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POSSIBLE LINKS BETWEEN OBESITY AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

In this article, an attempt has been made to explore a positive correlation between obesity and type 2 diabetes mellitus. The possible role of several important agents in causing both has been discussed in detail. From the discussion, it seems that obesity is definitely and intimately linked to type 2 diabetes.

INTRODUCTION: For many years a link between obesity and type 2 diabetes mellitus (T2DM) has been assumed but not proved [1]. The fact, that 80% of type 2 diabetics are also obese, provides an interesting clue to link the two [2]. Obese individuals have a greater than 10-fold increased risk of developing T2DM as compared to normal weight individuals [1]. Over the last decade, the escalation in diabetes cases has paralleled the rapid increase in obesity rates, constituting a global health crisis. Environmental risk factors attributed to the global increase in obesity include the consumption of high-calorie, high-fat foods and inadequate physical activity [3].

Obesity is a metabolic disease of pandemic proportions largely arising from positive energy balance, a consequence of sedentary lifestyle, conditioned by environmental and genetic factors.

Excess fat, particularly deposited in visceral organs, generates chronic low-grade inflammation that eventually triggers insulin resistance and the associated comorbidities of metabolic syndrome [4].

Metabolic syndrome, which affects more than a third of the US population, predisposes to the development of T2DM and cardiovascular diseases. The syndrome comprises abdominal obesity, elevated blood pressure and triglyceride, low high-density lipoprotein (HDL) cholesterol and hyperglycemia.

Insulin resistance appears to be a common link between these pathological features because insulin resistance leads to release of free fatty acids (FFAs) from adipose tissue, increased hepatic production of glucose and very low-density lipoprotein (VLDL) along with decreased HDL, decreased glucose transport across the cell membrane, β-cell dysfunction, and consequent hyperglycemia.

Thus, persistent insulin resistance and hyperglycemia lead to the development of T2DM [5]. Adipose tissue, besides its primary function of fat storage, also regulates appetite and metabolism by secretion of certain chemicals like an endocrine gland [6]. Moreover, FFAs (both dietary and endogenous), glucose toxicity, lipotoxicity and several adipocytokines like leptin,

adiponectin and pigment epithelium-derived factor (PEDF) are also involved in the development of insulin resistance and T2DM [7-12].

To establish a positive correlation between obesity and T2DM, extensive studies by several workers have been made on the role of carnitine, adiponectin, peroxisome proliferator-activated receptors (PPARs) and leptin, which appear to be quite encouraging and substantial. In this article, a detail discussion has been attempted to establish the participation of these agents in linking obesity and T2DM. Recently, some other agents, like PEDF, resistin, serpine, G protein-coupled receptor 40 (GPR40) and carboxypeptidase E (CPE), have also been implicated in the positive relationship between obesity and T2DM [10, 11, 13-16].

Agents linking obesity and T2DM: As has been mentioned, several investigators suspected the participation of carnitine, adiponectin, PPARs and leptin in linking obesity and T2DM. Accordingly, a discussion has been attempted to explore their exact role in causing both the diseases.

- **Carnitine:** Carnitine plays a unique role in energy metabolism of cells, specially getting involved in fatty acid metabolism and energy production [17]. This compound is present in yeast, milk, liver and particularly in large quantities in muscles and meat extracts. It is synthesized from lysine and methionine in the liver (principally) and the kidneys and is considered both as a vitamin and aminoacid like substance. In humans, carnitine is absorbed in the small intestine both by sodium-dependent active transport as well as passive transport. Synthetic carnitine occurs both as D- and L-isomers, out of which the later is physiologically active. In blood, it is carried both in free and acylcarnitine form [18].

  Fatty acid (FA) oxidation occurs in mitochondria and the concerned enzymes are located in the mitochondrial matrix. Short chain fatty acids can enter mitochondria without the help of membrane transporters but those having long chains (which constitute the majority of FFA in the body) cannot do so; they have to undergo the 3 enzymatic reactions of the 'carnitine shuttle'. In this shuttle, the fatty acid is converted into fatty acyl-CoA with the help of the enzyme acyl-CoA synthetase in the outer mitochondrial membrane. In the inner side of the outer membrane, the second reaction occurs and fatty acyl-CoA gets itself attached to the hydroxyl group of carnitine, the reaction being catalyzed by the enzyme carnitine acyltransferase I. The product, fatty acyl-carnitine, then enters the mitochondrial matrix by facilitated diffusion with the help of the mitochondrial inner membrane transporter acyl-carnitine/carnitine transporter.

  Inside the matrix, the fatty acyl group is enzymatically transferred from carnitine to intra-mitochondrial coenzyme A by the enzyme carnitine acyltransferase II and carnitine returns back to the outer membrane by the same transporter to continue the cycle (third reaction) (**Figure 1**). Inside the mitochondrion, the fatty acyl-CoA undergoes β-oxidation to give energy.

  As carnitine-mediated entry process is the rate-limiting step for oxidation of fatty acids in mitochondria [19], deficiency of carnitine function due to any cause can lead to an increase in plasma FFA concentration and impairment of their β-oxidation. Carnitine deficiency due to diabetes sepsis and other causes [20] may lead to increased accumulation of fatty acyl-CoA and saturation of the enzyme acyl-CoA synthetase resulting in increased concentration of FA in the cyotsol. This in turn may cause reduction/abolition of concentration gradient for FA across the cell membrane leading to its increased plasma concentration and subsequent conversion into triglyceride (TG) or synthesis of cholesterol, and thus, obesity and insulin resistance both in diabetics and non-diabetics.

  Relative carnitine deficiency may occur in prolonged metabolic stress because of its increased requirements during such conditions. This, in turn, may add to mitochondrial dysfunction and reduced glucose tolerance associated obesity. As carnitine deficiency is commonly found in several insulin resistance conditions, the above assumption appears to be true. To further substantiate these observations, rodents were fed a high fat diet for 12 months (considered as life long).

It was observed that these rodents developed a compromised carnitine status along with an increased accumulation of acylcarnitine esters in their skeletal muscles. Moreover, there was decreased synthesis of hepatic genes coding for biosynthesis, altered mitochondrial fatty acid oxidation and reduced formation of pyruvate from fatty acids. When these rodents were fed oral carnitine for 8 weeks, these abnormalities were found to be reversed along with an increased excretion of urinary acetylcarnitine and improved glucose tolerance of the whole body [21].

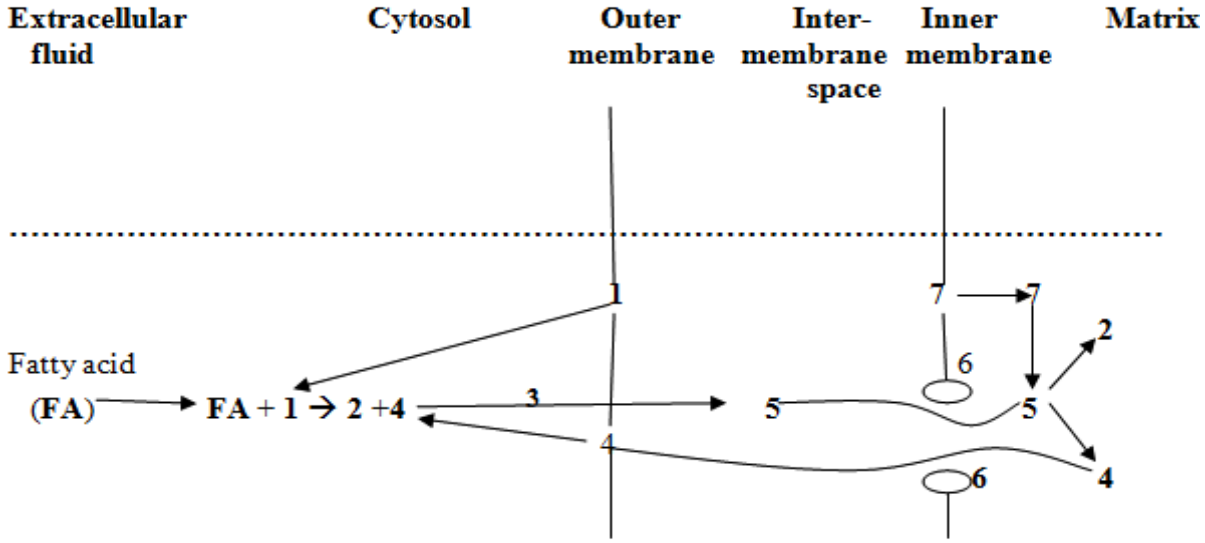

FIGURE 1: CARNITINE SHUTTLE REACTIONS

Key to numbers: 1- Acyl-CoA synthetase; 2- Fatty acyl-CoA; 3- Carnitine acyltransferase I; 4- Carnitine; 5- Fatty acyl-carnitine; 6- Transporter; 7- Carnitine acyltransferase II

To study the effect of carnitine on obesity, Youn-Soo [18] has conducted certain experiments. He observed that exogenously added carnitine decreased the triglyceride and total lipid levels in differentiated 3T3-L1 cells along with inhibition of the early stage of 3T3-L1 cell differentiation. In another study, he found that L-carnitine supplementation reduced serum leptin and abdominal fat weight caused by high-fat diet in C57BL/6J mice, and concluded that such supplementation may reduce the risk of obesity (and hence diabetes) caused by a high fat diet.

Moreover, in these mice, he observed a synergistic anti-obesity effect of genistein (the principal soy isoflavone) with L-carnitine, which, according to him, may be due to modulation of PPAR-associated genes. In another study on Korean diabetic patients, he also found a remarkable abnormality in their lipid profile along with carnitne metabolism. The same author administered L-carnitine and antioxidant to trained and nontrained animals and humans and observed that such supplementation improved their lipid profile, carnitine metabolism and exercise performance.

To know the effect of carnitine on carbohydrate metabolism, the same researcher used both non-diabetic and streptozotocin-induced diabetic rats, to which L-carnitine was administered. He observed that in diabetic rats, which had significantly lower carnitine concentrations in serum and liver compared with normal rats, L-carnitine modulated the insulin-like growth factors/ insulin-like growth factor-binding proteins (IGFs/IGFBPs) axis. Moreover, L-carnitine was found to increase the level of total serum IGF-1 dose-dependently which subsequently returned to near normal value [18].

Flanagan *et al*., [20] in 2010 have observed that nutritional supplementation of L-carnitine can improve nerve conduction, neuropathic pain and immune status in diabetics, which may also be beneficial in treating obesity, improving glucose intolerance and total energy expenditure.

Elevated levels of FFAs have been found to impair β-cell function through lipotoxicity [22]. Both in obese healthy and obese diabetic individuals raised FFA levels were found to produce peripheral as well as hepatic insulin resistance.

Moreover, it has been shown that physiological elevations of FFAs inhibit (acutely as well as chronically) insulin stimulated glucose uptake in a dose-dependent manner. The mechanisms involved in these observations may be a FFA-induced defect in insulin-stimulated glucose transport and/or glycolysis and inhibition of glycogen synthase, the rate limiting enzyme in glycogenesis. These two effects, in turn, may reduce the concentration gradient for glucose transport by carrier-mediated facilitated diffusion across the cell membrane by increasing intracellular concentration of glucose, as it is neither metabolized nor stored [23, 24].

Other investigators have also demonstrated a moderate increase in endogenous glucose production, by elevated FFA levels. Inhibition of β-cell function combined with inhibition of glucose transport, glycogenesis and glycolysis along with increased gluconeogenesis, may lead to insulin resistance and subsequent development of T2DM. Although FFA-induced insulin resistance is physiologically beneficial during starvation (which preserves carbohydrate for oxidation in CNS), in obesity, there is no need for such a spare. Hence, the developed insulin resistance may result in T2DM [24].

- **Adiponectin:** Adiponectin, an important adipocytokine, is specifically and exclusively produced by adipose tissue [19]. It is considered as an endogenous insulin sensitizer which plays a key role in the mediation of action of PPAR transcription factors. This adipocyte-secreted collagen-like plasma protein alters glucose metabolism and insulin sensitivity and exhibits antiatherogenic properties[9]. Hypoadiponectinemia, caused by altered genetic factors and factors causing obesity, has been found to play an important causal role in insulin resistance, T2DM and the metabolic syndrome [25].

  It is mainly synthesized in white adipose tissue and to a lesser extent in brown adipose tissue. Skeletal muscles, liver, colon, cardiac tissue, salivary glands and placenta also secrete it but to a much lower level. Its circulating concentrations are primarily determined by genetic factors, nutrition, exercise and abdominal obesity. Normal plasma adiponectin concentrations vary from 5-30μg/ml and are inversely proportional to those of abdominal adiposity, insulin resistance and T2DM. Its concentration is higher in women than men who may be related to concentration differences in oestrogen and androgen. After secretion, adiponectin circulates in multimers, i.e., as full-length or high-molecular-weight (HMW), medium-molecular-weight (or hexamer) and low-molecular-weight (or trimer) adiponectin complexes. The full-length multimer may be cleaved to form a smaller globular fragment which is thought to possess greater potency than the full-length form [26].

  Kadowaki *et al*., [25] have cited several references to state that adiponectin expression is reduced in obese and insulin-resistant rodent models, and also in obese rhesus monkey model that frequently develops T2DM. In these animals, a decrease in plasma adiponectin level was found to precede the onset of diabetes and was parallel with decreased insulin sensitivity. These works further reveal that plasma adiponectin levels are also reduced in obese humans, particularly in those with visceral obesity and are inversely correlated with insulin resistance.

  The two adiponectin receptor isoforms– Adipo R_1 and Adipo R_2, are 7-transmembrane proteins, dissimilar to G-protein coupled receptors (GPCRs). Both the receptors are present in almost every tissue but in a particular tissue, usually one type predominates. The degree of affinity of these receptors for different forms of adiponectin is different.

  Adipo R_1, is exclusively expressed on skeletal muscles, has high affinity for globular adiponectin and low affinity for full-length adiponectin, whereas Adipo R_2, mainly expressed in liver, has intermediate affinity for both the forms. Circulating adiponectin concentration is inversely related to muscle Adipo R_1/R_2, whereas it is positively related with subcutaneous AdipoR_2. Hypoadiponectinemia, associated with insulin resistance, up-regulates both the receptor types. Such upregulation also occurs in physical activity, suggesting an association between adiponectin hormone system and exercise-induced improvement in insulin resistance [26].

Adiponectin binding to its cell surface receptors activates several intracellular signaling pathways, of which AMP-activated protein kinase (AMPK) system and PPARs play an important and dominant role leading to modification of lipid and carbohydrate metabolism [26].

Intracellular concentration of AMP increases during reduced nutrient supply and exercise (consumes more ATP). A similar increase also occurs when adiponectin binds to its receptors in skeletal muscles, liver and other tissues. Rise in intracellular AMP activates AMPK which in turn causes phosphorylation and activation of key enzymes, concerned with fatty acid oxidation, glucose transport and activation of glycolysis resulting in increased fat and carbohydrate metabolism and hence increased energy production. The synthetic processes requiring energy expenditure like synthesis of fatty acids, cholesterol, protein and glucose (gluconeogenesis) are suppressed [19]. In cells overexpressing Adipo R_1/R_2, as in C2C12 myocytes and in hepatocytes, suppression of AMPK or PPAR-α, partially reduces adiponectin-stimulated fatty acid oxidation and glucose uptake [25]. Adiponectin, via AMPK, has been found to increase translocation of glucose transporter type 4 (GLUT 4), thereby increasing the transfer of glucose across the cell membrane (**Figure 2**) [27].

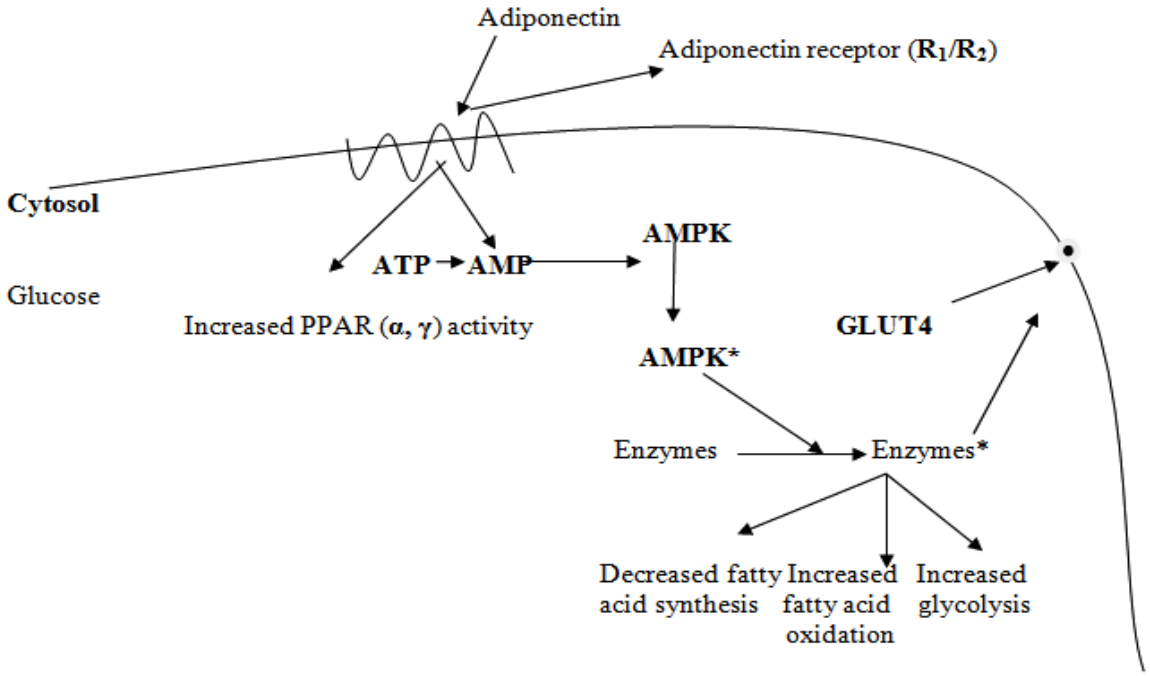

FIGURE 2: INTRACELLUAR MECHANISM OF ANTIOBESITY ACTION OF ADIPONECTIN

It has been demonstrated that insulin sensitizing drugs, thiazolidinediones (TZDs), not only mediate their action through PPAR-γ, but also stimulate adiponectin production and secretion, specifically increasing HMW/ total adiponectin concentration, which in turn activate AMPK and PPAR-α. Other experiments also show that dual activation of PPAR-γ and PPAR-α enhances the action of adiponectin by increasing both total HMW adiponectin level and adiponectin receptor number [25, 26]. Kadowaki *et al.*, [25] have found decreased adiponectin levels in KKA^{Y} mice (KK mice overexpress the agouti protein and is a model of the metabolic syndrome and type 2 diabetes linked to obesity), fed with a high fat diet. Replenishment of adiponectin in these mice significantly reduced the high-fat diet-induced insulin resistance and hypertriglyceridemia, which suggested the insulin sensitizing property of this adipokine. From these observations, they have concluded that reduction in adiponectin level due to high-fat diet and obesity is causally related to obesity-linked insulin resistance and metabolic syndrome. It has been observed that both in wild-type and type 2 diabetic mice when adiponectin level increases acutely, blood glucose level decreases for a short period, which may be due to inhibition of hepatic gluconeogenic enzymes leading to decrease in endogenous glucose production [25]. The enzyme acetyl-CoA Carboxylase plays a key role in fatty acid synthesis

and also is a powerful inhibitor of Carnitine acyltransferase I, the enzyme which starts the process of β-oxidation by transporting fatty acids into the mitochondria [19]. AMPK phosphorylates and inactivates acetyl-CoA Carboxylase which leads to inhibition of fatty acid synthesis and facilitation of β-oxidation [19, 25]. As adiponectin (via AMPK) increases fatty acid combustion and energy consumption, there occurs a decreased TG content in liver and skeletal muscles, leading to increased *in vivo* insulin sensitivity [25].

In adiponectin transgenic mice, Scherer and coworkers have demonstrated a reduced expression of gluconeogenic enzymes like phosphoenolpyruvate and glucose-6-phosphatase by activated AMPK. Quoting several other authors Kadowaki *et al*., [25] have stated that expression of Adipo R_1 and Adipo R_2 are significantly decreased in muscle and adipose tissue of insulin-resistant ob/ob mice along with impaired activation of AMPK by adiponectin on their skeletal muscles, which suggests that ob/ob mice show insulin resistance due to decreased expression of adiponectin receptors.

According to them, obesity creates a 'vicious' cycle by decreasing plasma adiponectin level and expression of Adipo R_1/R_2, which reduces the insulin sensitizing property of adiponectin leading to insulin resistance, which in turn increases hyperinsulinemia. These authors have cited a link between adiponectin receptor gene expression and insulin sensitivity in nondiabetic Mexican Americans with or without a family history of T2DM. In addition, they have quoted another observation, where a positive correlation has been found out between Adipo R_1 mRNA expression and *in vivo* insulin and C-peptide concentration along with first phase insulin secretion. Another report by these authors indicated the expression of both the adiponectin receptors in islet β-cells, which suggest their role in insulin secretion.

Adiponectin concentration has been found to be significantly lower in obese persons than the nonobese and the concentration markedly increases after prolonged caloric restrictions. The low concentration is more closely associated with visceral fat than with subcutaneous fat and is lower in diabetics and other states associated with insulin resistance. A meta-analysis study has shown a lower risk of T2DM in those having a higher adiponectin concentration. Moreover, the adipokine has been found to be positively correlated with plasma HDL cholesterol and negatively associated with serum triglyceride and apolipoprotein B-100 [26]. Analyzing the relationship between adiponectin gene, T2DM and metabolic syndrome, Kadowaki *et al.,* [25] have proposed the 'adiponectin hypothesis' and arrived at the conclusion that reduced plasma adiponectin levels, caused by interactions between genetic factors and environmental factors causing obesity (like sedentary life style and high fat diet), may play a crucial role in the development of insulin resistance, T2DM and metabolic syndrome.

From the above discussion, it appears that adiponectin, acting through AMPK and PPARs, modulates the sensitivity of cells and tissues to insulin and helps in combustion of fat. Hence, a decrease in its concentration due to any cause is expected to produce opposite effects (insulin resistance and obesity). Because of such observations, this adipocytokine may be considered as an important link between T2DM and obesity.

Galectin-3 (β-galactoside binding protein), an adipocytokine, whose level is elevated in T2DM and obesity. Adiponectin has been found to reduce galectin-3mRNA, its cellular and soluble form, and this effect was found to be impaired in T2DM patients [28, 29]. Moreover, metformin-incubated human adipocytes have shown reduced galectin-3, which may be another mechanism of antidiabetic action of this drug. These observations suggest a role of galectin-3 in linking obesity to T2DM via Adiponectin [29].

- **PPARs:** PPAR-α,γ and δ are ligand activated transcription factors, which belong to the nuclear hormone receptor superfamily and have an important regulatory role in the metabolism of glucose and lipids. As they are activated by fatty acids and their derivatives, changes in dietary lipids activate them leading to an alteration in the expression of genes involved in fat and carbohydrate metabolism [19]. PPARs bind to their ligands (both endogenous and exogenous) followed by heterodimeization with retinoid X receptors (RXRs); the heterodimer thus formed, moves towards DNA and binds to peroxisome proliferators response elements (PPREs) present in the

promoter regions of specific genes. Such binding causes activation of PPREs leading to increased transcription of target genes and hence, increases in protein synthesis [19].

PPAR-α receptors are abundantly expressed in hepatocytes [19, 30] whose responses have been explained by their activation with the exogenous ligand clofibrate, used as a hypocholesterolemic agent. Fibrates have been found to decrease plasma TG levels along with an increase in plasma HDL by interfering with several steps of lipid metabolism. Such interferences include increased plasma HDL level by an increase in the synthesis of apolipoproteins, apo AI and AII - the major apolipoproteins present in HDL.

Decreased plasma TG level is due to decreased apo CIII synthesis in hepatocytes and increased expression of lipoprotein lipase in muscle vascular beds leading to increased hydrolysis of TG in chylomicrons and VLDL (TG-rich lipoproteins) thereby releasing more fatty acids into circulation whose uptake and subsequent oxidation in muscle cells increases. Decreased apo CIII synthesis may potentiate this action by increasing receptor mediated endocytosis of TG-rich lipoproteins into cells (apo CIII inhibits this process).

Increased fatty acid oxidation is reflected on TG synthesis which is decreased leading to decrease in plasma TG level [30]. Moreover, as mentioned earlier, PPAR-α receptor activation along with the activation of PPAR-γ, leads to increased formation and secretion of adiponectin and upregulation of Adipo R_1 and R_2. All these effects of PPAR-α activation seem to ameliorate obesity-linked insulin resistance [25].

PPAR-γ receptors are expressed mainly in liver and adipose tissue, whose nuclear action leads to expression of genes necessary for differentiation of fibroblasts into adipocytes and for lipid synthesis and storage in adipocytes [19]. TZDs are exogenous agonists of these receptors and because of the above lipogenic action, are associated with body weight gain and seem to decrease insulin sensitivity rather than increasing it (because of lipogenicity) [25].

But lipid storage in adipocytes reduces lipotoxicity in liver and skeletal muscles and PPAR-γ activation by TZDs increases the number of small adipocytes which are more sensitive to the actions of insulin. In addition, these small adipocytes abundantly express and secrete the insulin-sensitizing cytokine, adiponectin, and reduce resistin and tumor necrosis factor (TNF)-α (which induce insulin resistance), thereby increasing insulin sensitivity further [25, 31].

PPAR-δ receptors, the key regulators of fatty acid oxidation, are activated by changes in dietary lipid. Their activation in liver and skeletal muscles stimulates the transcription of at least mice genes encoding proteins for β-oxidation and for energy dissipation through uncoupling of mitochondrial function. It has been observed that normal mice overfed with high-fat diets, accumulate large amounts of brown and white fat along with accumulation of fat droplets in the liver. But, when the same overfeeding is given to the genetically altered mice in whom PPAR-δ is always active, such fat accumulation is prevented. Thus, by stimulating fatty acid break down in uncoupled mitochondria, PPAR-δ causes fat depletion and weight loss and acts as a defense against obesity [19]. This may contribute towards increased insulin sensitivity.

- **Leptin:** Obesity is known to results from intake of more calories than it is expended on the body. The excess dietary calorie is disposed off in the body by conversion to fat (triglyceride) and its storage in the adipose tissue, its burning through extra exercise (fatty acid oxidation) and its conversion to heat (thermogenesis). In health, the fuel intake and expenditure is kept in balance by a coordinated but complex set of hormonal and neuronal signals, so that the amount of adipose tissue in the body is maintained at normal level [19]. The mechanism of such balance is explained by the lipostat theory according to which a feedback signal originating in adipose tissue influences the centers in the brain which regulate eating behavior and body activity (metabolic and motor). One such signal is leptin. It acts in the hypothalamus to alter the expression of several neuropeptides that regulate neuro-endocrine function and energy intake and expenditure [32].

Leptin, another adipocytokine, circulates in the blood both in free and bound form [32] and is carried to the hypothalamus where it acts on its receptors to inhibit appetite [19]. Small amounts of leptin are also secreted by epithelial cells of stomach and the placenta [33]. The amount of leptin produced by adipose tissue depends on both the number and size of adipocytes. Decrease in lipid tissue mass due to starvation reduces its blood levels [19]. It appears that adipocytes increase in size due to accumulation of triglycerides and hence, synthesize more and more leptin.

Moreover, short-term energy imbalance as well as serum levels of several cytokines and hormones influence circulating leptin levels [32]. Recent studies with obese and nonobese humans demonstrated a strong positive correlation of serum leptin concentrations with percentage of body fat along with a higher concentration of ob mRNA in obese compared to nonobese subjects. In essence, leptin seems to act as an index of nutritional status in the body [33]. Leptin is a product of ob (obese) gene, while its receptor is encoded by db (diabetic) gene. Mice with ob/ob gene have been found to be in a constant state of starvation with raised cortisol levels and unrestricted appetite, resulting in severe obesity. They also show metabolic disturbances very similar to those of diabetic animals and are insulin resistant. On leptin injection, these mice have been found to lose weight with improvement of other symptoms. Moreover, mice with db/db gene have been found to be obese and diabetic, which appears to be due to defective leptin receptor leading to loss of leptin function [19].

Leptin plays an important role in the long term regulation of body weight [33]. In the arcuate nucleus of hypothalamus there are two sets of neuro-secretory cells (neurons), one of which is orexigenic and secrete neuropeptide Y (NPY) (increase appetite) and the other is anorexigenic and secrete α- melanocyte stimulating hormone (α-MSH) (decrease appetite), when stimulated [19, 34, 35]. These neurons send signals to other neurons (via NPY and α-MSH) in the brain leading to either increase or decrease in appetite. The blood level of NPY has been found to be raised in starvation as well as in both ob/ob and db/db mice, which eat voraciously and are obese [19].

Both the NPY and α-MSH secreting neurons express receptors for leptin and insulin on their cell surface[35]. Leptin receptors are also expressed in T-lymphocytes and vascular endothelium[33]. Leptin from adipocytes and insulin from pancreas, released in proportion to the body fat mass, act on the corresponding receptors of these neurons to inhibit the secretion of NPY while stimulating that of α-MSH, the resultant effect being decreased appetite (**Figure 3**).

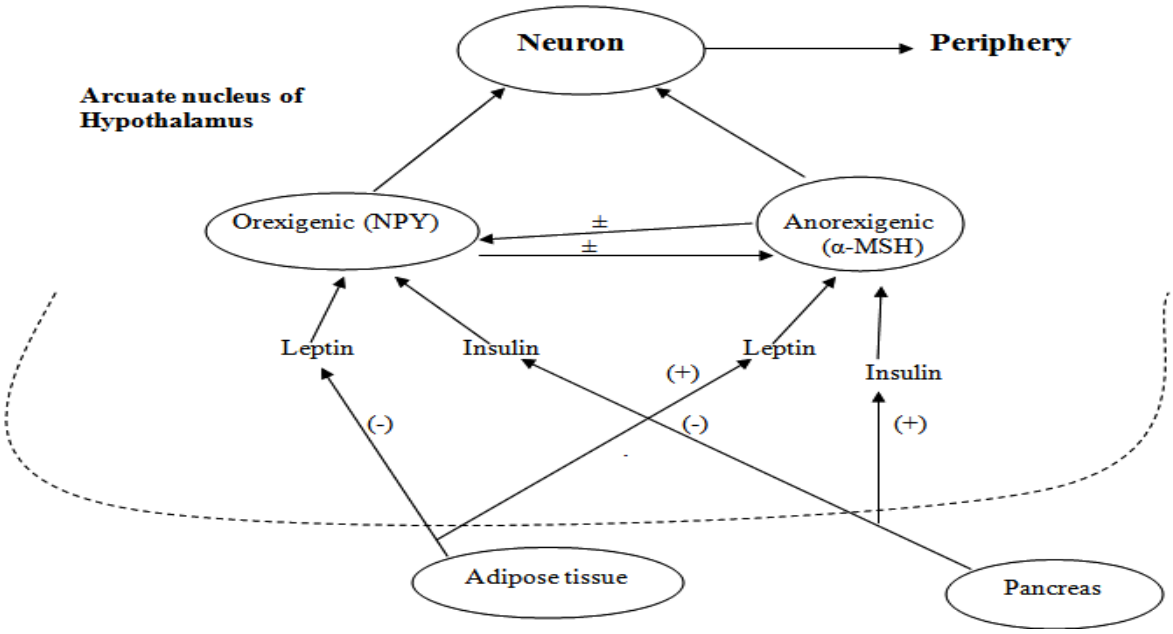

FIGURE 3: HORMONAL CONTROL OF APPETITE

Each set of these neurons also inhibit hormone production by the other, so that the stimulatory inputs to each of them is strengthened [19, 34]. Daily injection of recombinant mouse or human leptin into ob/ob mice have been found to produce a dramatic reduction in food intake within a few days, and to roughly a 50% reduction in body weight within a month [36]. But such injections to db/db mice (lack the leptin receptor) did not produce any effect. When injected to normal mice, leptin has been found to cause profound depletion of adipose tissue along with increase in lean mass [33]. Moreover, the gastric hormone ghrelin stimulates appetite by activating NPY-secreting cells [19, 34].

Receptor mediated leptin action has been found to be mediated via the janus kinase -signal transducer and activator of transcription (JAK-STAT) pathway [8, 35], leading to regulation of gene expression [8]. It also activates AMPK which regulates many aspects of fuel metabolism as mentioned earlier. The higher blood levels of leptin in obese animals including humans than the animals of normal body mass [19], appears to be due to downregulation of leptin receptors, as found in obese diabetics or some defective post receptor transduction pathway of leptin [19, 37]. Mention has been made about the concerted central actions of insulin and leptin leading to decrease in appetite and increase in fuel consumption. Though predominantly anabolic in nature, peripherally insulin also signals muscle, liver and adipose tissue to increase catabolic reactions, including fat oxidation, which results in weight loss.

Leptin seems to make these tissues more sensitive to insulin action, which may be due to cross-talk between the protein tyrosine kinases activated by leptin and insulin [8]. As both of them mediate their action through common second messengers, leptin triggers some of the same downstream events which are triggered by insulin, through insulin receptor substrate 2 (IRS 2) and phosphoinositide 3-kinase (PI-3K) [19]. Moreover, leptin-activated AMPK leads to increased fatty acid oxidation in muscles and hence decreased FFA in blood and subsequent increased insulin sensitivity (FFA is a potential precursor of insulin resistance) [8]. Because of such functional cooperation, it may be assumed that, obesity due to inadequate leptin action may predispose or get associated with insulin resistance and T2DM.

Some other endogenous products linking obesity and T2DM: Recently, certain other endogenous products have been found to act as links between obesity and T2DM. Though investigation into them is not sufficient, data available in this respect till now, suggest the need for further work to validate the link.

- **PEDF**: PEDF is another adipokine whose secretion has been found to be inversely regulated by insulin and upregulated in patients with T2DM [11]. The adipokine may play an important role in linking visceral obesity to T2DM, diabetes and obesity-related disorders [10, 11].

- **GPR 40**: Once considered as an orphan receptor, GPR 40 has been found to be abundantly expressed in pancreatic β-cells of obese individuals, whose agonists are FFAs. Activation of these receptors by FFAs has been found to amplify insulin secretion, though the exact mechanism is not understood clearly [38]. Mice with high level of FFA possess these receptors and found to develop both diabetes and liver diseases. On the other hand, mice with normal levels of FFAs did not have GPR 40 and were able to metabolize their food without weight gain or development of diabetes. Such observations point to a relationship between obesity and diabetes, which may be due to downregulation of peripheral insulin receptors leading to insulin resistance or downregulation of GPR 40s on β-cells, which no longer amplify insulin secretion [15].

- **CPE:** It is a protein in the pancreatic β-cells, which plays a key role in the production of insulin. After its discovery, it was found that increased levels of fat in the blood destroy islet β-cells by reducing CPE in pancreas, leading to T2DM [16]. According to Zhu *et al*., [39] defects in the gene encoding CPE in mouse and human lead to multiple endocrine disorders, including obesity and diabetes. Moreover, mice bearing CPE mutations exhibit an obese and diabetic phenotype [40].

Drug actions showing link between obesity and T2DM: Besides these endogenous products, the pharmacological actions of the anti-obesity drug orlistat point towards the link between obesity and diabetes.

Orlistat, during short- and long-term studies of up to 4 y duration has shown significant benefits in weight loss, along with reduction of lipids, glucose, glycosylated hemoglobin ($HbA1_C$), and the time of onset of T2DM compared with diet alone or placebo groups. Because of such associated functions, it can be suggested that obesity may be a causative factor for diabetes [41]. From experimental observations, the use of orlistat for prevention of diabetes in obese individuals has been suggested [42].

SUMMARY: Obesity, which is usually associated with dyslipidemia, is a proved risk factor for coronary and cerebral atherosclerosis [34, 43]. During the last two decades, this seemingly unrelated but suspected factor (obesity) has also shown a strong relationship with T2DM. From the discussions made in the article, basing on data from several investigations and authentic text books, it appears that obesity is definitely and intimately linked to T2DM and may precede, be associated or aggravate it.

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