Review Article and Clinical Experience: A Therapeutic Option in the Treatment of Pre-DM, IGT, and T2DM. (The Roles of Metformin: From Basic to Clinics)

Abstrak:

Minimally there are 30 hormones and biological substances secreted by Fat Cell can be summarized (Leptin, TNFα, IL-6, Resistin, Adiponectin = ACRP-30, HSL, Lipotransin, Perilipins, Aquaporins, etc). The relationship between Insulin Resistance (IR) and Adipose Tissue is exceedingly complex, and IR can be detected either in both Non-Diabetic Individuals, Pre-Diabetes (Pre-DM), or in patients with Type 2 DM (T2DM). Based on the staging of IR (Author’s Classification 1997), we will be faced with 3 groups of individuals, such as: Insulin Resistant-Normoinsulinemic (Stage-I, IIA, IIB), Insulin Resistant-Hyperinsulinemic (IIA, IIB, IIC), and Insulin Resistant-Hypoinsulinemic Individuals (Stage-IVA, IVB); of these all will be described in this paper. According to this classification, Pre-DM may be classified as Stage-I or Stage-IIA. Such a Classification can be described more detail as follows: Stage-I (Obese People or Pre-DM or Normoinsulinemia), Stage-IIA (Non-DM or Pre-DM: Hyperinsulinemia), Stage-IIB (IGT with Hyperinsulinemia), Stage-IIIB (DM with Hyperinsulinemia), Stage-IV (DM with Normoinsulinemia), Stage-IVB (T2DM or DM Type X-1 with moderately impaired &beta; cell-function with Low-Normoinsulinemia), Stage-IVA (T2DM with severe impaired &beta; cell-function: DM-Type X-2) and Stage-IVB (T2DM with very severely impaired &beta; cell-function with subnormal plasma insulin levels: totally insulin dependent T2DM = DM-Type-X3 = LADA: Latent Autoimmune Diabetes in Adults). Fasting and Post Prandial Cpeptide levels of these patients are less than 0.5 &mu;U/ml. Marked impairments in insulin’s intracellular Signaling Cascade (&plusmn; 30%) are present in Fat Cells of T2DM, including impaired IRS-1 Gene and Glut-4 expression, impaired insulin-stimulated PI3-Kinase and PKB/Akt activities. It is proposed that IR and/or its effectors are initiated in Fat Cells and this way secondarily encompasses other target tissues for Insulin, including impaired GLUT expression in the muscles. Insulin Receptor Substrate-2 (IRS-2) is the main docking protein for PI3-kinase activation in Fat Cells in case IRS-1 is markedly reduced, such as in T2DM. The downstream signaling events for insulin are also similarly impaired. The adipose tissue does not only produce peptides which can elicit IR (TNFα, IL-6, Resistin, etc) but also produce hormones which can improve insulin sensitivity such as Adiponectin. The circulating levels of Adiponectin are positively correlated to insulin sensitivity and negatively to BMI. Thus, it is most likely that the balance of the production of hormones from Adipose Tissue that accentuate (f.e. TNFα, IL-6, Resistin) or alleviate (Adiponectin) IR, as well as eliciting other effects, is due to several factors including Adipose Mass, Nutritional State, and Genetic background. Overstimulation of the &beta;-Cells of pancreas due to IR (Stage-I or II, or Obesity, or Pre-DM) may cause an impaired insulin secretion. Taken together, impaired &beta;-Cell function and IR are both responsible for the occurrence of T2DM, or may be DM-Type X-3 or LADA which are totally insulin dependent. Metformin with its 21 (9-3-9 effects) pleiotropic effects (metabolic and vasoprotective effects) is postulated to improve the receptor (IRTK) and post receptor defects of patients with Obesity, Pre-DM, or T2DM. Recent study reported that Thiazolidinediones (TZDS) increased the expression of IRS-2 in diabetic patients having low IRS-1. Conclusions: There is link between Insulin Resistance-Obesity-Pre-DM and T2DM, and usually such an IR is initiated in Fat Cell. Probably, the balance between TNFα, IL-6, Leptin, and Resistin in one side, with Adiponectin in the other side in Obesity, Pre-DM or patients with Stage-I or II plays a pivotal role in the development of T2DM. Hence, Metformin alone or in combination with TZDS can be recommended as promising drugs for those patients. In addition, Metformin with its 21 pleiotropic effects (9-3-9), may have potential therapeutic benefits in the prevention of diabetic vascular
complications as long as normal liver and renal functions of the patients are normal.

Keyword:

insulin resistance, obesity, pre-DM, IGT, T2DM, metformin

Daftar Pustaka: