INNOVARE JOURNAL OF HEALTH SCIENCES

Vol 5, Issue 1, 2017

ISSN - 2347-5544

Review Article

OBESITY, TYPE-2 DIABETES MELLITUS AND ITS MANAGEMENT

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Received: 14 November 2016, Revised and Accepted: 16 November 2016

ABSTRACT

Obesity is a clinical condition characterized by increased body mass index beyond 30 kg/m^2 that measures the distribution of body fat components more precisely, recent consideration on body fatty tissue index is waist circumference that exactly meters bodily adipocyte status which seems responsible to release various cytokines, the anticipated culprits contributing to the development of insulin resistance and thus act as triggering factor to exacerbate Type-2 diabetes mellitus. This review focuses on the obesity-linked Type-2 diabetes, conventional management, and newly discovered remedial measures to control the obesity and diabetes as a whole.

Keywords: Obesity, Adipokines, Insulin resistance, Type-2 diabetes mellitus.

INTRODUCTION

Obesity is a pro-inflammatory condition characterized by hypertrophied adipose tissue, and primarily lymphocytes and macrophages are activated to increase circulating levels of pro-inflammatory cytokines. The obesity is associated with the state of chronic low-grade systemic inflammation, termed "metabolic inflammation," which is considered to be a focal point in the pathogenesis of insulin resistance and Type-2 diabetes mellitus (DM) in humans [1-3]. Although systemic inflammation is mainly governed by white adipose tissue, liver and muscle also show obesity-induced mild inflammatory responses [4].

In 1987, Spiegelman groups grasped "big fish" by identifying peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-activated nuclear receptor transcription factor that plays pivotal role in the control of gene expression linked to a variety of metabolic processes, which are characterized by the master regulator for the development of adipose cells, the ligands of which include naturally occurring fatty acids and the rosiglitazone, a class of anti-diabetic drug [5] that binds to these ligands activates PPARγ, and hence ameliorates insulin sensitivity in rodents and humans through a combination of metabolic actions, including oxidation of lipid stores and the regulation of metabolic and inflammatory mediators termed adipokines [6].

Metabolic syndrome is thought to result from obesity which is characterized by adipocyte hypertrophy along with insulin resistance that participates in energy homeostasis and obesity acts as an important endocrine organ that secretes a number of biologically active "adipokines."

A high fat-containing diet which leads to the development of obesity prevents heterozygous peroxisome proliferator-activated receptor gamma which mediates release of beneficial adipokines such as adiponectin.

Animal study of this model suggests, overexpression of adiponectin/Acrp30 receptors are cloned in skeletal muscle (AdipoR1) and liver (AdipoR2), on signaling mediate increased AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor alpha ligand activities, and glucose uptake and fatty acid oxidation that appear to comprise a novel cell-surface receptor family, hence decreased expression levels of AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally leads to insulin resistance, the so-called "vicious cycle" and functional analyses have revealed that adiponectin serves as an insulin-sensitizing adipokines that down-regulated during obesity, the mechanism leading to cause insulin resistance and DM [7]. A recent study demonstrated osmotin, which is a ligand for the yeast homolog of AdipoR (PHO36), activated AMPK through AdipoR in C2C12 myocytes. This may facilitate efficient development of adiponectin receptor agonists. Adiponectin receptor agonists and adiponectin sensitizers should serve as versatile treatment strategies for obesity-linked diseases such as diabetes and metabolic syndrome [7].

Insulin signaling and molecular mechanism of insulin resistance

Insulin signaling comprises a network of convergence and divergence crosstalk of signaling cascade [8] initiated by insulin binding to its cell surface receptor, followed by intracellular moiety receptor autophosphorylation, and activation of receptor tyrosine kinases, which result in tyrosine phosphorylation of insulin receptor substrates (IRSs) including IRS1, IRS 2 link to activation of PI3kinase/Akt signaling pathway, activated Akt phosphorylates its 160 kDa substrate (AS160), which stimulates the translocation of insulin-mediated GLUT4 from intracellular vesicles to the plasma membrane in fat and muscle cells, this protein in adipocytes, designated AS160, identified its six sites *in vivo* that is phosphorylated by the insulin-activated kinase Akt at the 5th position of the site which contains a GTPase-activating domain for Rabs which are small G-proteins required for membrane trafficking of GLUT4, the defects of which is associated with the insulin resistance [9,10]. The major event in the development of Type-2 DM is the resistance of insulin signaling pathway to adipocyte, muscle, and liver cells where genetic and environmental factors play an important role in this process. Among the many molecules involved in the intracellular processing of the signaling provided by insulin, IRS-2, IRS-1 [11], the protein kinase B-beta isoform and the forkhead transcription factor Foxo1a (FKHR) are main, the dysfunction of these proteins results in insulin resistance *in vivo*. Furthermore, adipose tissue not only produces free fatty acids (FFA) that contribute to insulin resistance but also acts as a relevant endocrine organ producing mediators (adipokines) that can modulate insulin signaling and hence, insulin resistance [12].

Adipose tissue cellular remodeling in obesity

Adipose tissue composed of lipid-filled mature fat cell, stromal cells, premature adipocyte known as preadipocytes, endothelial fibroblast, and endothelial cells while in obesity progression white adipocyte tissue, as well as adipocyte and the stromal vascular fraction and immune cells, are modified, and the former enlarges and releases fatty acid and interleukin (IL) that engender insulin resistance [12,13].

Cellular modeling is the function of high fatty diet as exhibited by an experiment in rat that was fed with 60% calories diet that showed the result of cellular epididymal remodeling of fat depots that was invaded by many macrophages around the dead adipocytes after 16 weeks, but it is yet unclear that the reason of dead adipocyte consequence was whether due to direct effect of macrophage or by its responding mechanism but the certainty is that in later time, infiltrated macrophages phagocytosed the lipid and other cellular component which activates toll-like receptor on the macrophages and nearby adipocytes inducing release of cytokine and chemokine, the proinflammatory signal where the crosstalk appears among adipocyte, macrophages, and other cells that promotes extracellular matrix remodeling [14,15].

Eventually, macrophage presumes the appearance of lipid-laden foam cells, within week's adipose tissue is no more with lipid, instead, cellular debris is replaced by apparently populated new healthy adipocyte tissues. This remodeling phenomenon coincides with the formation of fatty acids that directly contribute in worsening of insulin resistance (Fig. 1), suggesting that in an organism level remodeling is a consequence of metabolic process [15].

Obesity as a promoter of insulin resistance

Size and number of adipocyte cells due to differentiation of adipocyte cell and mesenchymal cells mediated by activation of transcription factor PPARγ after signaling molecular induction by fatty acid that induces the expression of adipocyte-specific gene in preadipocytes which is its ligand results into adipocyte formation that leads to expansion of waist circumferences with measurement of BMI >30 kg/m^2, so-called obesity, the degree of which is determined by the balance between formation of adipocyte and accumulation of fat molecules during processing towards development of obesity. Preadipocytes are transformed into an adipocyte, so called mature adipocytes that secrete adipokines, such as tumor necrosis factor-alpha (TNF-alpha), IL-6, leptin and adiponectin, and lipokine, the palmitoleic acid omega-7 that possibly directly or indirectly contribute to initiate peripheral insulin resistance [16,17]. Enlarged adipocyte, so called hypertrophied status produces many proinflammatory cytokines such as IL-6 and TNF-alpha but secretes very limited amount of anti-inflammatory cytokines like leptin and adiponectin deemed to have properties to sensitize insulin, the so-called endogenous insulin sensitizer [18].

Adiponectin and insulin sensitivity

Adiponectin, an adipocyte adipokine is a protein complex that exists in high molecular weight and low molecular weight and that which exists in high molecular weight exerts an important role in sensitivity of liver, skeletal muscle, and the prominent effect of liver is on hepatocyte, thus, it is recognized as a key regulator of insulin sensitivity. Its secretion is inversely proportional to body fat content, thus, it is low in obese person and consequence of diabetes and coronary artery disease [19].

MECHANISM OF ADIPONECTIN

Mechanism of adiponectin is mediated by ubiquitously expressed receptor termed as AdipoR1 and AdipoR2, the former receptor is dominantly expressed in skeletal muscle coupled to activate AMPK internally that results into lipid oxidation whereas later one is highly expressed in hepatocyte cell of liver where signaling mechanism internally coupled to activate AMPK and increases peroxisome-proliferator-activated receptor alpha ligand activity that decreases statuses and enhances insulin sensitivity [20,21].

MANAGEMENT

Now, the authors would like to precisely deal with the therapeutic strategy/status of PPARγ agonists such as pioglitazone and rosiglitazone (derivatives of thiazolidinediones) and metformin (derivative of biguanide) which have been currently extensively used for the treatment of Type-2 DM. Moreover, metformin decreases body weight in obese patients.

Both pioglitazone and rosiglitazone act as agonists of PPARγ expressed mainly in liver, skeletal muscle, and adipose tissue. On activation, PPARγ increases the transcription of insulin-responsive genes controlling the metabolism of glucose and lipids and thereby, insulin sensitivity is enhanced resulting in decreased insulin resistance in Type-2 DM subjects. They inhibit gluconeogenesis in liver and increase peripheral uptake and utilization of glucose, the plasma concentration of high-density-lipoprotein-cholesterol is also increased. These two drugs are specially used in insulin resistant Type-2 DM patients whose daily requirements of insulin exceeds >100 U/day.

Pioglitazone: Dose: 11-45 mg once daily orally and rosiglitazone: 4-8 mg once daily orally and duration of action of both the drugs is more than 24 hrs.

The noted adverse effect is that these drugs induce weight gain and edema due to retention of fluids leading to heart failure and also decrease blood hemoglobin concentration. They are contraindicated in cardiac failure and hepatic failure, pregnancy and lactating mother and by reducing insulin resistance they induce ovulation in anovulatory women [22].

Metformin: This has been emerged as the first-line therapy for the treatment of Type-2 DM especially associated with obesity because apart from controlling blood sugar level, it also decreases cardiovascular outcomes in such patients. The prevalence of cardiovascular complication is the leading cause of morbidity and mortality in Type-2 DM patients. Metformin has cardioprotective effect; it prevents/retards cardiac remodeling and other pathological changes too. Moreover, it decreases body weight in obese diabetic patients by reducing appetite,

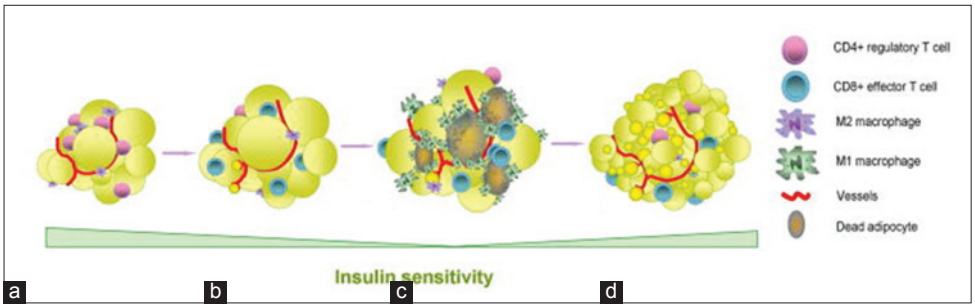

Fig. 1: Adipose tissue remodeling in obesity (adapted from, [19]). (a) In well-vascularized healthy adipose tissue, CD4+T-cells, and M2 macrophages restricting inflammation and improving insulin sensitivity, (b) With increasing adipocyte hypertrophy, the ratio of CD8+/CD4+T-cells increases and this may help recruit macrophages, (c) With the further expansion of adipose tissue, more macrophages acquire a proinflammatory, M1 phenotype, restrictions of blood flow and hypoxia stimulate inflammatory cytokine production and worsen adipocyte dysfunction, (d) With time, macrophages clear out the dead adipocytes which are replaced by the newly-differentiated, insulin sensitive adipocytes

decreases glycogen content of liver, inhibits hepatic gluconeogenesis, reduces renal and hepatic output of glucose, decreases and delays intestinal absorption of glucose, the peripheral utilization of glucose is increased due to enhancement of anaerobic glycolysis and the most important noted effect is that it decreases insulin resistance and acts as insulin sensitizer both in adipose tissue and skeletal muscles, hence, also decreases hyperinsulinemia, even has moderate effect on inflammatory markers, reduces plasma total low-density lipoprotein cholesterol and triglycerides, decreases FFA production and lipolysis oxidation of lipids and enhances plasma fibrinolytic activity.

Dose of metformin: 500 mg twice daily and gradually increased up to 2000 mg daily or metformin-SR tablet 500 mg once daily [23].

Obesity: It is pandemic with potentially fatal consequences on human health both morbidity and mortality are increased. Besides sedentary lifestyle, eating plenty of high-fat containing junk foods, there is definitely inherited tendency to become obese. The obesity is ultimately associated with comorbidity such as Type-2 DM, metabolic syndrome, coronary artery disease, hypertension, stroke, osteoarthritis, and there is also higher incidences of colorectal cancer in males and cancer of endometrium, cervix, and breast in females, hence, now the public awareness of health complication of obesity has been increased to find out its preventing measures as well as its effective remedies [24].

I. Non-pharmacological basis of treatment of obesity.
   Permanent modifications/changes of lifestyle:
   i. Diets: Avoidance of high-fat containing junk foods and taking low-calorie diet rich in high fiber-containing foods rich in vegetables and pulses.
   ii. Regular Aerobic isotonic exercises, yoga, and meditation help in reducing body weight.
   iii. Walking: Minimum ½ h brisk walking daily preferably in morning and evening hours.
   iv. Alcohol consumption should not exceed one ounce per day.
   v. Sedentary lifestyle should be avoided as far as possible instead 30 minutes being active by doing moderate exercise for at least 5 days in a week reduces 30% chances to have diabetes [25].

II. Pharmacotherapy of obesity: The following drugs are recommended as adjuvants to above described non-pharmacological basis of treatment.
   A. The weight reduction induced by anorectic drugs such as metformin and fluoxetine does not last long.
   B. Sibutramine produces its anorexigenic effect by preventing reuptake of both serotonin & norepinephrine in CNS, and daily dose is 10-15 mg once orally.
   C. Oristat is an inhibitor of both pancreatic and gastric lipases which cause hydrolysis of dietary fats into fatty acids, hence, it acts as anti-absorbent of fat and fat-soluble vitamins in the intestine. The recommended daily oral dose of 120 mg three times reduces fat absorption by 30%. It is suitable for obese Type-2 DM [26].

III. Surgery: This is undertaken when diet, other due changes in lifestyle and particularly medications fail to adequately control the obesity.
   a. Lipectomy
   b. Bariatric surgery is done in a resistant type of obese patients. In this procedure, the size of the stomach is reduced which affords the most effective long-term treatment for obesity and thus it reduces mortality and morbidity.

IV. Gene therapy may also help in preventing obesity in hereditary cases.

Newly discovered triple agonist therapy in the management of obesity and diabetes

Triple agonists of glucagon-like peptide (GLP)-1 receptor, GIPR and GcgR are preclinically demonstrated as potent therapeutics for the management of obesity and glycemic control respectively, comparison of the segregated treatment of acylated monoagonist with equmolar mixture of validated acrylated coagonist of GIP1 and coagonist GLP in diet-induced in mice. GIP analog diminishes the appetite and hence decreases body weight by 6.4%, GLP1 agonist reduces body weight by 12.6% and reduces cumulative food intake by more than 50%, the glucagon analogs decrease body weight by 11.1% without any effect to cumulative food intake, the GLP1/GIP co-agonist decreases body weight by 15.4% outperforming the effect to any of the monoagonist is of course due to lower cumulative food intake relative to that observed with GLP1 analog, coadministration of the GLP1/GIP co-agonist with an equimolar dose of glucagon analog decreased body weight by 20.8% without suppression of food intake than that co-agonist alone, moreover, simultaneous administration of the GLP1/GIP co-agonist and the gcg R agonist was able to lower blood glucose level to a point lower than the respective single treatments despite the hyperglycemia propensity of the GcgR agonist alone, therefore, these observation led to pursue the discovery of Suni-molecular tri-agonist simultaneously targeting GLP1, GIP, and glucagon receptors [26,27].

CONCLUSION

As obesity seems to be leading causative and precipitating factor of Type-2 DM, at the outset, it is therefore necessary to undertake possible preventive remedial measures to reduce body weight or decrease waist circumference either first by non-pharmacological or then by pharmacological measures that diminish preadipocytes transformation into mature adipocyte which releases adipokines responsible to cause insulin resistance leading to the development of Type-2 DM. Moreover, from the therapeutic point of view, the newly discovered novel animalcular polypharmacy drugs could be the most effective approach in reverting obesity and Type-2 diabetes or even other associated metabolic disorders.

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