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Review Article

DIABESITY - 21st CENTURY THERAPEUTIC CHALLENGE

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ABSTRACT

The significant relationship between obesity and Type 2 Diabetes has been evidenced since ancient times. Ayurveda, Traditional Indian system of medicine, categorizes *Prameha* (diabetes) into two types i.e. *Sthula prameha* (diabetes in obese people) and *Krisa prameha* (diabetes in lean individuals). The alarming rise in prevalence of these disorders without any sign of decline in near future represents a global burden. Several prospective studies present impaired insulin release, impaired glucose tolerance, low grade inflammation and insulin resistance as the major factors for the development of type 2 diabetes. The low grade inflammation that dominates in obesity is the permanent elevation of plasma FFA and the predominant utilization of lipids by the muscle interfering with the uptake of glucose in skeletal muscle. This review article aims at understanding the potential mechanisms that lead human obesity to type 2 diabetes and therapeutic interventions for treating these disorders with a focus on the side effects of the conventional oral hypoglycemic agents and antiobesity agents. WHO and IDF moving with a goal for prevention of this global dual epidemic rather than curing by emphasizing the targets in various pathways and weight loss interventions. In this context, the review article highlights the potential targets for new therapeutic interventions and significance of weight loss for preventing and decreasing the progression of this multifactorial disorder.

KEYWORDS: Adipokines, Diabetes, Diabesity, Incretins, insulin resistance, Glucolipotoxicity, obesity.

INTRODUCTION

The current prevalence of Type 2 Diabetes Mellitus (T2DM) and associated obesity constitutes a major global health crisis with critical complications. The close relationship between the diabetes and obesity highlighted by term 'DIABESITY', coined by Sims and colleagues[1]in 1970's suggesting a casual pathophysiological link between the both phenomena. Type 2 diabetes and obesity are major health problems that have reached epidemic proportions and are growing at alarming rates around the world and a drastic increase in the population who are managing both the chronic diseases. The world health organization (WHO) stated the obesity and diabetes as '21st century epidemic' [2] referring to joint and parallel increase in global prevalence.

Global estimates

According to International Diabetes Federation, the facts and figures represent the therapeutic challenge which is grim and shocking. According to the IDF diabetic atlas 2012 update 371 million people are living with diabetes. Approximately 63 million people are suffering with diabetes in India and china holding the top position among the countries with 92.3 million. Four out of 5 people are living with diabetes among low and middle income countries [3]. The statistics of IDF state two individuals develop diabetes for every 10 sec globally and two individuals die of diabetes and its associated complications worldwide[4]. Overweight and obesity are the fifth leading risk for global deaths causing 2.8 million adults deaths approximately. Obesity accounts for 44% of the diabetes burden. Global estimates for 2008 are more than 1.4 billion adults, 20 and older, were overweight. Of

these overweight adults, over 200 million men and nearly 300 million women were obese. Overall, more than one in ten of the world's adult populations were obese [5]. Many hypotheses and statistics clearly represent a strong defining link between the obesity and diabetes. Clinical evidence manifest to the relationship between being overweight or obese are at an elevated risk for development of Type 2 diabetes and adverse cardiovascular events. The risk intensifies with the degree of excess weight, increasing threefold with (BMI) of 25.0-29.9 kg/m^2 and 20 fold with a BMI over 30kg/m ^{2}. Peculiarly, the increase abdominal fat accumulation exacerbates insulin resistance and confers a strong, independent link for the development of diabetes. The two twin epidemics frequently occur together and statistics show that 60-90% of all patients with Type 2 Diabetes mellitus are or have been obese. The relative risk for a given obese patient to develop T2DM is 10 fold for women and 11.2 fold for men [7]. The Population Attribution Factor (PAF) lay down strong defining link to express the relationship, and T2DM have a PAF of 88.6% due to obesity.

UNDERSTANDING MOLECULAR LINKS BETWEEN OBESITY AND DIABETES

Many approaches are proposed linking obesity to diabetes. The obesity leading to the insulin resistance and impaired glucose tolerance and May further progresses to the chronic condition of T2DM in vulnerable individuals.

Insulin Deficiency and Insulin Resistance

The plasma glucose levels are monitored and maintained by coordination between absorption from intestine, production by liver, uptake and metabolism by peripheral tissues. Deregulation between these physiological process leads to the disturbance of glucose homeostasis [8]. Insulin plays a key role in coordinating these activities by increase glucose uptake in muscle and fat, inhibits production of glucose by liver and serves as regulator of glucose. The other activities mediated by insulin involving in the coordination are stimulation of lipogenisis, glycogen and proteins, and inhibition of lipolysis. Loss of coordination between these factors and processes produce elevation in fasting & postprandial glucose levels and lipid levels. Defects at many levels and alterations in concentration of receptor and enzymes involved in cascade of metabolic process are characterized in insulin resistance states in obesity and diabetes [9].

Several longitudinal studies revealed that people who are genetically predisposed to impaired insulin secretion develops diabetes when they have acquired obesity induced insulin resistance[10]. T2DM may develop once insulin secretion declines at a level at which it cannot further indemnify for insulin resistance. Physical inactivity, Life style and dietary changes are relatively susceptible causes for insulin resistance rather than genetic predisposed insulin resistance. Insulin sensitivity is negatively correlated with the age and body fat of individuals [11]. Insulin resistance indirectly caused due to increase in lipid oxidation and high plasma Free Fatty Acids (FFAs) levels in obese non diabetic subjects [9]. Chronic decrease in glucose oxidation occurs in muscle resulting from preferential use of lipids as an energy source limiting the use of glucose form glycogen stores. In obesity the preferential use of FFAs by muscle tissue, resulting in higher circulating levels, is a limiting factor for glucose oxidation [12]. The resistance to glucose uptake in obesity after glucose load leads to a greater rise in both plasma glucose and insulin concentration. This in turn facilitates glucose storage and equilibrium is obtained with the compensation for resistance to glucose storage by increasing its stimulation by elevated glucose and insulin levels. The persistent resistance to glucose uptake, in spite of the compensatory mechanism of elevated glycaemia and insulinemia, gradually leads to type 2 DM on prolonged obese state of an individual. This happens generally when the glucose uptake by muscles cannot be regulated in spite of the compensatory mechanism of elevated glycaemia and insulinemia. Muscles are the major sites for insulin resistance, where the chronic disease in glucose utilization from glycogen limits the further uptake of glucose, which as a consequence, remains in the circulation [2].

Visceral fat and Intra Myocellular Lipids (ICML)

Preferential upper body accumulation of fat and increase in fatness are related to insulin resistance. Insulin resistance is correlated to visceral fat mass independent of body mass index (BMI). Visceral fat plays a key role in the pathogenesis of insulin resistance. Visceral fat in excess has been associated with decrease sensitivity of insulin mediated uptake of glucose and decreased FFAs re-esterification [13]. The visceral adipocytes produce FFAs which enter portal circulation into liver can induce hepatic insulin resistance. The visceral fat was positively correlated with the gluconeogenisis flux but was

reciprocally associated with glycogenolysis in T2DM patients and accumulation of visceral fat has a significant negative impact on the circulating glucose levels through a decrease in peripheral insulin sensitivity and an enhancement of gluconeogenisis [14]. Recent studies reveal that ICML's exhibit a better correlation factor relating to insulin sensitivity rather than circulating plasma FFAs [15]. H^1Nuclear magnetic resonance (NMR) studies have shown that ICML's is a strong determinant of in vivo insulin release in humans. Drastic weight loss induced by surgical procedures like biliopancreatic diversion (BPD) decreases 86% ICML's and normalizes insulin sensitivity [16]. Good fat oxidation capacity in obese patients could help to maintain normal ICML concentrations and normalize insulin sensitivity thus preventing the ectopic fat accumulation. The good ICML's stored as an adaption to endurance training are constantly mobilized for physical exercise. On the contrary, the bad lipids stored in obese patients are not mobilized and may affect insulin sensitivity by the production of lipid peroxidation byproducts like 4-HNE and/or malondialdehyde [17].

Free Fatty Acids (FFAs)

In general plasma FFAs are elevated in obese individuals mainly due to increased FA release associated with the expansion in fat mass. According to Randle hypothesis [18] the insulin resistance associated with obesity demonstrated by using isolated rat heart muscle and rat diaphragm muscle. The underlying mechanism for insulin resistance could be the competition between increased circulating FFAs and glucose for oxidative metabolism in insulin responsive cells. The mechanism that they proposed to explain the insulin resistance was that elevated intramitochondrial acetyl CoA / CoA and NADH/ NAD^+ ratios and inactivation of pyruvate dehydrogenase leading to increased intracellular citrate concentrations in turn inhibits phosphofructokinase (a key rate controlling enzyme in glycolysis). Subsequent accumulation of Glucose-6-Phosphate would inhibit hexokinase II activity, resulting in an increase in intracellular glucose concentrations and decrease glucose uptake [19].

Any disruption that leads to the accumulation of intracellular fatty acyl CoA or other fatty acid metabolites in the muscle and liver, either through increased delivery and/or decreased mitochondrial metabolism might be underlying cause for insulin resistance. Increase intracellular fatty metabolites (diacyl glycerol, fatty acyl CoAs, etc) activates serine /threonine kinase cascade possibly iniated by protein kinase C, IKK-β, c-Jun amino-terminal kinase (JNKs), leading to phosphorylation of serine sites on insulin receptor substrates. Serine phosphorylated forms of these proteins fail to associate with and activate PI-3-kinase, resulting in decreased activation of glucose transport and other downstream events [20].

Oxidative Stress

Persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen) and antioxidant defenses correlates with fat accumulation in humans and mice [22]. The oxidative stress is a causative factor and plays a key role in development of insulin resistance which was supported by several studies that showed that reversal of imbalance between the ROS (reactive oxygen species) and antioxidant improves insulin resistance in mice and humans [21]. Human studies defining link between oxidative stress and insulin resistance focus on the generation of ROS by hyperglycemia in diabetic patients, implicating ROS as a consequence of diabetes induced hyperglycemia and not a cause for insulin resistance [20]. Obesity induced elevations of FFAs increase ROS in the prediabetic stage [22]. The FFAs cause oxidative stress due to increased mitochondrial uncoupling and B-oxidation, leading to increased production of ROS. In healthy subjects, infusion of FAs causes increased oxidative stress and insulin resistance that is reversed by infusion with antioxidants such as glutathione. In vitro, ROS and oxidative stress lead to the activation of multiple serine/ threonine kinase signaling cascades The activated kinases can act on number of potential targets in the insulin signaling pathway, including the insulin receptor and the family of IRS proteins. When concentrations of ROS reach high levels, they can cause structural and functional damage to proteins, lipids and DNA [23]. The recent studies and currently favored hypothesis reveal oxidative stress as common pathogenic factor leading to insulin resistance, β-cell dysfunction and impaired glucose tolerance eventually leading to T2DM in obese patients [24]. Endoplasmic reticulum induces Obesity associated insulin resistance by imposing strain on ER setup there by activating the JNK and impairs the insulin signaling pathway [25].

LIPO→GLUCOTOXICITY

The common findings of hyperglycemia and hypertriglyceridemia in the blood of diabetic patients led to the hypothesis of glucotoxicity [26]

and lipotoxicity [27]. Elevated glucose levels can generate excessive levels of ROS. These include biochemical pathways like glycolysis, oxidative phosphorylation; methylglyoxal formation, glycation and sorbital metabolism. β-cells on prolonged exposure to high glucose concentrations, glucose saturates the normal route of glycolysis an increasingly is shunted to alternate pathways, such that the ROS are generated form distinct metabolic process within and outside the mitochondria. Studies indicate excess levels of palmitate are associated with excessive lipid esterification that, in turn, can generate ceramide, thereby increasing oxidative stress causing abnormal islet function. It seems unlikely, however, that the circulating lipid itself, such as triglyceride or cholesterol would be main culprits in damaging islet tissue. Glucose might lead to lipotoxicity by virtue of its ability to drive synthesis of malonyl Coenzyme a, which inhibits β-oxidation of free fatty acids. This in turn diverts the FFAs towards esterification pathways, there by forming triglycerides, ceramides and other fatty acid metabolites [26, 28].

Many physical, pathological and hormonal pathways are the causative factors for Insulin resistance. Obesity, pregnancy, excess growth hormone, glucocorticoid levels and lack of exercise are a few that play a significant role in developing the insulin resistance. Little evidence from research studies also suggests that oxidative stress plays a key role in insulin resistance and in cellular damage of tissues that lead to microvascualr and macrovascular complications of diabetes. Abnormal levels of FFAs, TNF-α, leptin and resistin prominently found in obese individuals mentioned as potential mediators of insulin resistance. Free fatty acids have been reported to impair insulin action via oxidative stress induced activation of NF-κB [21].

Obesity: Low-grade Inflammatory State

There is compelling evidence that the large component of obesity-associated pathophysiology results from a low grade proinflammatory state [30]. Past decade scientists research concerns have come to view obesity as low grade inflammatory state. Elevated plasma concentrations of circulating mononuclear cells and lymphocytes in obese persons, as well the adipose tissue and whole body's increased concentration of c-reactive protein(CRP), tumor necrosis factor(TNF-α), IL-1, IL-6, MCP-1, PAF-1, activation of NF-κB and Jun N-terminal kinase systems, are compatible with this considerations [21]. Adipose tissue is considered as the initial site of proinflammatory state generation which eventually explores the whole body. Visceral fat appears to be an active secretor of proinflammatory markers more than subcutaneous adipose tissue.

This confirms the crucial role of visceral fat in central obesity and in the pathogenesis of obesity associated morbidities. The hypothesis suggests that the pathogenic mechanism involves several heterogeneous factors in the generation of state of inflammation within the adipose tissue hypoxia, adverse effects of excessive fat storage, gut derived pathogen associated molecular patterns (PAMPs), infiltration of macrophages and increased adipocytes necrosis. The underlying metabolic and inflammatory signaling pathways impair the insulin effect in the peripheral tissues demonstrated linking the obesity related proinflammatory state to Insulin Resistance and diabetes. Locally within the fat tissue inflammation affects the adipocytes which become less sensitive to insulin. The resultant suppressed pre-adipocytes differentiation and the increased NEFA efflux in the systemic circulation increase the ectopic fat storage and affect the peripheral glucose metabolism [30].

Influence of Adipokines

Adipose tissue not only stores triglycerides but also it is a major endocrine and secretory organ, which release a wide range of factors like adipokines, signaling through various paracrine and hormonal mechanisms. Adipocytes secrete metabolically active proteins which are involved in inflammatory process, such as TNF- α, IL-1β, IL-6 and MCP-1. Adipokines has a significant role in the pathogenesis of obesity induced proinflammatory state and insulin resistance. The serum concentrations of adipokines are altered in the obese individuals, where these factors can act as predictors for future risk and for early diagnosis of the pathogenic states [31].

Among the various adipocyte secreted hormones Leptin was the first adipokine discovered by friedman and colleagues in 1994 influencing the body mass. Its absence correlated with dramatic metabolic derangements. The discovery of leptin led to correlation between the obesity and pathological changes of insulin regulating adipokines [32].

Adiponectin is significant adipokine specifically expressed in differentiated adipocytes. Its levels are low in obesity. It is relatively highly expressed in the systemic circulation than other

adipokines. Administration of adiponectin improved insulin resistance in animal models and mice models deficient of adiponectin developed premature diet-induced impairment in glucose tolerance insulin resistance, and increased serum FFAs. Transgenic mice models with over expression of adiponectin lead to improvement in insulin sensitivity, glucose tolerance and lower serum FFAs. Adiponectin increases insulin sensitivity in liver, decreases influx of FFAs and increase FA oxidation via activation of AMP-activated protein kinase(AMPK)[33]. It regulates glucose and lipid metabolism by targeting the liver and skeletal muscle through two transmembrane receptors AdipoR1 and AdipoR2. While AdipoR1 is most abundant in skeletal muscle, AdipoR2 is predominantly expressed in liver [34].

Resistin is an adipocyte-specific secreted protein, whose expression is significantly reduced by anti-diabetic drugs targeting the nuclear receptor Peroxisome Proliferative-Activated Receptor γ (PPAR- γ). Its expression and secretion pattern differs in humans and rodents. In rodents, resistin is predominantly secreted from mature adipocytes with weak expression in pancreatic islets and hypothalamus. In contrast, humans express resistin primarily in macrophages where it thought to be involved in secretion of proinflammatory factors and recruitment of other immune cells Serum resistin levels is elevated in rodent obesity and infusion or sustained expression of resistin produce insulin resistance. Resistin has been shown to induce the expression of suppressor of cytokine signaling-3 (SOCS-3), a well known negative regulator of insulin signaling both *in vitro* and *in vivo* [34]. But the role of resistin is less significant in humans; some of the interesting studies in humans reveal consistent association between resistin and inflammation.

Plasminogen activator inhibitor-1(PAI-1), an inflammation associated adipokine belonging to serine protease inhibitor family and is primary inhibitor of fibrinolysis by inactivating tissue type plasminogen activator. Elevated levels of Plasma PAI-1are reported in obesity and insulin resistance individuals and predict future risk of T2DM [35].

Interleukin IL-6 is a cytokine is closely related with obesity and insulin resistance Circulating IL-6 concentrations can be positively correlated with obesity, impaired glucose tolerance and insulin resistance. Plasma IL-6 predicts the development of T2DM and its peripheral administration appears to induce hyperlipidemia, hyperglycemia and insulin resistance in rodents as well as humans. IL-6 down regulates IRS and involved in up-regulation of SOCS-3 leading to impairment of insulin signaling [36].

Tumor Necrosis Factor α (TNF- α) is the first cytokine to be implicated in the pathogenesis of obesity and insulin resistance, which is earlier described as an endotoxin-induced factor. Adipose tissue expression of TNF- α is elevated in obese rodents and humans and is being positively correlated with adiposity and insulin resistance Recent research studies suggest that macrophages are the major contributors of TNF- α in adipose tissue. Chronic exposure to TNF- α induces insulin resistance both *in vivo* and *in vitro*. Targeted deletion of TNF- α or its receptors significantly improves insulin sensitivity and circulating FAs in rodent obesity. Potential mechanism for TNFα's metabolic effects have been described, including the activation of serine kinases such as JNK and P38, Mitogen Activated Protein Kinases(MAPK) that increase the serine phosphorylation of IRS-1 and IRS-2, making them poor substrates for insulin receptor-activating kinases and increasing their degradation. In humans, circulating TNFα level is significantly increased in obese non diabetic and T2DM individuals, but the correlation between the TNF α and insulin resistance levels are relatively weak[37, 38].

Retinol Binding Protein 4(RBP-4) was identified as an adipokine, expressed in liver as well as adipose tissue whose elevated concentrations have been shown to correlate with obesity and insulin resistance in rodents. This is the most recent adipokine to emerge as contributor to obesity induced insulin resistance [39].

The entire hypothesis is presented in the form of **flow chart** indicating gradual progression of obesity leading to insulin resistance and diabetes.

11β-HSD1 and its association with obesity

The other endocrine factors related to the obesity and insulin regulation gains the attention of glucocorticoid levels. Elevated glucocorticoid levels cause insulin resistance and T2DM, primarily by opposing the anti-gluconeogenic effects of insulin in liver [40]. Adipose tissue contains 11β-Hydroxysteroid dehydrogenase type-1(11β-HSD1), which converts the inactive metabolite, cortisone to cortisol in humans and 11-dehydrocarticosterone to corticosterone in rodents. Transgenic overexpression of 11β-HSD1 selectively in mouse adipose tissue produces a syndrome of visceral obesity, insulin resistance and diabetes in part due to increase delivery of

glucocorticoids to the liver via portal vein [41]. 11β-HSD1 inhibitors could be explored for designing therapeutic approaches for glucocorticoid suppression and could be promising therapeutic agents for treating the metabolic syndrome. Indeed, liver-specific antagonism of glucocorticoid action reduces hepatic glucose output and improves glucose control in animal models of obesity-associated insulin resistance. The increased delivery of FA and cortisol, as well as adipokines, could promote hepatic insulin resistance [42].

THERAPEUTIC OPTIONS

Antidiabetic Agents

Many conventional antidiabetic agents including the thiazolidinediones (TZDs), insulin, meglitinide and sulphonylureas are associated with weight gain, an exception for metformin which is associated with weight neutrality or modest weight reduction [43]. The newer basal formulation insulin determir exhibits limited weight gain in comparison to neutral protamine Hagedron (NPH) insulin and detemir. NPH insulin and insulin glargine have demonstrated modest weight reductions in combination with oral antidiabetic drugs in a real world setting [44]. Conventional antidiabetic treatments include insulin; insulin secretagogues and modulators of hepatic glucose production (Metformin). Metformin, a biguanide commonly recommended as initial pharmacotherapy in type2 diabetes, inhibits hepatic gluconeogensis and increase tissue sensitivity to insulin mediated glucose transport [44]. Sulphonylureas are glucose dependent insulin secretogogues which bind to SU receptor on β-cell thereby stimulating the insulin release [45]. Modulation of PPAR-γ by TZDs (Rosiglitazone and Pioglitazone) results in transcription of number of genes involved in glucose and lipid utilization. This results in improved insulin sensitivity of adipose, liver and muscle tissue. While each of this classes of agents can be effective initially in controlling hyperglycemia and lower glycated hemoglobin (HbA1c) by 0.5-1.5%, their efficacy progressively weakens as insulin resistance increases and β-cell function decreases [46]. Weight gain, hypoglycemia and other treatment-associated adverse effects can also demerit the therapeutic benefits of antidiabetic agents. In particular weight gain is problematic for people with type2 diabetes, as even a modest increase in weight can increase insulin resistance. Weight gain can be a psychological barrier to pharmacotherapy as suggested by diabetes Attitudes and wishes, and needs study, which found that more than 50% of people with T2DM are worried about starting insulin therapy because of concern of weight gain and 33% of physicians postpone their insulin treatment until it is absolutely essential [10]. The clinical efficacy of rosiglitazone and pioglitazone as monotherapy or combination therapy with insulin, sulphonylureas or metformin is well established [46]. Various longitudinal studies reported a weight gain of up to 4-5 kg with these agents. These agents are also associated with edema and risk of congestive heart failure exacerbation. Results from RECORD (Rosiglitazone Evaluated for cardiac outcomes and regulation of glycaemia in diabetes) trial found that rosiglitazone, metformin and sulfonylureas (its comparators) were associated with similar risk for cardiovascular hospitalization rates and cardiovascular mortality, but the rosiglitazone was associated with significant greater risk of heart failure [48]. Increase in weight with antidiabetic drugs, resulting in a secondary increase in insulin resistance, which subsequently intensifies the medication requirements to maintain glucohomeostasis leading to the patient noncompliance.

Incretins: Newer Oral Antihyperglycemic Therapeutic Agents

The recent clinical studies revealed that administration of GLP-1 has shown to normalize β-cell sensitivity to glucose and restore first-phase insulin response, while suppressing the glucagon levels in people with T2DM. It may also have extra-glycaemic including satiety induction and cardio protection [49]. The native GLP-1is rapidly degraded and metabolized by the enzyme DPP-4 enzyme. This hypothesis led to the development of new therapeutic interventions, GLP-1 agonist and DPP-4 inhibitors for clinical use. GLP-1 receptor agonist has different structure from endogenous GLP-1, altering their pharmacokinetic properties like longer half lives. Exenatide, Exenatide LAR (long acting, once week formulation of exenatide), Liraglutide are included under this class. These agents reduce blood glucose dose-dependently as both monotherapy and in combination with other agents. They slow gastric emptying and increase satiety, mechanisms that are in part responsible for weight loss associated with this class. Recent studies providing evidence demonstrating that treatment with GLP-1 agonist reduce systolic blood pressure and triglyceride levels and exert beneficial effects on cardiovascular risk factors [50]. While GLP-1 agonists directly act and stimulate the incretin system, DPP-4 inhibitors indirectly

enhance the endogenous incretin levels by preventing the degradation of endogenous incretin levels by preventing the degradation of GLP-1 and GIP. Treatment with these agents tends to have weight neutral effects which are better tolerated in obese T2DM individuals preventing weight gain in them. This class of agents includes sitagliptin, vildagliptin and saxagliptin.

These agents tend to have significant weight lowering effects on co-administration with metformin and no significant effect on weight when administered alone [51]. Significant reduction of glycated hemoglobin (HbA1c) levels was observed in T2DM individuals on treating with these agents. Concerns rose about long term usage of DPP-4 inhibitors on immune function because of its expression in lymphocytes [51]. The weight loss or weight neutrality, seen with various incretin agents confers considerable potential benefits on cardiovascular parameters in people with T2DM.

Pharmacological and non pharmacological strategies to combat obesity

Weight loss is of extreme importance in Diabesity to limit the development of glucose intolerance and progression form impaired glucose tolerance to diabetes. Significant effects observed with weight loss in the target diabetic population was found to have beneficial effects on β-cell function. Improved glycaemic control, glucotoxicity and lipotoxicity were reversed in the individuals with decrease in weight. Weight loss may reduce risk factors such as elevated lipid levels and blood pressure [52].

The two primary weight loss interventions are life style modifications and pharmacotherapy.

Life style modifications include regulation of diet, regular exercise and behavior changes. The pharmacotherapy is used later along with the life style modifications. The pharmacotherapy includes Sibutramine and Orlistat. These are the only two agents currently approved for long term use in the treatment of obesity. Orlistat, a gastrointestinal lipase inhibitor, reduce weight by approximately 3kg on average, improves cardiovascular risk factors and decreased progression to diabetes in high risk individuals. It can be used in individuals with ≥27 with comorbidities and in patients with >30 without comorbidities. Sibutramine is a monoamine reuptake inhibitor with weight loss effects associated with increase in satiety. It is associated with small increase in blood pressure and pulse rate in those who are normotensive, but reduce blood pressure in hypertensive. Adverse effects include insomnia, nausea and constipation. Rimonabant was approved for use in Europe for treatment of overweight or obese individuals with type2 diabetes. But it is withdrawn for market because of its side effects which include depression and anxiety. It was first of a new class of drugs that acts to suppress appetite by selectively inhibiting CB-1, an endocannabinoid receptor in adipose tissue and brain [53,54].

ADIPOKINES: EMERGING THERAPEUTIC TARGETS IN DIABESITY

It is understood that increased production of adipokines in obese individuals resulting metabolic dysregulation and vascular disturbances such as leptin, resistin, and retinol-binding protein-4. The production of protective adipokines, like adiponectin, is reduced causing hypoadiponectinemia which appears to play an important causal role in insulin resistance, T2DM, and the metabolic syndrome. The adiponectin receptors, which mediate the antidiabetic actions of adiponectin, are down-regulated in obesity-linked insulin resistance. In addition to its protective metabolic effect, adiponectin also has beneficial anti-inflammatory and vascular actions. Low adiponectin levels have emerged as an independent predictor of early atherosclerosis in obese patients. Considering all the significant effects of adiponectin on the metabolic and vascular irregularities, future strategies on focusing on up-regulation of expression of adiponectin (and/or its receptors) or on targeting adiponectin receptors through the development of specific agonists represent potential versatile targets in patients with Diabesity.

Another novel peptide system with an emerging physiological and pathophysiological role in metabolism and cardiovascular homeostasis is the apelin/APJ system. Apelin is secreted by adipose tissue that influences glucose and lipid metabolism as an adipokine through binding with a specific G protein-coupled receptor (GPCR) named APJ. Apelin treatment appears to be effective in obese insulin-resistant mice and improves the altered glucose metabolism by increasing glucose uptake in skeletal muscle. Apelin causes endothelium-dependent vasodilatation that appears to be mediated predominantly through nitric oxide-dependent pathways: in vitro, apelin stimulates transcription and phosphorylation of endothelial nitric oxide synthase (NOS) and in vivo it increases plasma nitrate and nitrite concentrations [55]. Overall, given the promising preclinical and emerging clinical data on the important metabolic and vascular

effects of apelin, the potential role of APJ agonism in preventing Diabesity and its related vascular disease certainly needs exploration in developing new therapeutic interventions for Diabesity.

Di.E.T. and Diabesity

This acronym **Di.E.T.** (**Dietary interventions, Exercise and Treatment**) introduced by the corresponding author, gives the holistic approach towards the management of diabesity. Dietary intervention means selection of foods and drinks which nourishes the body and in turn intervene the disease process. The sequence also signifies the acronym i.e. dietary modification comes first in the management of Diabesity; exercise to mean life style modification and last choice is treatment/ management.

CONCLUSION

The aim of this review article is to draw the attention of clinicians and researchers for the urgent and demanding need for novel potential candidates for prescription of Diabesity. The intention of this article clearly projects the necessity of potential therapeutic agents in obese T2DM individuals and weight gain due to conventional antidiabetic agents. Exploration of complementary and alternative medicine in this area might provide a solution for this multidimensional pathogenesis. Given the current global scenario of T2DM and obesity, the evidence of this pathogenic interrelationship constitutes a major global health problem. The ongoing worldwide epidemic of Diabesity being a disaster itself, it strikingly increases the risk of possible comorbidities. The pathological mechanisms underlying the Diabesity needed to be explored to identify the potential pharmacological targets for prevention of this multifactroial and pathogenic complex disorder in order to alleviate the human suffering. The effective weight loss interventions (life style and pharmacotherapy) must be incorporated in daily life as soon as the diabetes is diagnosed. Effective pharmacotherapy along with the life style modification might provide a significant relief to this unmet medical need.

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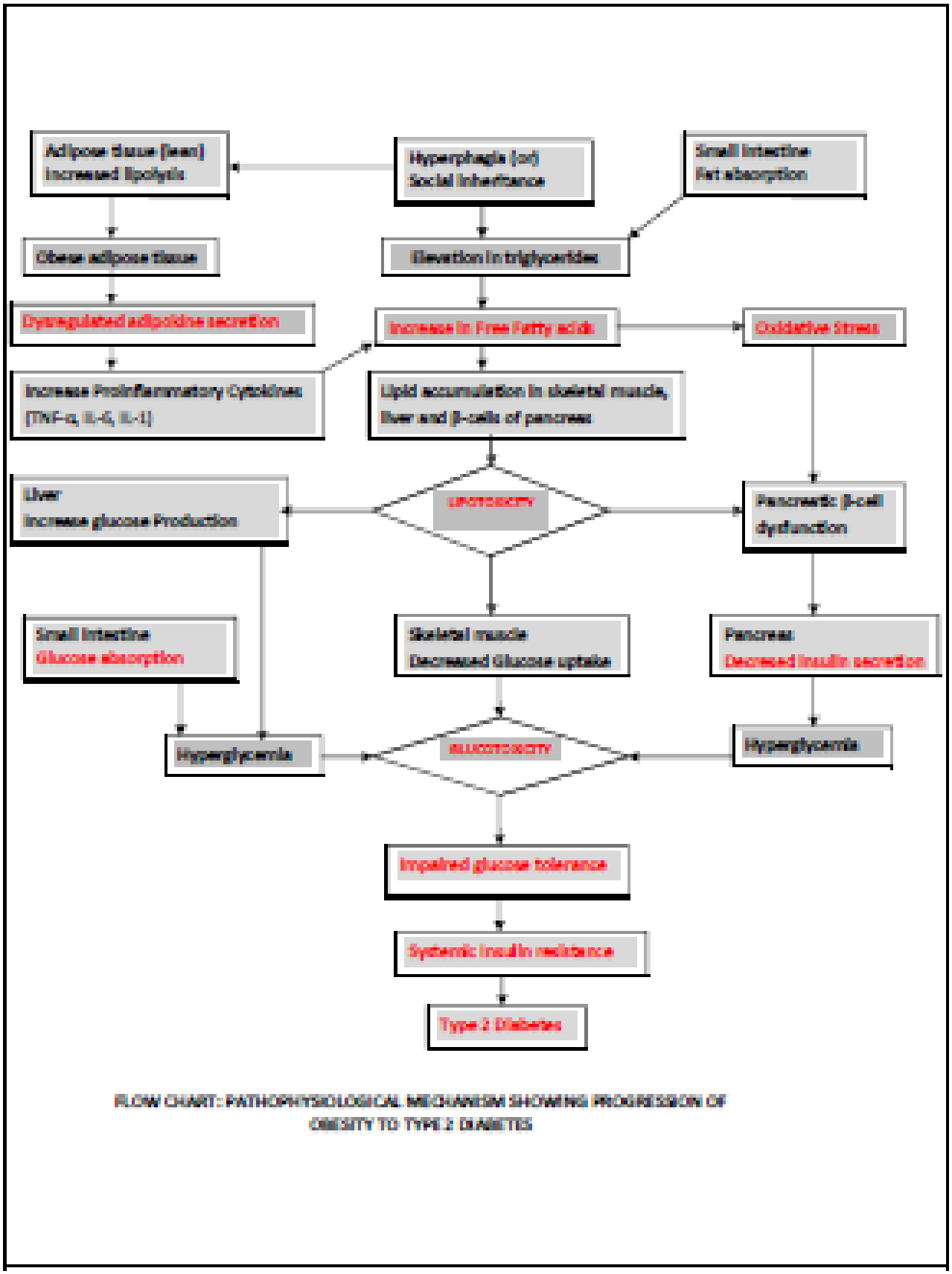

FLOW CHART: PATHOPHYSIOLOGICAL MECHANISM SHOWING PROGRESSION OF OBESITY TO TYPE 2 DIABETES