development of insulin resistance in ob/ob mice [90,94], whereas suppression of both receptors simultaneously prevented insulin resistance [95]. Some authors found that suppression of TNFR1 in the hypothalamus prevented insulin resistance in mice, and lowered blood leptin and insulin levels even when on a high-fat diet [14,29,95-97].

The promising results in obesity prevention were obtained by suppression of TNFR1 with

infliximab directly into the hypothalamus through a stereotaxic canule [11,98,99]. As authors showed, prevention of obesity was due to increasing heat production and also suppressing of TNF- $\alpha$  production and TNFR1 signaling in the hypothalamus in high-fat diet induced obesity [90,94,96]. Increasing heat production was linked to high expression of UCP1 and UCP3 protein in fat and muscle without significant changes in cytochrome 3 and mitochondrion contents.

IL-6, IL-17, and TGF- $\beta$  C-reactive proteinw (CRP) were found to be involved in tissue inflammation in DM2. TNF- $\alpha$  was also shown to be involved in tissue inflammation through TNFRs signaling by demonstrating development of insulin resistance in rats, where GLUT4 activity affected adipose tissue [100,101]. Interestingly, tissue inflammation was prevented in mice by TNF- $\alpha$  gene suppression [101,102]. Moreover, the injection of the Ig-G antibody to TNFRs showed improved sensitivity to insulin [99,101,103], but the mechanisms by which are not clear yet.

Meta-analysis of 23 studies have showed a significant increase in blood serum TNF- $\alpha$  levels in people with type 2 DM, which was more significant in the subgroups by age, ethnicity, and disease duration [104].

Some authors showed the role of TNF- $\alpha$  in the development of diabetes with complications in experimental and clinical studies [104]. For example, increasing TNF- $\alpha$  expression in orbital tissues were shown in rats with experimental diabetes [105,106]. Injection of anti TNFRs antibody infliximab lowered the expression of TNFRs, which was associated with decreasing p38 and protooncogene bRAF, and suggested the involvement of TNFRs in the development of inflammation [107].

TNF- $\alpha$  was also found to be involved in the development of hypertension and kidney damage in experiments on rats treated with Angiotensin II. Whereas addition to diet TNFRs inhibitor Etanercept, prevented elevation of blood pressure, promoted lower expression of Monocyte chemoattractant protein type 1 (MCP1) and CD68+, and increased Cyp2c23 protein expression in the kidneys vessels [99,108]. The results showed the harmful effects of TNF- $\alpha$  in the development of hypertension and potential damage to kidney vessels structure and function [108,109].

In clinical studies, authors showed vision improvement in patients with diabetic retinopathy and macular edema when treated with infliximab [107]. Similarly to retinopathy, TNF- $\alpha$  levels increased in serum as well as in urine in patients with nephropathy, and was correlated with microalbuminuria levels [105].

Unfortunately, there were no more clinical studies on TNF- $\alpha$  inhibition in obesity and DM2. We speculate that by suppressing TNF- $\alpha$ , it will be possible to prevent obesity and the development of DM2 in early stages, which can stop epidemics, save peoples lives, and support the health care budget.

## 8. CONCLUSION

Obesity and DM are worldwide pandemics that have huge impacts on health care and the economy. TNF- $\alpha$  is shown to be involved in the pathogenesis of many neurodegenerative, vascular, and metabolic disorders like obesity and DM. In theory, obesity and DM could easily be prevented and treated by antagonizing the effects of TNF- $\alpha$ . Although studies have shown the role of TNF- $\alpha$  in the development of obesity, insulin resistance, and type 2 DM [100], more questions remain unclear, and are sometimes contradictory. We need more evidence about the safety, advantages and disadvantages of TNF- $\alpha$  inhibitors as a new prevention and treatment of obesity and DM. In our view, deeper investigations are needed for further development of new therapies based on the antagonism of TNF- $\alpha$  and TNFRs effects.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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