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The Effect of Obesity on Insulin Resistance in Terms of Cytokines and Hormones

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Abstract: With the increasing incidence and mortality of obesity, obesity-related health problems have become a worldwide priority. Clinical observation shows that obesity related to adipocyte differentiation is an important pathogenic factor of insulin resistance, and weight loss can reduce insulin resistance, indicating that obesity is related to insulin resistance. As the understanding of mechanism between obesity, cytokines, hormones and insulin resistance becomes clear, it is possible that these cytokines or hormones could be used in the use of biomarkers and the design of targeted therapies for insulin resistance. This review provides an overview of how obesity effect adipokines，hepatokines and inflammatory cytokines whose changes result in or exacerbate insulin resistance.

Keywords: obesity, insulin resistance, cytokines, hormones

1. INTRODUCTION

Obese patients are often accompanied by insulin resistance (IR). Insulin resistance (IR) is the reduction or disappearance of the response of target organs and tissues of insulin action, such as liver, muscle and adipose tissue, to the biological effect of insulin, resulting in a series of pathophysiological changes and clinical manifestations.

Adipokines are a class of cytokines or hormones secreted by white fat cells. It has shown that the occurrence of obesity is mainly due to abnormal secretion of adipocytes, large increase of adipocytes and excessive deposition of lipids in cells. Hepatokines are liver-derived proteins. The first hepatokine that has been proven to have a major pathogenetic role in metabolic diseases is α2-HS-glycoprotein (fetuin-A).Inflammatory cytokines are various cytokines involved in the inflammatory response. Mainly has the tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin 6 (IL - 6), transforming growth factor β (TGF - β), etc.

There is clear evidence that adipokines, hepatokines, inflammatory cytokines play an important role in the development of abnormal glucose and lipid metabolism, especially about the cause of insulin resistance. In this article I discuss some of the cytokines or hormonal changes caused by obesity that cause or exacerbate insulin resistance.

2.ADIPOKINES

Adipokines are produced by white or brown fat tissue. As a result patients that are obese or overweight will change the body fat rate or the ratio of white to brown fat which will change the level of adipokines content in serum.

2.1 Leptin

Leptin and its receptors play an important role in the process of glucose metabolism. Leptin can enhance the sensitivity of surrounding tissues to insulin and the uptake of glucose. As a negative regulator of insulin, leptin may be partly involved in insulin resistance. The insulin reactivity and inhibition of glycogen synthesis were reduced in

hepatoma cells and isolated fat cells exposed to high concentrations of leptin. Lu Hongyun et al. found that the variation frequency of THE leptin receptor gene at exon 203057 G-A was significantly different between T2DM and normal glucose tolerance group. It is the abnormal expression of leptin that damages the feedback regulation system of the hypothalamic-pituitary-adrenal axis in OB/OB mice, thus causing insulin resistance. Studies have shown that serum leptin levels are associated with body mass index, and levels of the adipocytokine gene rise when body fat levels are high.

2.2 Resistin

Resistin is a kind of peptide hormone secreted by fat cells in the body. As it is related to insulin resistance, it was named resistin. Studies have found that resistin has a significant pro-inflammatory effect. Resistin is closely related to inflammatory responses, and many inflammatory responses are accompanied by the elevation of resistin. It was found that the expression level of inflammatory factors in monocytes of human peripheral blood was significantly increased by stimulating human peripheral blood monocytes with high concentration of resistin. Steppan found that resistin does not directly reduce phosphorylation of IRS-1 serine residues, but indirectly by reducing phosphorylation of IR tyrosine residues. Resistin induces insulin signaling abnormalities by stimulating inflammatory signaling pathways. Both theory and experiment suggest that obese people have higher levels of resistin.

2.3 Adiponectin

Adiponectin (ADI) was first discovered to be an endocrine active serum protein secreted by adipose tissue. ADI in human body is not only mainly produced by white fat, but also can be produced in small amounts in liver, myocardium, fetal disk and other tissues. [1] Adiponectin can stimulate the body to release anti-inflammatory cytokines, inhibit the production of pre-inflammatory factors, and play an anti-inflammatory role. But, when the body remains in the prolonged state of insulin resistance, inflammation would expand gradually, forming of chronic inflammation. [2] However, after obesity is reached, the ability of adipose tissue to secrete ADI decreases, and the body becomes less sensitive to insulin, resulting in IR。[3] Kralisch et al. used the mouse model of adiponectin gene elimination, and found that mice showed severe insulin resistance. And they also indicates that adiponectin is involved in the occurrence and development of insulin resistance.

2.4 Zinc-α2-glycoproteins，ZAG

ZAG, a soluble protein with a molecular weight of about 43kDa, is a member of the major histocompatibility complex Type I family. Studies suggest that the increase of circulating ZAG level can increase insulin sensitivity and reduce the body’s insulin resistance through the glucose metabolism signaling pathway. The new study found that ZAG interacts with adipokines，such as adiponectin (ADI), in different tissues to regulate the body's insulin sensitivity. A study on metabolic syndrome suggested that serum ZAG level and ADI level of newly developed metabolic syndrome patients were lower than those of healthy control group, both of which were significantly negatively correlated with BMI. Studies on subcutaneous fat ZAG reported that the level of subcutaneous fat ZAG in people with normal body mass index was about 3.3 times higher than that in visceral fat tissue. However, the difference disappeared among the extremely obese.[1]

In summary, adipose tissue in obese people changes the amount of these adipokines they secrete. Then some adipokines would cause inflammation at last which contribute to the insulin resistance. And others can reduce insulin resistance by making cells more sensitive to insulin. After all their working mechanism are similar in general.

3 HEPATOKINES

Obesity has a huge impact on the liver, changing the amount of hepatokines.

3.1 Fibroblast Growth Factor,FGF-21

FGF21, a member of the FGF superfamily, is a secreted protein expressed mainly in the liver[4]，It is mainly regulated by the peroxisome proliferator-activated receptor and the insulin/protein kinase 1 pathway. It can be expressed in liver, fat, pancreas and muscle tissues, and plays an important role in improving insulin sensitivity and glucose and lipid metabolism. Xu Tongyu et al. speculate FGF21 improving insulin resistance in type 2 diabetic model mice may be by reducing inflammatory factors. The study of Zhang Nan et al. showed that the serum FGF21 level of obese or overweight patients was significantly increased, which was related to BMI, IR and other factors. The mechanism may be related to “FGF21 resistance” caused by compensatory increase of serum FGF21 level in pathological conditions such as obesity or overweight, hyperglycemia, etc.

3.2 Hepassocin

Hepassocin is a liver-specific growth factor that has been found to participate in the regulation of proliferation of hepatocytes and regeneration of the liver. The study of Wu Hung-Tsung et al. which based on HepG2 liver cancer cells showed that Hepassocin could block insulin signaling pathway and induce insulin resistance through an ERK1/2 dependent signaling pathway. The study of Ru-Lai Huang et al. provides evidence that subjects who are overweight or obese had significantly higher hepassocin concentrations than those of subjects who had a normal weight. Taken together, it suggest that hepassocin might be a link between obesity, and IR, and could be a potential candidate in developing comprehensive diagnostic/therapeutic approaches to manage these diseases.

3.3 Fetuin A

Fetuin-A is an endogenous natural insulin receptor tyrosine kinase inhibitor. It can directly inhibit the phosphorylation of insulin receptors, alter the downstream signaling molecules AMPK (AMP kinase) and AKT, and cause signal transduction disorder, causing IR.[5] Free fatty acids are known to stimulate the secretion of pro-inflammatory cytokines by adipocytes through toll-like receptor 4 (TLR4), leading to IR. Pal and Dasgupta et al. have shown Fetuin-A ACTS as an adaptor protein between free fatty acids and TLR4, and these findings suggest that Fetuin-a can enhance IR by this pathway.[6] To establish the link with obesity, the study showed that fetuin-A concentration in the T2DM group was higher than that in the control group.

3.4 Fetuin B

Fetuin B is the second member of the fetuin family, an endogenous inhibitor of the insulin receptor tyrosine kinase, and is produced primarily in liver tissue. In hepatocytes, fetuin B inhibits glucose metabolism pathways by inhibiting genes encoding 6 phosphoglucose and phosphoenolpyruvate carboxykinase, thereby reducing insulin sensitivity. [7] However, further studies are needed to elucidate the differences between in vitro and in vivo results and the specific molecular mechanisms by which fetuin B affects glucose metabolism. In humans, plasma fetuin B levels are increased in obese individuals with hepatic steatosis and T2D, and associated positively with intrahepatic triglyceride and insulin resistance.[8] Besides, Serum fetuin B levels were significantly higher in obese adults in relation to the metabolic syndrome than in the control group.

In conclusion, Liver factors can affect insulin resistance by affecting insulin-related pathways or changing other inflammatory cytokines, making the IR better or worse.

4 INFLAMMATORY CYTOKINES

Obesity is now widely recognized as a chronic inflammation which means that inflammatory cytokines and BMI have a strong relationship.

4.1 Secreted Frizzled Related Protein5,SFRP5

Secreted frizzled related protein 5 (SFRP5), which is one of the members of the SFRP protein family, can be

secreted by adipose tissue and is considered to be a bioactive substance closely related to autoinflammatory. Long-term chronic autoinflammation in the body is closely related to the occurrence of insulin resistance. Currently, it is believed that it can reduce the level of autoinflammation by antagonizing WNT/β -catenin pathway, and play a role in improving insulin resistance. Studies have found that the lung tissue expression of SFRP5 of the insulin resistance mice is less than that of mice without insulin resistance. Liu et al. believed that Sfrp5 may play an induction role in the proliferation, differentiation and maturation of adipogenic precursor cells, thereby reducing lipid deposition. And SFRP5 was negatively correlated with BMI.

4.2 TNF-α

TNF-α is the first inflammatory factor to link inflammation with insulin function. Studies have shown that increased production of fat-derived TNF-α has an important impact on insulin resistance in obese people. TNF-α can affect insulin function directly or indirectly through a variety of pathways. Direct pathways include induction of IRS-1 serine phosphorylation, down-regulation of IRS-1 expression, and reduction of GLUT-4. TNF-α can also indirectly induce insulin resistance in a number of ways. One of the most important is to increase FFA levels in the blood by stimulating MAPK mediated lipolysis of fat cells, which is activated by multiple pathways. Gasic et al. found that TNF-α induced G protein reduction is the most important mechanism causing lipolysis in rodents. In humans, increased levels of perilipin phosphorylation and decreased expression are the main factors causing the lipolysis effect of TNF-α. In addition, TNF-α can induce insulin resistance by inducing chronic inflammation in adipose tissue.[9] And Levels of TNF- were higher in both normal and T2DM patients than in non-obese patients.

4.3 IL-6

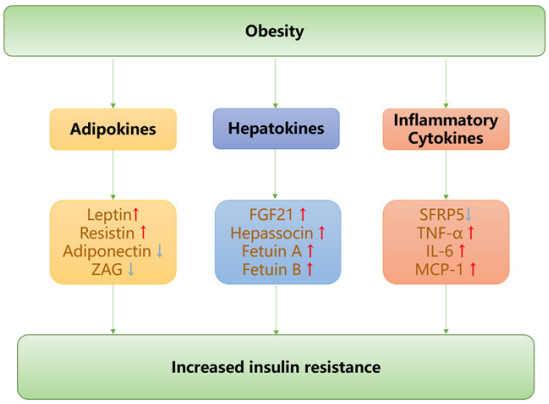
Adipose tissue is the main secreted tissue of IL-6, and the concentration of IL-6 in blood is positively correlated with obesity, impaired glucose tolerance and insulin resistance. IL-6 has a direct effect on insulin conduction in adipocytes and hepatocytes. In fat cells, IL-6 reduces protein expression of insulin receptor subunits and IRS-1, lowers insulin-mediated tyrosine kinase phosphorylation levels and insulin receptor subunit activity, and inhibits insulin-mediated glucose transport and fat formation by down-regulating glut-4 expression. In the adipose tissue of insulin resistant people, IL-6 mRNA expression increases, leading to a decrease in the insulin-mediated glucose treatment ratio. Studies have shown that IL-6 enhances glucose transport by enhancing the intrinsic activity of Glut-1 after treatment of 3T3-L1 fat cells. And BMI is an independent influence factor for il-6 elevation.

4.4 MCP-1

MCP-1 is a member of the monocyte chemotactic protein family. MCP-1 promotes the migration of inflammatory cells through chemotaxis in upregulated inflammatory molecules in adipose tissue of obese animals and humans. JIMENEZ - SAINZ et al. study found that activated by MCP - 1 extracellular signal regulating kinase (ERK) can cause a variety of downstream signal transduction events. MCP - 1 separately passivation of muscle cells and skeletal muscle insulin signaling and insulin stimulates glucose uptake, the two ways of alternating [10] may lead to insulin resistance. Tang et al. found that the McP-1 level of simple obesity patients was 25% higher than that of the normal control group, and the difference was statistically significant.

Inflammatory cytokines often act directly on insulin signaling pathways or glucose signaling pathways, causing or exacerbating insulin resistance. Many of these receptor channels have been used as therapeutic targets for insulin resistance.

5 CONCLUSION:



The conclusion for the content of hormones and cytokines in obese people which increased insulin resistance(↑stands for higher concentration levels in serum ,↓stands for lower concentration levels in serum than that in normal weight)

Obesity can change the secretion of cytokines, thus affecting metabolism and immune regulation pathways, leading to or promoting metabolic disorders. These cytokines are part of a complex network that mediates communication between fat, liver, muscle and immune system. Disorders in the content of certain hormones and cytokines can lead to metabolic disorders. At present, these hormones and cytokines have not been all used directly in the clinical treatment of insulin resistance. To my knowledge, leptin is used as a drug which is the treatment of congenital leptin deficiency obesity only, not used to treat IR.

However, given the disease-related changes in levels of relevant cytokines, the factors may serve as biomarkers for the early detection of insulin resistance, for instance, the rise of leptin, reisitin, adiponectin, FGF21. Moreover, based on preclinical studies, certain cytokines (FGF21, leptin, adiponectin, ZAG, MCP-1) can improve insulin sensitivity and may emerge as novel targets for broader and more efficient treatments as well as for prevention of insulin resistance. For example, thiazolidinediones is currently used to reduce insulin sensitivity, it works by increasing circulating adiponectin levels.Celastrol can increase insulin sensitivity by increasing leptin levels (which has not been used clinically)

Some cytokine especially the inflammatory cytokines and hepatokines or others like reisitin that cause insulin signaling abnormalities due to their elevated levels can be a target. The decomposing enzymes or inhibiting enzymes of them should also be considered as targets for treatment of endocrine disorders caused by obesity (not only insulin resistance, but also other diseases, such as atherosclerosis).

It is also worth investigating whether the use of external factors to force the increase of certain hormones and cytokines (such as ZAG, SFRP5) can reduce insulin resistance. After all, there is only evidence that BMI and IR affect the levels of some cytokines, and there is no evidence that increasing their levels reduces insulin resistance. Last but not least, methods of targetting specific insulin receptors is also a question worth thinking about in drug development.

The exact cause of insulin resistance has not yet been determined, but once it is, the mechanism by which these hormones and cytokines act will become clearer. And in the future drug research will also be more clearly targeted.

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