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OBESITY AND ITS COMPLICATIONS: ROLE OF AUTOPHAGY

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ABSTRACT: Obesity is the primary cause of metabolic syndrome (MS), further developing to atherosclerosis, hypertension, insulin resistance and diabetes in different individuals depending on their predisposed genetic background. Though adipose tissue acts as endocrine gland, as storage for energy reserve and insulation to vital organs but overloaded adipose tissue, turns inflammatory and induces systemic low grade inflammation (LGI), affecting the normal physiology. The endothelial cells, the innermost layer of a blood vessel, are the most affected ones and responsible for micro and macro-vascular complications. Obesity is linked to dysfunction of endoplasmic reticulum and mitochondria in variety of cells resulting oxidative stress, accumulation of residual damaged cell organelles and ER stress leading to UPRs (unfolded protein responses) accumulation in the cytoplasm. This is also associated to low autophagy. The whole process activates the innate immunity and attracts macrophages towards adipose tissue and secretes abnormal adipokines and inflammatory cytokines. At physiological level it is manifested as changed neurological secretions, sleep pattern, appetite, and hunger signals. Thus, activation of antioxidant enzymes and autophagy by changed life style (sleep cycle resonance with circadian rhythm), regulation of digestive power and food habits (energy intake/expenditure balance), medicinal supplements (medicine and herbal) and behavioural changes (psychological and environmental factors) may prove effective in management of obesity and related complications. Here, we have discussed the etiological factors responsible behind the pathogenesis of MS and involved signaling pathways with reference to autophagy.

INTRODUCTION: Obesity is a public health problem with continuous rising trend. In 2010, overweight and obese persons were estimated to cause 3.4 million deaths, 3.9% of years of life lost, and 3.8% of DALYs (disability adjusted life years) globally [1]. Another study of 2015 indicates that, a total of 107.7 million children and 603.7 million adults were obese. High BMI accounted for 4.0 million deaths globally and its 40% occurred in persons who were not obese.

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Among them about two thirds of deaths were related cardiovascular disease [2]. A report of 2016 further reported that more than 1.9 billion adults older than 18 years (39%) were found to be overweight [3], measured by anthropometric parameters *e.g.* body mass index (BMI-kg/m^2; Body weight in kg divided by the square of height measured in meters), height/wt ratio, waist-hip ratio, visceral fat and body fat percentage.

As per WHO, the persons having BMI between 25.0 and 29.9 kg/m^2 are overweight and greater than that are obese. The obesity is being considered as the mother of other non-communicable diseases (NCDs), such as diabetes, cardiovascular diseases (CVD), breast cancer, chronic obstructive pulmonary diseases and hypertension (collectively named as metabolic syndrome-MS) and imparts

high financial burden to any nation. Earlier it was thought that NCDs are more prominent only in developed countries, but now low and middle income countries are also under this cover. Recently, India has been identified as the hub of diabetes, because about 18% of world population lives in India [4]. The obesity is mainly considered as the outcome of diet imbalance *i.e.* high energy intake and lower expenditure [5]. Defects in the hypothalamic leptin-melanocortin circuits have been implicated in its pathogenesis. According to nutrition - immunity hypothesis, over-nutrition promotes inflammation, particular attributed to visceral adipose depots. This systemic inflammation further damages the normal biochemistry of other cells and tissues in the body affecting the overall physiology and initiating pathogenesis of NCDs [6, 7, 8].

Obesity and Low Grade Inflammation (LGI): It is the 1st sign of obesity-associated complications and can be measured in terms of blood-hsCRP, TNF-α, Interleukin-1 (IL-1), Interleukin-6 (IL-6) *etc* [9]. It is mainly attributed to adipose tissue embedded macrophages (ATM) affecting the secretions of adipokines from fat-overloaded adipocytes, ROS generation and ER stress. This tissue microenvironment is accelerating the macrophages polarization to M1 type, which further enhances the process of LGI by secreting more inflammatory cytokines. In fact induction of LGI is natural reaction to counter the odd physiological conditions, which are attributed to oxidative stress due to dysfunction of mitochondria and endoplasmic reticulum. However, its longer persistence becomes pathogenic [10, 11].

Obesity and Immune System: The LGI in a tissue attracts immune cell and induces plasticity, depending on the microenvironment of that tissue. It has extensive implications in pathogenesis and resolution of these chronic diseases and it is influenced by nutritional status. In obesity, immune cells interact differently with various classes of lipids which affect the plasticity of macrophages and T lymphocytes, finally affecting the innate and adaptive immune responses. The adipose tissue, overloaded with fat, attracts the monocyte differentiated macrophages and depending on the quality of fat store, these mcrophages get polarized either to classical (M1) or alternative (M2) types. The M1 are inflammatory and M2 are responsible for innate immunity, tissue repair and remodeling. The M1 polarization is identified by the presence of cellular makers CD319, CD274 and CD38 and they are predominant in visceral adipose tissue. These are termed as ATM (adipose tissue macrophages), and produce abnormal adipokines. They secrete inflammatory markers interferon gamma (IFN-γ), interleukins IL-1β and IL-6, C-X-C motif chemokines CXCL10 and CXCL9 and tumor necrosis factor TNF-α.

On the contrary, the M2 macrophages are defined by cell surface markers CD206, CD301 and CD163 and they predominantly express anti-inflammatory cytokines like IL-4, IL-13 and / or IL-10 [12]. These adipose tissues also attract the CD4 Th1 lymphocytes, especially in visceral fat, which are primarily responsible for causing insulin resistance. In contrast, CD4 Th2 lymphocytes protect against diet-induced obesity and insulin resistance. Similarly, Th17 cells are key players in the development of hypertension.

Quality of Lipid and Macrophage Polarization: The quality of fat in adipose tissue directly determines the polarization pattern of ATM. The saturated fat produces more M1 than the PUFA. An experimental study has shown that treatment of macrophages with palmitate (saturated fatty acids) induces TNF-α gene expression. In contrast, unsaturated fatty acids (oleate) particularly polyunsaturated fatty acids (PUFAs), linoleic acid, alpha-linolenic acid and docosahexaenoic acid (DHA) resolved the inflammation. The short-chain fatty acids (SCFAs) such as acetic acid, propionic acid and butyric acid, are produced in the gut by bacterial fermentation of dietary fiber.

They regulate T lymphocyte activation and differentiation and also the macrophage polarization, and finally contributing to induction of inflammatory process. Thus it could be inferred that elevated dietary intake of saturated fatty acids (SFAs) and GI function are strongly correlated to LGI and finally complications of MS. Although fatty acids are good substrate for mitochondria for beta oxidation but excess accumulation of FA leads to mitochondrial dysfunction attributing to macrophage inflammation a state of high metabolic rate and low energy production. Thus, LGI

established due to obesity indices several complications, which are considered as NCDs. Some of them are being described here [13, 14].

Obesity and NAFLD: The visceral fat directly affects the function of liver. The ATM produces extra inflammatory cytokines, which reaches to hepatocytes to induce OS (oxidative stress) and ER (endoplasmic reticulum) stress. Further the state of insulin resistance in adipocytes, mobilizes more fat from adipocytes to produce energy. As its side effect, there is increase in the circulating free fatty acids (FFA) in the blood, further promotes insulin receptor desensitization and also promotes ectopic lipid storage in different tissues *e.g.* liver and muscle [15]. This FFA is taken up by the liver to synthesize TG and VLDL resulting hyper-lipidemia state. The de-novo synthesis of TG in liver from carbohydrate or non esterified fatty acids could be another factor for hyperlipidemia. The pathogenesis of NAFLD could also be attributed to defective lipophagy (autophagy of lipid droplets) in hepatocytes [16]. The abnormal hepatic cholesterol homeostasis is also a significant contributor to NAFLD. The hepatic bile acid synthesis is the major catabolic mechanism for cholesterol elimination and its defect is also involved in pathogenesis of NAFLD. The bile acids are also the signaling molecules to regulate liver metabolism and inflammation, which is influenced by autophagy in hepatocytes and macrophages [17]. High fat diet further represses the endoribonuclease activity of inositol-requiring enzyme 1α (IRE1α), a transducer of UPRs due to ER stress in hepatocytes, resulting hepatic steatosis and nonalcoholic fatty liver disease (NAFLD). The IRE1α is critical for maintaining lipid homeostasis in the liver by repressing the biogenesis of micro RNAs (miRNAs) leading to decreased abundance of lipid metabolism enzymes. This results to lipid accumulation in the liver [18].

Obesity and Atherosclerosis: Although both obesity and atherosclerosis are considered as different disease but several commonalities have been reported in their pathophysiology [19]. They includes activation of innate and adaptive immunity due to chronic inflammation, ectopic lipid accumulation, cytokine production, inflammatory cell infiltration, and apoptosis [20, 21]. Persistent secretion of inflammatory cytokines from ATM (adipose tissue embedded macrophages-M1) induces endothelial dysfunction with reduced eNOS secretion, more platelet activation and high oxidative stress. The free radicals generated due to abnormal functioning of mitochondria further oxidize the LDL (oxLDL), which is engulfed by macrophages and converted to foam cells. The excess accumulation of foam cells in the layer of VSMC (vascular smooth muscle cells), followed by apoptosis produces plaque and narrowing of blood vessels. The VSMC changes their contractile property to synthetic phenotype by dedifferentiation and produces high levels of tumor necrosis factor-α (TNF-α). The autophagy and mitophagy becomes dysfunctional in plaque macrophages, VSMCs, and endothelial cells (ECs), regardless the presence of many autophagy-stimulants in the plaque surroundings *e.g.*, ROS, oxLDL, and inflammatory cytokines. The inflammatory phenotype of VSMCs results more migration, proliferation and secretion of IL-6, type I collagen and osteopontin, promoting plaque formation. Thus inhibition of autophagy could prevent these TNF-α-induced phenotypic changes [22]. The homeostasis of autophagy may reduce the apoptosis of conditioned VSMCs, by blocking generation of ROS, from defective mitochondria [23].

On the contrary, age-related change in redox balance, rise in age-related senescent cells and the decline in effective autophagy may trigger the inflammasomes, responsible for LGI and related pathogenesis. Infact, the etiological mechanisms behind obesity indicate the involvement of energy imbalance and neuro-hormonal dys-regulation and both are tightly regulated by autophagy. The decrease in autophagy facilitates the deposition of cholesterol in athero-prone macrophages and the subsequent development of vulnerable atherosclerotic plaques due to impaired catabolism of lipid. Thus, it has become an important target to treat obesity [24]. Another study indicates that activation of AMPK inhibits the production of ROS-mediated mitochondrial dysfunction, ER dysfunction, activation of NADPH oxidase and production of pro-inflammatory cytokines, collectively preventing the endothelial dysfunction by increasing the bioavailability of nitric oxide [25]. The AMPK also activates autophagy resulting inhibition of cell apoptosis and inflammation and promotes cholesterol efflux and efferocytosis.

It is also reported that mammalian target of rapamycin (mTOR) that controls autophagy and lipid metabolism is pivotal for atherosclerosis initiation and progression. Thus, blocking the mTOR function with rapamycin and its analogs may stimulate autophagy and consequently attenuate lipid storage and atherosclerotic lesions [26].

Obesity and Hypertension: The obesity is also linked to hypertension, attributed to systemic and tissue inflammation. Over-activation of cannabinoid receptor 1 (CB1R) in adipose tissue is proposed in the pathophysiology of metabolic disorders in adipose tissue and deregulates production and secretion of adipokines. Thus, a peripheral CB1R antagonist may be effective in reducing this obesity linked BP [27]. Mitochondria are key inflammatory element in vascular and adipose tissue and serve as potential pharmacological targets.

The Melatonin, secreted by the Pineal gland, also protects against mitochondrial dysfunction and reduces blood pressure. It is attributed to its anti-inflammatory/antioxidant potentials. However, adipose tissue dysfunction disturbs this secretion [28]. The disturbed sleep-wake cycle and unsynchronized body rhythm with nature's cycle disturbs, melatonine secretion. The simple anthropometry data, related to obesity, especially the waist circumference (WC) in young age may predict the chances hypertension in later part of life [29].

The ATMs secrete a number of adipokines, vasoactive factors and components of the renin-angiotensin system, which may act at local or at systemic level. The anti-contractile effect of perivascular adipose tissue (PVAT) is lost in obesity, probably as a consequence of the development of adipocyte hypertrophy, inflammation, and oxidative stress thus contributing to endothelial dysfunction observed inobesity and hypertension.

Thus, decreased local adiponectin level, macrophage recruitment and infiltration, and activation of renin-angiotensin-aldosterone system could play an important role in hypertension [30]. The patho-physiological links between obesity mediated diabetes and hypertension is another important mechanism. It disturbs the renal sodium handling because there is an up-regulation of sodium transporters in the kidneys.

In this condition, the renin-angiotensin-aldosterone system is up-regulated, leading to hypertension through a direct effect mediated by angiotensin II, as well as indirectly through up-regulation of sympathetic activity. Diabetes frequently has autonomic dysfunction, which could contribute to hypertension through increased sympathetic tone and through stimulation of renin production. Almost 90% of hypertension patients have internal co-morbidities, in particular hypothyroidism. It leads to hyperlipidemia, blood coagulation disorders, adrenal glands activation, cardiac, renal and hepatic damage, and negative adaptive responses. Obesity also disturbs the psychological state of an individual causing depression and stress. It is linked to more secretion of catecholamines, which is another etiological factor for induction of Blood pressure [31, 32, 33].

Obesity and Diabetes: Obesity mediated LGI is attributed to insulin receptor desensitization. The cytokines secreted by ATM is controlled by NF-κB, which is also a significant contributor of this insulin receptor desensitization is also linked to high level of circulating FFA in the blood. The insulin receptors are abundant on adipocytes, hepatocytes, and muscle and in each organ different pathologies get developed. In type 2 diabetes (T2D), hepatic insulin resistance is strongly associated with non-alcoholic fatty liver disease (NAFLD). This diabetic condition further activates lipolysis in adipose tissue, due to activated adrenal gland resulting high circulating FFA in the blood, which further induces insulin receptor desensitization.

The imbalance in synthesis of microRNAs (miRNAs) display a critical role in fine-tuning of the circadian system and energy metabolism. It is linked to disruption of the peripheral clock. Diabetes and obesity are known to be risk factors that exacerbate sarcopenia further promoting diabetic condition. The impaired transport of leptin across the blood-brain barrier (BBB) is the cause of leptin resistance, which is a cause of over eating even after obese condition. Both hypo-methylation at a CpG site in PDGFA (encoding platelet derived growth factor alpha) genes, resulting itsover-expression is associated with increased T2D risk, hyper-insulinemia, increased insulin resistance and increased steatohepatitis risk.

Fibroblast growth factor 21 (FGF21) is another critical regulator of nutrient homeostasis. It is an endocrine hormone derived from the liver. Low protein diet (LPD) exerts reno-protection through improvement of glomerular hyper-filtration / hypertension, which is due to reduction of intra-glomerular pressure. It improves tubulo-interstitial damage, inflammation and fibrosis, by restoration of autophagy via the reduction of a mammalian target of rapamycin complex 1 (mTORC1) activity and adequate autophagy induction described below [34, 35, 36, 37].

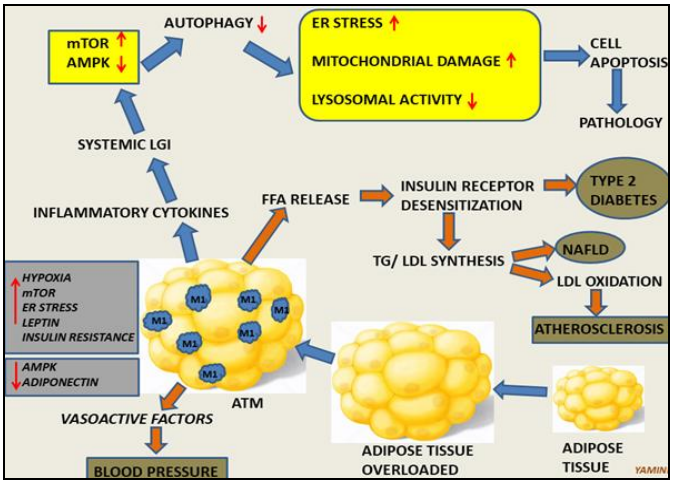

FIG. 1: PATHOGENESIS OF ADIPOSE TISSUE AND ASSOCIATED COMPLICATIONS

Obesity and Cancer: A study has shown that about 20% deaths of cancer patients are linked to obesity, where it grows faster and often resistant to treatment along with more chances of metastasis. There may be different types of cancer, which may be linked to obesity but, its link with breast cancer has been extensively studied. A study on US population has reported that more than 62% women have high risk for cancer specially the colorectal, liver, gallbladder, pancreas, esophageal, kidney, prostate, breast, uterine, endometrial, and ovarian cancers [38]. The micorbiome disturbance may be one of the common factors, linked to obesity and cancer. It has been recently reported that presence of some microorganisms in GIT improves the therapeutic effect of anticancer drugs. On the other hand role of microbiome in induction of obesity is already established [39].

Another link between obesity and cancer is the hypoxia, which is common in obese adipose tissue and cancer tumors. In the fat overloaded adipose cells, there is more expression of VEGF, which is also reported in cancer tissue. Further, some indirect evidences include the role of rapamycin in reducing both obesity and cancer, especially in obese mice. The obese persons with cancer have p53 gene alterations, finally activating mTOR activity [40]. Adipose-associated polypeptides such as leptin, adiponectin, insulin-like growth factors and ghrelin represent potential mechanisms promoting cancer development. Both in obesity and cancer, mTOR activity is raised because of upstream activation of PI3K signaling pathway. Thus, its down regulation is an important approach to treat both pathogenesis. More secretion of collagen VI and endorphins by obese persons are another link to cancer pathogenesis [41].

On the contrary, the cancer cells also have reciprocal effects on adipocytes [42]. Thus, it can be summarized that at molecular level, adipocytes and cancer cells adopt common signaling pathways that help them in their survival such as angeogenesis and inflammation to bring more nutrients to growing tissue.

Further, microRNA-504 is also a negative regulator of p53 genes [43]. In cancer, there is increased synthesis of lipid because it is required for cell membrane formation. in rapidly growing cancer cells [44]. This pathway is governed by activation of PI3K signaling pathway, which activates pro-lipogenic factor SREBP1 and mTORC1.

Obesity and Hunger: The overloaded adipocytes secrete abnormal adipokines, affecting the regulation of appetite and growth. It secretes comparatively low adiponectin and high leptin, the characteristic features of obesity [45]. The Leptin regulates the hunger signals, adaptive and innate immunity, but its continuous raised level in the blood, ultimately desensitizes its receptors in the brain. This initiates a vicious circle inducing more leptin secretion from adipocytes. Since low leptin induces tendency to eat more, because it is a sign of starvation or mal-nutrition, so that obese person develops a pseudo state of hunger (because of leptin-receptor desensitization, a pathological state). In case of un-healthy obesity, there is ectopic lipid deposition further manifesting the phenomenon of leptin-receptor resistance. These obese persons also show a state of immune suppression [46, 47].

Obesity and Autophagy: All the factors described above, collectively suppress autophagy and allow accumulation of undesired proteins. If not removed properly, these accumulations induce pathological conditions. The autophagy (Macroautophagy) is a catabolic process, where old cell-organelles and unused-protein and lipid droplets, accumulated in the cytoplasm, get degraded by cellular proteases, especially by lysosomal enzymes. The autophagy is an evolutionarily conserved lysosomal degradation pathway that controls cellular bioenergetics (by recycling cytoplasmic constituents) and cytoplasmic quality (by eliminating protein aggregates, damaged organelles, lipid droplets, and intracellular pathogens) [48].

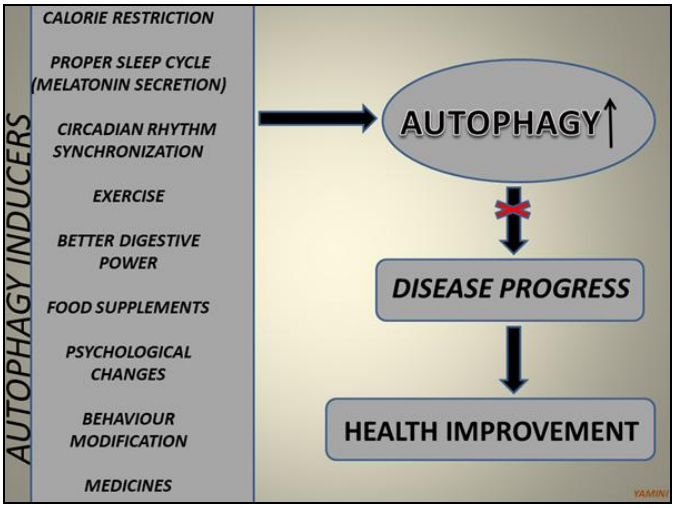

FIG. 2: AUTOPHAGY INDUCERS IN HEALTH CARE

It is generally active during starvation or negative energy balance, when the cell needs nutritional molecules to synthesize its own cellular molecules (substrate for de novo synthesis) and energy production. In this stage, the external nutrition sources are limited. Depending on the target cells, it is named as mitophagy, lipophagy *etc*. There are 3 prominent sensors for assessment of nutritional status [49]. These are mTOR, AMPK and Sirutin and their activity regulates the overall metabolism of food in the body including autophagy [50].

Autophagy is not only important for cell survival by providing fuel through the self-digestion of large molecules and cellular damaged organelles, at the time of nutritional stress, but it is also essential for maintaining cellular health by removing and cleaning up the misfolded molecules and aged/ dysfunctional cellular organelles [51]. Autophagy normalizes the dys-regulation, induced by oxidative stress, inflammation, immunological over-activity. Its down-play has been reported in several infectious diseases, NCDs, neurodegeneratiion, aging and inflammatory conditions and metabolic diseases. The autophagy is known to have a role in thymic selection of T cells, survival of B cells, immune tolerance, and antigen presentation [52].

In Ayurveda, similar phenomenon has been reported in terms of "Ama Dosha", which has been attributed to "suppressed Agni, which is of total 13 types. Although at present we not have clearcut explanation to these terms, but it may be compared to low metabolic activity in GIT, Tissues and cells. In GIT, it has been compared to digestive power attributed to hormones and enzymes involved in digestion and it is termed as Jatharagani, one of the total 13 agnies. The "Ama Dosha*"* has been referred as the basic cause of all the chronic diseases, as per Ayurveda [53, 54].

The lipophagy dys-regulation (inhibition of adipose tissue autophagy), is associated with human obesity [55]. High levels of glucagon, lesser insulin, lower amino acid availability are some of the factors to activate autophagy, through modulation of mTOR-or/and Akt-dependent pathways [56]. Low expression of classical lipases in abdominal SCAT is accompanied by an increased expression of autophagy-related genes (ATG) 5, 7 and 12 in SCAT has been reported to be higher along with lower expression of the classical lipases HSL (hormone sensitive lipases) in obese persons. The ATG12 mRNA has been positively correlated with raised BMI. More significant correlation has also been reported between ATG7 mRNA with waist/hip ratio (WHR) [57]. Further, altered endogenous glucocorticoid metabolism, including 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which generates active cortisol from cortisone, and 5α-reductase (5αR), has also been reported in obesity. Thus its inactivation may be another approach to reduce obesity induced insulin intolerance [58].

Epinephrine is another body secretion, which is secreted by adrenal glands by sensing glucose drop in blood. It activates β-adrenergic receptors on peripheral tissues and promotes the mobilization of stored triglyceride through increased autophagy. Thus raised FFA and TG in blood further reduce

autophagy. The reduced level of circulating growth factors inhibits the downstream signaling via theAKT1/mTORC1 pathway along with inhibiting the glucose uptake. In summary, drop in the extracellular availability of INS, IGF1, and growth factors coupled to increase GCG signaling, provoking a robust autophagic response [59, 60, 61].

Both pharmacological and non-pharmacologic interventions are in practice to enhance the down regulated autophagy. Increasing obesity has also been linked to lesser sleep duration. The awaken-state allows more food intake and lesser glucose response to its receptors, creating a state of pre-diabetic condition in obese subjects. In humans, continuous sleep for 7 - 9 h is a normal physiological process. In this period, there is continuous fasting, which influences the pancreatic β-cell function and also the insulin sensitivity. Thus, circadian rhythm and sleep plays important role. Plasma glucose responses to exogenous glucose are markedly higher in the evening than in the morning, and glucose tolerance is at its minimum in the middle of the night [62]. Thus in evening or at night the glucose tolerance and insulin secretion are lower than the morning or awaken period. Further, in sleep curtailment, the leptin, an anorexigenic hormone produced by adipocytes, is decreased and sympathetic nervous system gets activated, resulting increased food intake decreased reduction in insulin release respectively [63]. It also induces release of inflammatory cytokines resulting establishment of LGI [64].

Caloric restriction, yoga, naturopathy, regular exercises, periodical eating habits, resonance of wake-sleep cycle with solar rhythm, deliberate starvation is some of the non-pharmacological approaches to regulate autophagy. The starvation state, attributing to drop of nutrients in the extracellular fluids, below a threshold level, activates autophagy to replenish the nutrients by activating the sensors to mobilize the intracellular stores. The starvation decreases the cytosolic acetyl-CoA in skeletal and cardiac muscles but not in brain and induces autophagy in somatic organ. This indicates condition of caloric restriction. Abstaining from frequent feeding induces a kind of periodical starvation attributing to reduction of circulating insulin (INS) and insulin-like growth factor 1 (IGF1) and increase in insulin-like growth factor binding protein 1 (IGFBP1, an IGF1 antagonist) and glucagon (GCG). This phenomenon inhibits the nutrient uptake and also inactivates mTORC1, favoring a compensatory autophagic response. Thus, organ level autophagy regulation is also of great therapeutic benefit. The ketogenic diet (*i.e*., a high-fat, low-carbohydrate, and low-protein diet supplemented with ketogenic essential amino acids) also stimulates autophagy, by inhibiting mTORC1 [65]. The inhibitors of mTOR, EGFR and tyrosine kinase, carbamazepine, trifluoperazine are some of the other pharmacological activator of autophagy. Besides the direct effect of low nutrients, some cells also secrete neuroendocrine secretions which also induce autophagy. These organs are liver, adipose tissue, or skeletal muscle, which try to restore the depleted level of nutrients. Thus these organs show feedback inhibition of autophagic responses.

The specific nutritional manipulations (*e.g*., methionine restriction, polyamine supplementation) can also induce autophagy. Chemicals like rapamycin, resveratrol, and spermidine (a natural polyamine) food supplements like secondary metabolites of medicinal plants and fruits, coffee and Vitamin D *etc*. have been also reported to induce autophagy [66, 67]. Caffeine-induced autophagy reduces hepatic steatosis in mice with nonalcoholic fatty liver disease [66]. Vitamin D is a potent inducer of autophagy [67]. In case of obesity management, the pharmacological activation of liver autophagy is important therapeutic target [68]. The reduction in circulating leptin levels is also related to raise autophgy [69].

It is known that insulin suppress autophagy by activating mTOR. This in case of insulin resistance (a condition of pre-diabetes, when BMI is higher than normal), there is more circulating insulin, indicating towards better process of autophagy and better health, but the actual situation is opposite. Based on several experiments it has been postulated that persistant increase in blood insulin desensitizes this signaling pathway and eventually reduces autophagy resulting accumulation of these undesired macromolecules [70]. The pathogenesis of fatty liver is one of its results in case of pre-diabetics [71]. The reduced level of circulating growth factors inhibits the downstream signaling *via* the

AKT1/mTORC1 pathway along with inhibiting the glucose uptake. In summary drops in the extracellular availability of INS, IGF1, and growth factors coupled to increase GCG signaling, provoking a robust autophagic response. Epinephrine secretion is also dependent on blood glucose level. At time of glucose drop, it activates β-adrenergic receptors on peripheral tissues and promotes the mobilization of stored triglyceride through increased autophagy. Thus, raised FFA and TG in blood further reduce autophagy [72].

Obesity and mTOR: The mammalian target of rapamycin (mTOR) pathway responds to nutrients and controls the growth of a cell by regulating cellular metabolism. It senses the fed and starved conditions through circulating nutrients and growth factors and accordingly initiates either anabolic or catabolic processes. Thus, fed condition activates glycogen synthesis, lipid uptake in adipose tissue, reduced protein breakdown, gluconeogenesis and lipolysis. The hypothalamus is another organ, specially the arcuate nucleus (ARC) region, which is governed by circulating nutrients (glucose, amino acids, lipids) and hormones (leptin, insulin) to control energy balance and obesity. The mTORC1 activity in the ARC is governed by uptake of leucine or leptin and reduces food intake in a rapamycin sensitive fashion by promoting the expression of the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) [73].

The Elevated circulating levels of insulin, pro-inflammatory cytokines, and nutrients (branch-chain amino acids and glucose) activate mTOR. The high rate of protein synthesis associated with mTORC1 activation may also induce insulin resistance by promoting ER stress and the unfolded protein response (UPR) [74]. High fat feeding or obesity disturbs this control impair the central anorectic action of insulin and leptin, which likely promote obesity by deregulating the control of energy balance [75]. It blocks the action of these factors to activate hypothalamic mTORC1 resulting reduction of food intake.

The *in-vitro*, inhibition of mTORC1 blocks adipogenesis and impairs the maintenance of fat cells [76]. The S6K1 regulates the commitment of embryonic stem cell to adipogenic progenitors by regulating the expression of early adipogenic transcription factors and the 4E-BPs control the terminal differentiation of adipocytes through the translational control of the master regulator of adipogenesis, PPAR-γ [77]. In muscle also mTOR activation enhances muscle hypertrophy and protein synthesis. Loss of mTORC1 in muscle also reduces the intensity of the negative feedback loop to IRS1, which increases Akt activation and promotes glycogen accumulation in muscles. The high activation of mTORC1 in the muscle of obese and high fat-fed rodents drives S6K1-mediated feedback inhibition of insulin signaling, which reduces glucose uptake by the muscle and contributes to systemic insulin resistance the impaired insulin signaling in muscle may also contribute to the muscle loss observed in obesity/insulin resistance by promoting protein catabolism through the expression of ubiquitin ligases by FoxO1 [78].

This opposite action prevents the muscle development in mTOR activated conditions. Strangely, despite high mTORC1 activity, high fat feeding, obesity, and type 2 diabetes impairs mitochondrial biogenesis/function in muscles [79]; the mTORC1 controls the hepatic production of the ketone bodies that peripheral tissues. The elevated hepatic mTORC1 could explain why lipogenesis remains active while the suppression of glucose production becomes insulin resistant in the liver of obese/insulin resistant conditions. Here the constitutive activation of mTORC1 in β-cells causes a decrease in blood glucose, hyperinsulinemia, and improves glucose tolerance, with β-cell size and number [80].

Because them TOR belongs to the family of phosphatidy linositol kinase-like kinases, which is a unique family of large proteins with Ser/Thr kinase activities. The mTOR is the target of a molecule named rapamycin or sirolimus, which is a macrolide produced by Streptomyces Hygroscopius bacteria. Chronic activation of the mTOR/S6K1 pathway by insulin, amino acids, or TNF-α promotes insulin resistance in fat and muscle cells through increased IRS-1 serine phosphorylation and degradation. It is a convergence between growth factor signaling, metabolism, nutrient status and cellular proliferation. The mTOR pathway integrates the insulin and nutrient signaling in numerous cell types.

Amino acids, particularly leucine and arginine, also activate mTORC1. The phosphatidic acid (PA) has also been identified as an activator of mTORC1. Protein synthesis isthe best characterized process controlled by mTORC1, which directly phosphorylates the translational regulators eukaryotic translation initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) and S6 kinase 1 (S6K1), which, in turn, promote protein synthesis [81, 82].

Obesity and AMPK: The AMPK is another important therapeutic target to treat obesity. It is an energy sensor in the cell and gets activated when ATP is low. It phosphorylates the enzymes involved in ATP metabolism and suppresses anabolic ATP-consuming pathways along with stimulation of the catabolic ATP-generating pathways. The AMPK stimulation corrects the increased BMI through correcting the metabolism in adipose tissue, liver and muscle. The secretions of Gastro intestinal tract (GIT), (defined as Jatharagani in Ayurveda) also plays significant role in regulation of obesity. It attenuates lipotoxicity. The ghrelin (GHRL), the "hunger signal, is secreted in the gut, after stomach empties. It is linked to relaxation of the gastric wall after passing the food to duodenum. It acts by up-regulating autophagy *via* AMPK/mTOR restoration and inhibition of translocation of NF-κB into the nucleus [83]. However, *in-vitro* experiments show that ghrelin mediates both autophagy-activating through AMPK activation and autophagy-inhibition through inhibition of proteasomal protein degradation.

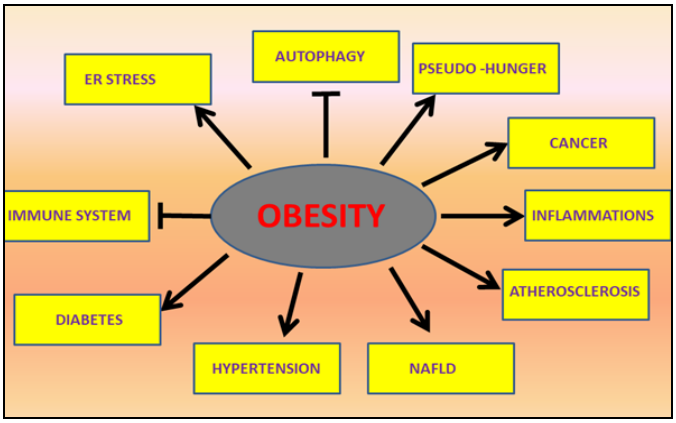

FIG. 3: OBESITY AND METABOLIC DISORDERS

Epinephrine is another hormone to regulate blood glucose and FFA. It is secreted by adrenal glands by sensing glucose drop in blood in response to starvation state. It promotes autophagy in the peripheral tissue upon binding to adrenoceptor β2 (ADRB2) and promotes the mobilization of stored triglyceride. Further, adiponectin (ADIPOQ), secreted by the adipose tissue, stimulate autophagy by inhibiting mTORC1 and promoting the activation of 5′ AMP-activated protein kinase (AMPK). In addition, drops in the availability of growth factors promote autophagy by limiting the expression of nutrient transporters [72, 84, 85].

AMPK activation also reduces the pro-inflammatory signals, inhibits mTORC1 and also activates ULK1 by phosphorylation. The depletion of amino acids inhibits mTORC1 and hence activates autophagy. It can be activated allosterically by salicylate, metformin, 2-Deoxy-glucose, exercise, periodical starvation, metabolic poisons such as arsenite, oligomycin, antimycin A, azide, or dinitrophenol, (inhibit ATP production via oxidative phosphorylation) or by ischemia. All these factors deplete net ATP resulting negative energy balance in the cell thus activation AMPK [86, 87].

The AMPK activation induces autophagy to maintain the supply of basic nutrients by degrading the cell's own unutilized-accumulated proteins/ damaged non functional cell-organelles. This whole process results to normalization of that cell physiology. In pancreas it helps the β-cell function and mass [88]. In Liver it prevents the pathogenesis of NAFLD. In adipose tissue it prevents the polarization of macrophages to M1 type. In brain it prevents the accumulation of amyloid bodies. In autoimmune disease it helps in removal of antigen-antibody complex, deposited in the cells [89, 90]. Thus, it can be summarized that activation of AMPK not only reduces the obesity but it also reduces the cellular garbage (in Ayurveda it has been termed as "Ama".), responsible for several disease pathology.

In fact AMPK increases β-oxidation in mitochondria by inhibiting the activity of acetyl-coA carboxylase (ACC) through phosphorylation. The enhanced β-oxidation of lipids induces the anti-inflammatory phenotype in macrophages (M2). On the contrary, under excess nutrition, hyperlipidemia and obesity, the AMPK is down regulated and mTOR is activated, resulting

inhibition of beta oxidation and activation of fatty acid synthesis. This leads to accumulation of more lipid- intermediates, finally resulting polarization of macrophages to inflammatory M1 type [91]. In obesity and hyperlipidemia, there is also accumulation of cholesterol and fatty acids. They are associated with uncoupling reaction in mitochondria, by opening of the permeability transition pores, thus reducing ATP synthesis. It also generates more free radicals, inducing oxidative stress and ER dysfunction and finally suppresses the process of autophagy in the target cell [92].

The Insulin is responsible for adiposity. It allows TG synthesis via enhanced glucose uptake in to the cell through higher expression and activity of GLUT4 transporters (glucose transporter 4) in adipose tissue. Here ACC (acetyl-CoA carboxylase) is activated and allows esterification of FFA to TG, for storage. It reduces AMPK activity. On the contrary, the adrenergic hormones like glucagon, epinephrine *etc.* activate PKA through activation of adenyl-cyclase to generate cAMP as 2nd messenger. This further activates HSL (hormone-sensitive lipase), by phosphorylation, attributing to fat removal through lipolysis. In this process FFA is released in the blood for utilization by tissues to produce ATP through beta oxidation, but at the same time it is also responsible for insulin receptor desensitization and insulin resistance. The insulin opposes this activation by degrading the cAMP directly and also by activating the phosphatases to counter the PKA mediated phosphorylation [93, 94, 95].

The HO-1(heme oxygenase-1 (HO-1) induction and/or Nrf-2 activation is involved to reduce obesity and related inflammation. The Nrf2 is a member of the basic leucine zipper family of transcription factors. It regulates the expression of endogenous antioxidants by binding to antioxidant response element (ARE) pathway in the nucleus. The Nrf2 is released from Keap-1 repression under stress conditions and translocates to the nucleus to bind with antioxidant response element (ARE) regulate expression of several genes including HO-1. Thus its activator *e.g.* hemin, *Schisandrae fructus*, which are the dried fruits of *Schisandra chinensis* (Turcz.), attenuate the hydrogen peroxide (H_2O_2)-induced inhibition of growth and scavenge the intracellular ROS. It inhibits the DNA damage, induces heme oxygenase-1 (HO-1) and phosphor-rylation of nuclear factor-erythroid 2 related factor 2 (Nrf2) [96].

Further, activation of Nrf-2 becomes more significant when there is presence of some co-factors like sulforaphane, found in cruciferous vegetables and curcumin. The microbiome is also important in this process because it converts the dietary phenolic acids, found in fruits and vegetables to 4-vinylcatechol and / or 4-ethylcatechol., which is a prominent inducer of Nrf-2. The presence of *Lactobacillus plantarum*, *Lactobacillus brevis* and *Lactobacillus collinoides*, found in fermented foods and beverages are reported to facilitate this bioconversion. Similarly, alkyl catechols are found in wood smoke are also activator [97]. Several miRNAs like miR-144, miR-28, miR-153, miR-27a, miR-142-5p, and miR144 are also reported to directly downregulates Nrf2 activity in different cell systems. The phyto-source involved in down regulating the activity of Nrf-2 *e.g.* curcumin, ginger extract, isothiocyanates, specifically phenylisothiocyanates found in broccoli and anthocyanins berries and grapes, epigallocatechingallate, sulforaphane, resveratrol, lycopene, and extracts green tea and citrus fruit are prominent [98]. Thus such agents might be helpful to reduce obesity by maintaining the hepatic mitochondrial oxidative capacity in obese condition.

The Sirtuin activation is another target to treat obesity. Mammalia have seven Sirtuin isoforms, Sirt1 to Sirt7. Among them, Sirt1, 6, and 7 are mainly located in nucleus and Sirtuins, Sirt-3, 4, and 5, are located to mitochondria [99]. The SIRT1 expression and activity is down regulated by high-fat diet and obesity and activated by caloric restriction. SIRT1 liver-specific knockout (SIRT1 LKO) mice fed with high-fat diet, have shown high TG accumulation and pathology of NAFLD [100]. It constitute a family of NAD+-dependent class III histone deacetylases that catalyze the deacetylation of protein substrates coupled to the generation of nicotinamide and 2′-O-acetyl-ADP-ribose. The sirtuin-1 (SIRT1) is mainly located in the nucleus, where it deacetylates various histones and transcription factors and promotes autophagy.

Several phytochemicals, specially chalcones (butein), flavones (quercetin), and stilbenes (resveratrol) other polyphenols, analogs of resveratrol, including SRT1720, SRT2183, and SRT1460, non-polyphenolic SIRT1 activators, including new small-molecule (i.e., SRT2183, SRT1460, and SRT1720 have shown their significant potential in different experimental models retard aging, Alzheimer's, cancer, diabetes, and obesity *etc* [101]. Resveratrol is a stress-response lipophilic polyphenol, one of the active ingredients in red wine, is reported to variety of health benefits [102]. Two new dammarane triterpenes, dammar-20(22), 24-diene-3β, 6α, 12β-triol and 20S-ginsenoside Rg3, showed potential as SIRT1 activators [103].

Recent studies also suggest that this pathway negatively modulates insulin signaling to phosphatidylinositol 3-kinase/Akt in adipose and muscle cells. Its activity is increased in obesity and also reduces the process of autophagy. The rapamycin inhibits the mTOR/S6K1 and also improves the process of autophagy. ThemTOR and S6K1 activation by insulin was accelerated in tissues of obese rats and also improves the insulin sensitivity.

Thus it can be summarized that obesity is a multi-etiological problem and success rate may not be very significant only by using pharmacological agents, developed so far. The change in life style and food habits are very essential component to control obesity. Thus its awareness programme must be activated at primary schooling itself, otherwise the body becomes addict to high glucose intake. For management of MS and other obesity linked NCDs, it is important to regulate obesity rather than focusing on these complications, which are the outcome of the basic cause that is "OBESITY".

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