



## Role of Inflammation in Obesity and Diabetes

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### Abstract

In this advanced world, one of the major health problems the world facing is obesity. This is a worldwide problem which can lead to the occurrence of many serious illnesses like diabetes and heart diseases. It is now crystal clear that obesity not only perturbs lipid and glucose homeostasis but also it damages the pathways of the body. As the excess adiposity can integrate many pathways it will result in immune responses in the body like inflammation. The need to understand how the body react to such alterations in its metabolic functions, resulting in chronic autoimmune diseases like diabetes is very important. A deep and clear understanding of these responses is important to fully aware and treating chronic metabolic diseases.

**Keywords** Inflammation; Obesity; Health; Infection; Diabetes

### Introduction

In modern society there is reduced physical activity resulting in caloric abundance which in turn peaked the incidence of obesity and led to an array of metabolic pathologies like type 2 diabetes and heart diseases. Many intense research efforts are being done to understand the hidden mechanisms of these diseases, but these diseases remain a threat to the modern world by increasing the global mortality and morbidity rate [1,2]. This empathize the need of novel effective and therapeutic and preventive measures. However there are many mechanisms which are taking place during obesity and diabetes, the plasma concentration of inflammatory mediators, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), is increased in the insulin resistant states of obesity and type 2 diabetes. In this review we highlight how the shift in the metabolic balance of the body is resulting in a chronic inflammatory state, referred to as “meta-inflammation,” that targets metabolically critical organs and tissues to adversely affect systemic homeostasis.

### Literature Review

#### Inflammatory signalling in obesity

Modulation of Nutrient and pathogen sensing or response systems by obesity or infection can lead to overlapping physiological outcomes. For instance, the chronic inflammation of obesity leads to elevated plasma lipid levels and the development of insulin resistance, eventually resulting in fatty liver disease, atherosclerosis, and diabetes. Infection typically leads to a more transient and robust inflammatory response and short-term hyperlipidaemia that aids in the resolution of the infection.

The increased expression of tumour necrosis factor (TNF), pro-inflammatory cytokine in adipose tissue of obese mice was discovered almost 2 decades ago. This was the first indication that inflammatory mediators are associated with obesity [3,4]. The key features of obesity induced insulin resistance and associated metabolic disease in animal

models and humans are inflammatory signalling by adipocytes and infiltration of adipose tissue by immune cells, which is now well accepted too. Both adipocytes and macrophages of obese mice residing in adipose tissue secrete a number of cytokines including TNF  $\alpha$ , interleukin (IL)-6, IL-1, and migration inhibitory factor. Visceral fat of obese humans showed an increased expression of inflammatory mediators [5,6].

Through several mechanisms, there is disruption of insulin signalling by cytokines. This also includes induction of the suppressors of cytokine signalling (SOCS) family of proteins, which have been shown to inhibit insulin receptor kinase activity, interfere with binding of insulin receptor substrate (IRS)1 and IRS2 to the insulin receptor, and promote IRS degradation [7,8]. Increased inflammation and direct inhibition of insulin action takes place because cytokines activates inflammatory signalling via c-Jun N-terminal kinase (JNK) and inhibitor of kappa beta kinase (IKK-beta) pathways in both immune and neighbouring non immune cells [9,10]. Thus the increased inflammatory signalling due to the increased adipocytes (obesity) results in increasing the metabolic deterioration resulting in diabetes.

#### Inflammation and diabetes

Another important function of adipocytes which is disrupted in obesity is the signalling function of adipocytes. This has a potential impact on the immune signalling resulting in many metabolic as well as immunological disorders. Metabolic signalling and immune function can be modulated by adipokines [11,12]. Adiponectin, which acts to improve systemic insulin sensitivity, also display anti-inflammatory properties [13]. Resistin can interfere with insulin action, glucose homeostasis and also boosts inflammatory responses [14]. Chemerin and vaspin are emerging as potential regulators of insulin sensitivity [15]. Clearly the diverse range of proteins secreted by adipocytes act in coordination to propagate specific signalling patterns that can modulate inflammation. Those proteins also have roles in energy homeostasis, and metabolism of glucose and lipids.

During obesity, a deviation in the profile of adipokines and cytokines released by adipocytes has the capability of directly influencing both metabolic and immune signalling systemically. Thus

the adipocytes have a real commanding role in the insulin mechanism so it clears the link between obesity and diabetes.

### Immune system activation in adipose tissue during obesity

Adipocytes store excessive nutrient load and progressively become hypertrophic. Cell hypertrophy leads to a pro-inflammatory response mainly through hypoxia and endoplasmic reticulum (ER) stress-related mechanisms. Eventually, this may lead to adipocyte death. Furthermore, stressed adipocytes produce a wide range of cytokines and chemokines, including TNF- $\alpha$ , that in turn promote immune cell accumulation and activation in adipose tissue. Therein, numerous macrophages create a local pro-inflammatory loop with adipocytes. Other immune cells, such as T cells, might also contribute to inflammation. In parallel, circulating FFAs and mLDL particles may directly bind to TLR2 and TLR4, inducing NF- $\kappa$ B activation and production of various pro-inflammatory factors including pro-IL-1 $\beta$ . In the meantime, hyperglycaemia promotes the activation of the NLRP3 inflammasome through the binding of TXNIP in macrophages. Lipid species such as ceramides may directly activate the inflammasome. The NLRP3-caspase-1 complex promotes IL-1 $\beta$  secretion through cleavage of the proform. IL-1 $\beta$  strongly contributes to adipose tissue inflammation through auto amplification and paracrine activation during obesity.

### Tackling diabetes and obesity

The basis of therapeutic interventions in inflammation and insulin resistance is to ameliorate obesity by physical exercise and diet control. The significance of chronic inflammation and its molecular mechanisms when the development of type 2 diabetes is demonstrated in mice, suppression of inflammation-related molecules has successfully improved glucose intolerance. The contribution of exercise and diet is generally admitted to be effective to attenuate obesity and sustain health. Also Clinical applications of anti-inflammatory drugs such as Aspirin/salsalate, IL-1 $\beta$  and TNF $\alpha$  can reduce the activity of inflammasome by blocking the inflammatory response in different ways.

A well-established drug Metformin enhances the oxidation of fat and glucose presumably by activating adenosine monophosphate kinase [16]. A newer class of insulin-sensitizing drugs used are thiazolidinediones. These drugs are consistent with the theory that obesity-induced adipose tissue inflammation is a pivotal mediator of insulin resistance and provide additional scientific basis for therapy with PPAR- $\gamma$  agonists. Additional approaches that could be used to treat obesity and its effects on hyperglycaemia include drugs that attenuate appetite and enhance energy expenditure [17-19].

### Epidemiology

Type 2 diabetes which was since thought to be a metabolic disorder exclusively of adulthood has become increasingly more frequent in obese adolescents in the past few decades.

Type 2 diabetes occurs in all races even though a very high prevalence of type 2 diabetes has been observed in non-Caucasian groups (African Americans, Native Americans, Hispanics [20-24]). In recent studies diabetes is in the highest rates among youths aged 15-19 years in minority populations with incidence rate per 100,000 person-year. In particular, the reported incidence rate was 49.4 for Native Americans, 22.7 for Asian/Pacific Islanders, 19.4 for African

Americans, 17 for Hispanics, and 5.6 for non-Hispanic whites. Type 2 diabetes in youth is reported worldwide.

As there is an increase in the prevalence of type 2 diabetes in the obese paediatric population there is also an increase in the prevalence of the pre-diabetes conditions. There is a drastic growth in the number of obese children and adolescents affected by type 2 diabetes. In addition to this there is also an upraise in the deregulation of glucose homeostasis. This explains the link between both obesity and diabetes as well as points out why type 2 diabetes is becoming one of the most important public health problems. Therefore, identifying the factors that causes obesity is of primary importance in order to interrupt its progression and the diabetes-related cardiovascular complications.

### Discussion and Conclusion

The alarming increase in obesity rate makes it more widely discussed field of research. Obesity which is associate with adipocyte dysfunction, results in releasing and altering of adipokine production and signalling. Along with the systemic effects on metabolic regulation, these changes also promote infiltration of a wide range of immune cells into adipose tissue. The activation state and signalling of these immune cells is further varied by these factors, leading to initiation of metabolically driven, pro-inflammatory signalling cascades that inhibit insulin signalling in adipocytes. It also further enhances pro-inflammatory signalling in immune cells. As an outcome, adipocyte function is disrupted, they become insensitive to insulin and a vicious inflammatory cycle is engaged. This internal inflammation precedes the development of diabetes.

In a nut shell, the increased concentrations of TNF- $\alpha$  and IL-6, associated with obesity and type 2 diabetes, might interfere with insulin action by suppressing insulin signal transduction. This might interfere with the anti-inflammatory effect of insulin, which in turn might promote inflammation. Body mass index has a strong relationship to diabetes and insulin resistance. In an obese individual, the amount of NEFA, glycerol, hormones, cytokines, pro-inflammatory substances, and other substances that are involved in the development of insulin resistance are increased. Insulin resistance with impairment of  $\beta$ -cell function leads to the development of diabetes.

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