INTRODUCTION

Asthma is a disease that affects the breathing passage, or airways of the lungs. Asthma is a chronic inflammation disease that causes difficult breathing. When an exacerbation or attack of Asthma take place. The inflammation of the airways causes the linning of the breathing passages to swell. This swelling narrows the diameter of the airways eventually to a point that it is hard to exchange enough air to breath comfortably. This is when coughing, wheezing and the sensation of distress start ***(Chung et al., 2013).***

Insulin resistance is a physiological condition where the natural hormone insulin becomes less effective at lowering blood sugar. The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effect. Insulin resistance is a key component of the metabolic syndrome. Metabolic syndrome and insulin resistance are two terms that have been associated with conditions such as cardiovascular diseases, central obesity, glucose intolerance, dyslipidemia and hypertension ***(Gozal et al., 2008).***

Relationship between asthma and insulin resistance has been known to exist, but the possible reasons for this connection have been harder to pin down. In related researches, insulin resistance can occur due to intermittent hypoxia ***(Louis and Punjabi, 2009).*** Another cause that lead to insulin

resistance is pro-inflammatory cytokines such as (tumor necrosis factor-α and interleukin-6) that is increased also in asthma ***(Bradding et al., 2008 & Gokhan et al., 2007).***

Childhood obesity is a significant problem that has reached epidemic proportions around the world and is associated with several metabolic complications. Recently large body of epidermiologic data have linked obesity with development of asthma. That can be attributed to mechanical effects, gastroeosophageal reflux or through production of pro-inflammatory cytokines in adipose tissue and through hormonal action. It is well known that increased body mass index is associated with insulin resistance ***(Arshi et al., 2010).***

The degree of insulin resistance is estimated by the ***homeostasis model assessment of insulin resistance (HOMA-IR).*** The HOMA-IR is an index which is valid method for insulin resistant estimation in children ***(Matthews et al., 1985).***

AIM OF THE WORK

The aim of this study is to assess the incidence of insulin resistance among asthmatic children together with other parameters of metabolic syndrome (body mass index, blood pressure, lipid profile).

Chapter （1）

INSULIN RESISTANCE IN CHILDREN

Insulin hormone physiology in children

Insulin is an anabolic hormone that is produced by beta cells of the pancreas. The insulin produced is released into blood stream and travels throughout the body. Insulin is an essential hormone that has many actions within the body. Insulin is the dominant hormone driving metabolic process in the fed state; it acts through insulin receptors and also acts via the insulin like growth factor (IGF-1) ***(Samuel, 2011)***.

In a normal metabolism, any food contining glucose causes blood glucose level to increase, the elevated blood glucose stimulate B-cells of pancreas to release insulin. Normally, insulin binds to insulin receptors on target organ cells, resulting in a series of cellular events that promote intracellular glucose transport and metabolism ***(Ünal et al., 2012).***

Insulin Signaling:

Insulin signaling involves a complex signaling cascade downstream of the insulin receptor. This signaling cascade branches into two main pathways. The first is the phosphatidyl-inositol 3-kinase (PI3K), also called protein kinase B (PKB)

pathway which is largely responsible for insulin action on glucose uptake, as well as other metabolic actions of insulin, including the suppression of gluconeogenesis. The second pathway is the Ras-mitogen-activated protein kinase (MAPK) pathway which mediates gene expression, but also interact with the PI3K pathway to control cell growth and differentiation. The common intermediate to these pathway is insulin receptor substrate (IRS), which include four distinct family members, IRS 1-4. Activation of the insulin receptor leads to tyrosine phosphorylation of IRS1 which facilitate translocation of glucose transporter 4 (GLUT-4) to the sacrolemma to facilitate glucose entery into cell ***(Carl and Gerrold, 2009)*** **(Fig. 1).**

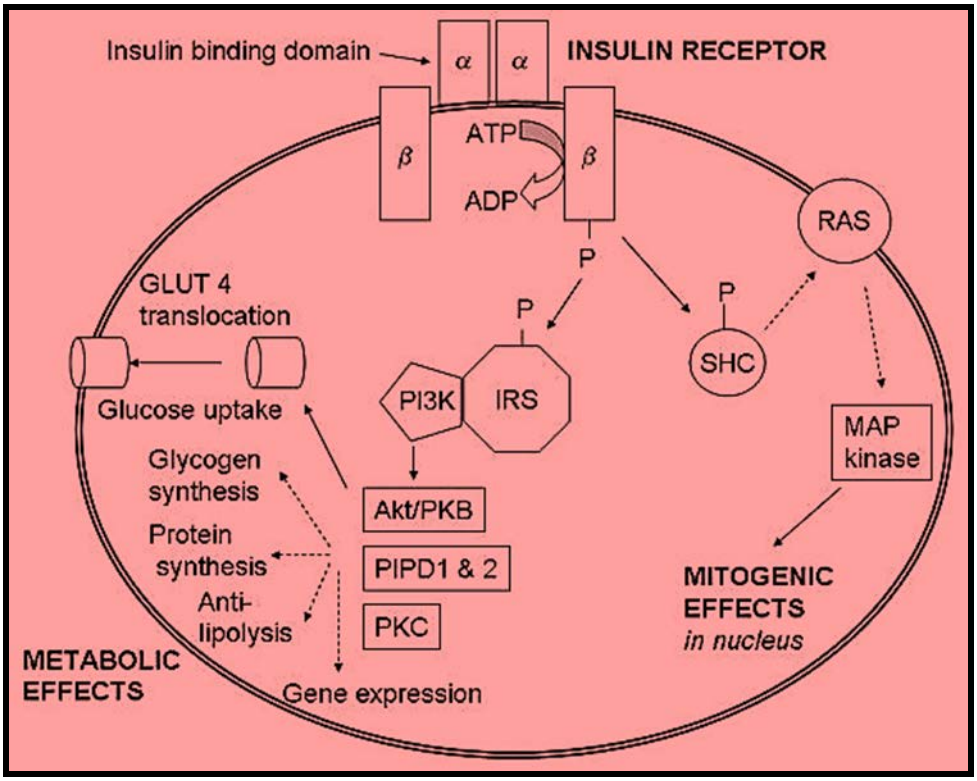

Fig. (1): Schematic presentation of insulin signaling pathways ***(Giorgino et al., 2008).***

Akt/PKB = protein kinase B; GLP-1 = glucagon-like peptide 1; ATP = adenosine triphosphate; IRS = insulin receptor substrate; ADP = adenosine diphosphate; MAP kinase = mitogen activated protein kinase; cAMP= cyclic adenosine monophosphate; PACAP = pituitary adenylate cyclase-activating polypeptide; DAG = diacylglycerol; PI3K = phosphatidylinositol 3-kinase; GIP = gastric inhibitory peptide; PIPD1 & 2 = phosphatidylinositol dependent protein kinases 1 & 2; Glucose-dependent insulinotropic polypeptide; PKC = protein kinase C; Glucose- 6- P = glucose 6 phosphate; RAS = rat sarcoma protein; GLUT 2 = glucose transport protein 2; SHC =adaptor protein with src-homology; GLUT 4 = glucose transport protein 4; VIP= vasoactive intestinal peptide.

Insulin Resistance:

Definition:

Insulin resistance is a state in which cells fail respond to the normal actions of the insulin hormone that over time leads to compensatory hyperinsulinemia ***(Samuel, 2011).***

Pathophysiology of insulin resistance:

In insulin resistance the normal levels of insulin don't have the same effect in controlling blood glucose levels. During the compensatory phase the pancreas produce more insulin called hyperinsulinemia and the blood glucose levels are still maintained. If compensatory mechanism fails, inappropriate insulin levels was secreted, impaired fasting glucose and impaired glucose intolerance ***(Eckel et al., 2009).***

Several mediators are thought to signal the pancreatic B cells to respond to insulin resistance. These potential signaling mediators include glucose, free fatty acids, autonomic nerves, fat derived hormone (e.g., a diponectin) and gut hormone (glucagon like peptide 1 "GLP-1"). GLP-1 is an incretin hormone that stimulates insulin secretion causes B cell mitosis while inhibiting apoptosis, inhibit glycogen secretion and delay gastric emptying ***(Samuel, 2011)***.

Insulin resistance in the liver cells result in reduced glucose uptake by their cells and also, decrease glycogen synthesis and storage and failure to suppress glucose production and that lead to increase glucose in blood.

Insulin resistance in fat cells, resulting in decreased uptake of circulating lipids and increased hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevate free fatty acids in the blood plasma, elevated amount of triglycerides and low density lipoprotein (LDL) in the blood and decreasing the amount of high density lipoprotein (HDL) ***(Hoehn et al., 2010).***

Causes:

Several factors can influence insulin sensitivity such as: Diet, Obesity, Inflammation and inflammatory cytokines, Hypoxia, Stress, Inactivity and excess weight, During steroid therapy, The metabolic syndrome (which is a group of conditions involving excess weight, high blood pressure and elevated level of cholesterol and triglyceride in the blood) ***(Fransesco et al., 2009)***.

I- Diet :

It is well known that insulin resistance commonly coexists with obesity. However, causal links between insulin resistance, obesity, dietary factors are complex and controversial. It is possible that one of them arises first, and tends to cause the other; or that insulin resistance and excess body weight might arise independently as a consequence of a third factor, but end up reinforcing each other. Some population groups might be genetically predisoposed to one or the other ***(Roger et al., 2010).***

Dietary fat has been implicated as a driver of insulin resistance, as elevated levels of free fatty acids and triglycerides in the blood stream and tissues have been found in many studies to contribute to diminished insulin sensitivity. Saturated fatty acids induce hepatic insulin resistance through activation of Toll-like receptor 4 (TLR-4) in the liver which in turn activates hepatic ceramide synthesis leading to inhibition of insulin signaling ***(Galbo et al., 2013).***

Several recent studies suggested that the intake of simple sugars and particularly fructose is also a factor that contributes to insulin resistance. Fructose is metabolized by the liver into triglycerides and tends to raise their levels in the blood stream. Therefore, it may contribute to insulin resistance ***(Pham, 2009)***.

Insulin resistance would result in increased circulating levels of insulin. Since insulin is the primary hormonal signal for energy storage into fat cells, which tend to retain their sensitivity in the face of hepatic and skeletal resistance. IR stimulates the formation of new fatty tissue and accelerates weight gain ***(Sluij et al., 2010)***.

Vitamin D deficiency also contributes to insulin resistance ***(Chiu et al., 2010)***.

II- Obesity:

Childhood obesity is a significant health problem that has reached epidemic proportions around the world and is associated with several metabolic and cardiovascular complications. Insulin resistant is a common feature of

childhood obesity and is considered to be an important link between adiposity and the associated risk of type 2 diabetes and cardiovascular disease. Insulin resistance is also a key component of the metabolic syndrome. Adipose tissue seems to play a key role in the pathogenesis of insulin resistance through several released metabolites, hormones and adipocytokines that can affect different steps in insulin action ***(Tateya et al., 2013).***

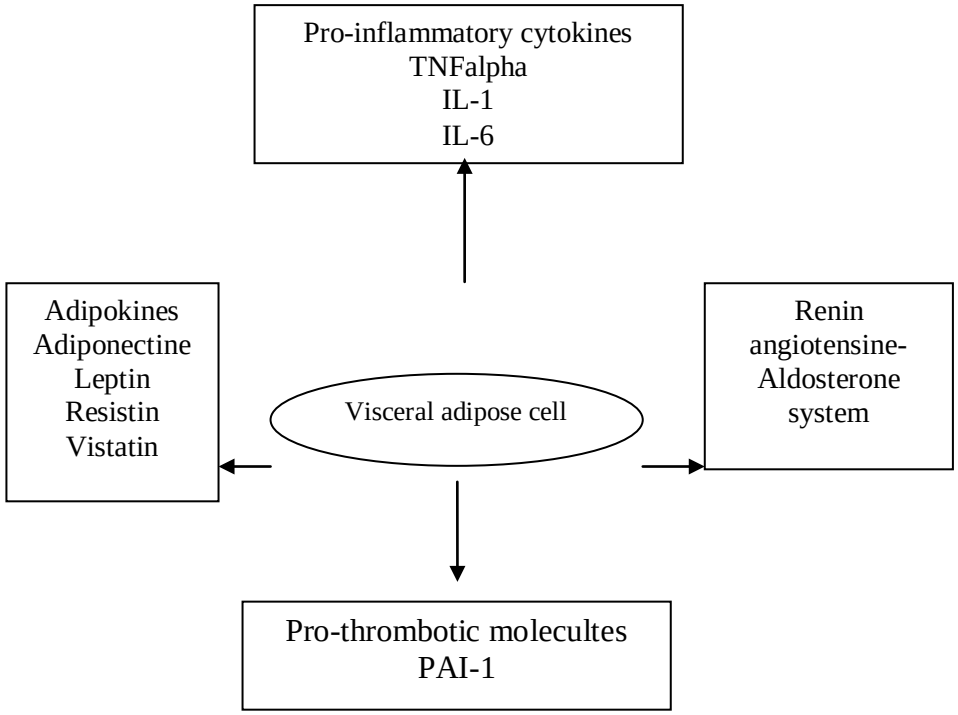

Figure (2): Adipokines secreted by adipocytes ***(Fulop et al., 2008).***

Adipocytes produce non-esterified fatty acids, which FA inhibit carbohydrate metabolism and impaired intracellular insulin signaling ***(Matsuzawa, 2008).***

Also, adipocytes produce adipokines such as leptin, resistin, adipsin, visfatin. Leptin is produced from adipose

tissue and bind to its receptor in the arcuate nucleus. Its concentration increases with increasing fat mass there is close relation ship between leptin and insulin resistance in children ***(Weiss and Caprio, 2009).***

Resistin may contribute to insulin resistance and its effect are mediated at target tissue such as liver, skeletal muscle and adipose tissue, as resistin antagonize glucose uptake in adipocytes and skeletal muscle ***(Claire and Mitchell, 2010).***

Obesity is a very common cause of insulin resistance. A potential mechanism for this relationship is ectopic lipid accumulation. However, obesity is also associated with a systemic chronic inflammatory response characterized by altered cytokine production and activation of inflammatory signaling pathways. Recent reports indicates that over nutrition and physical inactivity can lead to low-grade inflammation and oxidative stress. Low grade inflammation of resulting from chronic activation of the innate immune system and which can lead to insulin resistance. White adipose tissue is characterized by increased production and secretion of a wide range of inflammatory cytokines such as (TNF-α and interleukin-6, leptin and resistin) ***(Aparna et al., 2012).***

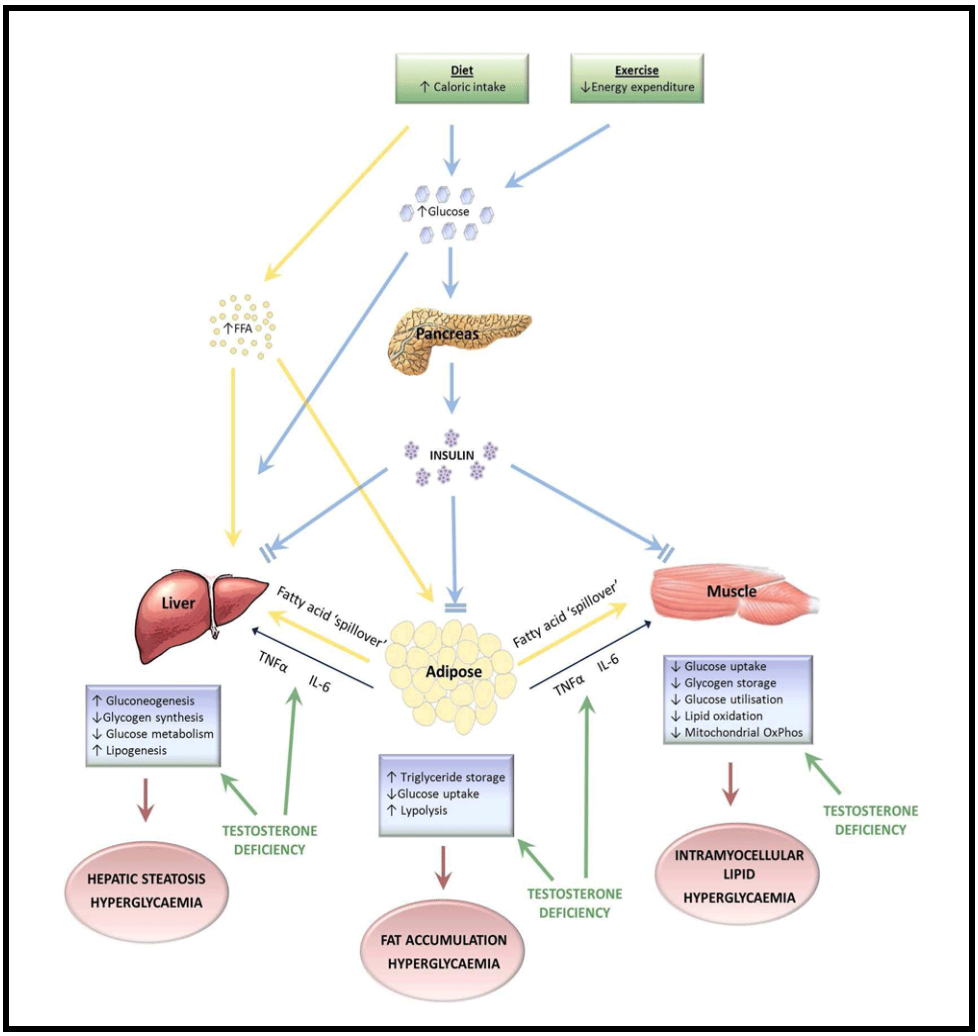

Fig. (3): Obesity induced insulin resistance ***(Aparna et al., 2012).***

III- Inflammation:

Excessive activation of inflammatory pathways and oxidative stress may represent fundamental steps in the development of insulin resistance, and inflammatory cytokines likely contribute to the link between inflammation, oxidative stress and skeletal muscle insulin resistance ***(Agrawal et al., 2011).***

Pro-inflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction. The sources of cytokines in insulin resistant states are the insulin target tissue themselves, primarily fat and liver but to a larger extent the activated tissue resident macrophages, chronic inflammation in these tissues could cause localized insulin resistance via autocrine/paracrine cytokine signaling and systemic insulin resistance via endocrine cytokine signaling all of which contribute to the abnormal metabolic state ***(Agrawal et al., 2011)***.

Several members of the cytokines network have the potential to affect insulin action, possibly through a common molecular mechanism. Cytokines such as tumor necrosis (TNF-α), TNF-β, interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-11 (IL-11) and interferon can alter insulin sensitivity by triggering different key steps in the insulin signaling pathway ***(Bouzekri et al., 2007)***.

TNF-α is a pleitrophic cytokine which occur in many pathological process including inflammation and allergy. TNF-α is produced by many cells including macrophages, T lymphocytes, mast cells and epithelial cells, but the principle source is the macrophage. The secretion of TNF-α is greatly enhanced by other cytokines such as interleukin-1 (IL-1), gamma interferon (INF-γ) ***(Swardfager et al., 2010).***

Role of TNF-α in insulin resistance (IR):

TNF-α activates and increase expression of several proteins that suppress insulin signaling at the level of insulin receptor substrate, making human body less responsive to insulin and increasing the risk of insulin resistance ***(Swardfager et al., 2010).***

TNF-α decreases tyrosine phosphorylation of IR-1 and increase IRS-1 serine phosphorylation. This relative increase in serine to tyrosine phosphorylation may lead to increased proteosomal degradation of IRS-1 or decreased ability of IRS-1 to engage p85 subunit of P13K (phosphatidylinositol 3-kinase) leading to decrease insulin metabolic signaling ***(Yong-Zhong et al., 2008).***

Also, TNF-α through $TNFR_1$ suppress Ras-migogen activated protein kinase (AMPK) activity via upregulation of protein phosphatase 2C. Activation of this phosphatase, in turn, reduces skeletal muscle acetyl COA carboxylase phosphorylation, suppress fatty-acid oxidation and increase intramuscular diacylglycerol accumulation, that lead to insulin resistance ***(Yong-Zhong et al., 2008).***

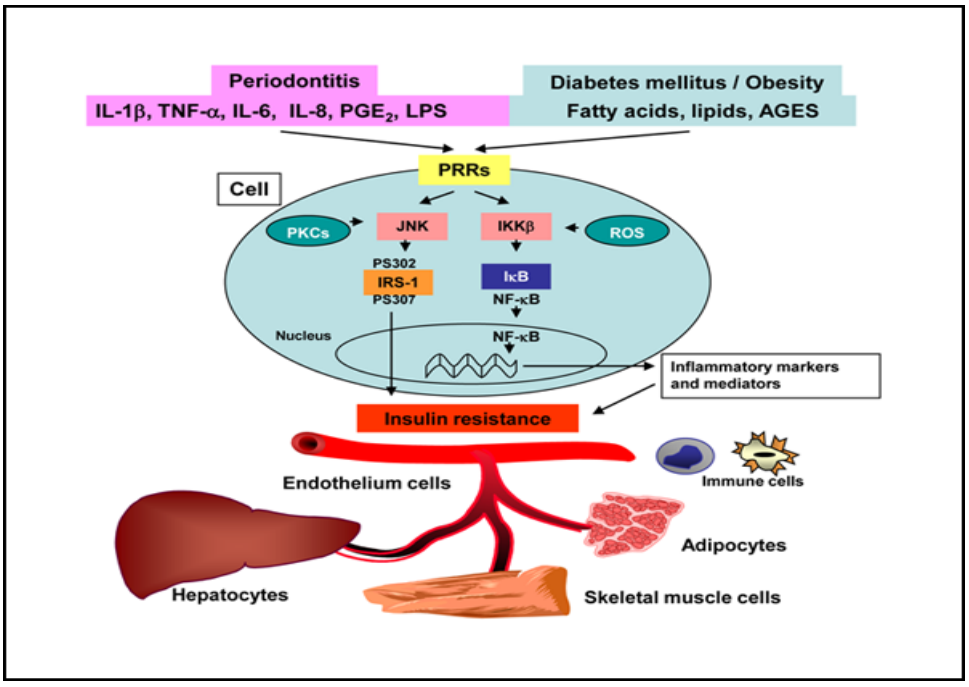

Fig. (4): Effect of inflammatory medictors on insulin resistance ***(Tunes, 2010).***

Interleukin-6 (IL-6):

IL-6 is a pleitropic cytokine secreted by macrophages, T-cells, B cells and other cells including fibroblasts. IL-6 has also been localized to eosinophil granules. Also it is produced by adipose tissue and its level are increased in obesity. IL-6 stimulate liver production of C-reactive protein and this can explain state of inflammation associated with obesily and could mediate insulin resistance ***(Fransceco et al., 2009).***

Accumulating evidence also indicates that IL-6 is involved in glucose metabolism and insulin action. Long-term exposure of IL-6 could exert deleterious effects in insulin action and glucose homestasis. As it lead to defects in IR S-1/P13-kinase activity and increases in fatty-acyl CoA levels in Skeletal muscle. IL-6 also has inhibitory effects on gene transcription of IRS-1, $GluT_4$ glucose – transporter -4 ***(Petersen et al., 2010).***

III- Oxidative stress and insulin resistance:

Reactive oxygen species there are several prominent ROS, including superoxide (O_2), hydrogen peroxide (H_2O_2) and peroxynitrite (oNoo). ROS can be generated by various cell organelles and enzymes. Such as mitochondria, NAD(P)H oxidoses, xanthine oxidoreductase, nitric oxide syntheses. Normally, ROS play an important physiologic roles in many organs. However, excess ROS overwhelms antioxidant defenses, leading to oxidative stress, and this, in turn, play an