Abstract

There is an epidemic of obesity worldwide and its inherent risks of associated chronic illnesses like type 2 diabetes, cardiovascular disease, hypertension, dyslipidemia, degenerative joint disease, obstructive sleep apnea. Here we summarize different measures by which various adipose tissue (AT) compartments can be measured with importance of visceral adipose tissue (VAT) more linked to metabolic ailments. Details of genetic factors have been discussed to see why two people respond differently with similar AT distribution or do not respond in same way to medical treatment along with importance of transcriptomics and epigenetic changes. Having reviewed the advantages of combination therapies like Qsymia (phentermine/topiramate) and Contrave (bupropion/naltrexone)advantages over surgery we further try to discuss more novel strategies involving targeting Mc4 receptor, GLP1 coagonist and several neural stimulation therapies which include vagus nerve stimulation (VNS), Vagal blocking (VBLOC), high frequency deep brain stimulation (hfDBS), transcranial direct current stimulation (Tdc)

Key Words: Obesity’ type 2 Diabetes; Qsymia; Liraglutide; Contrave; hfDbS (High Frequency Deep Brain Stimulation; VNS (Vagus Nerve Stimulation); VBLOC (Vagal Blocking)

Introduction

The incidence of obesity in developed countries has increased sharply with parallel increases in developing countries like India and China having the highest populations [1]. This marked escalation is associated with availability of palatable highly processed, energy foods as well as decrease in the physical activity which contribute significantly to the environmental factor’s contribution to obesity. Yet one perplexing thing is that a big proportion of the population maintain normal weight, although live in obesogenic settings, which suggests that the extent to which people or populations respond to influences in their surroundings may be determined by innate factors like genetic makeup. The heritability of BMI has been consistently estimated at roughly 40-70% [2-5], which suggests that approximately half of variations between individuals in body size can be attributed to genes, while other half is due to environmental factors adipose tissue. In our previous reviews we had extensively reviewed the etiopathogenesis and modern strategies of treatment [6,7]. Here we concentrate on the genetic aspects of obesity, update of newer treatments in pipeline and methods of assessing various compartments of body fat be it subcutaneous (superficial and deep) adipose tissue (sSAT and dSAT), visceral AT (VAT) and ectopic fat.

Genetic Factors and Obesity

Both experimental and epidemiological data have given great evidence for an interplay between gene and environment in the regulation of body weight and energy balance [8,9]. Besides routine genetic studies [10] family and twin studies also give evidence regarding how a person’s genetic makeup, plays in response to either weight gain or loss, where body weight was manipulated by overfeeding or exercise in monzygotic (Mz) twin in studies by Bouchard et al. a high concordance between the twin pairs for both weight gain (rwithinpair= 0.74; F=6.8) [12]. The same authors later described that a variant in the resistin gene (RETN, IVS2+39C >T) was associated both abdominal visera and total body fat following total fat following overfeeding in Mz twins with individuals with the TC genotype having a significantly higher values of both measures compared with TT homozygotes [13]. Hainer et al. [14], used a similar Mz twins design where he induced a daily 400kcal/day energy deficit by a energy restricted diet, he found 12.8 times more variation in weight loss in between pairs than within (rwithinpair=

Review

Further Update on the Management of Obesity with Emphasis on Genetic Perspective

Kulvinder Kochar Kaur*, Gautam Allahbadia and Mandeep Singh

1Kulvinder Kochar Kaur, Scientific Director, Centre For Human Reproduction 721,G.T.B. Nagar Jalandhar-144001 Punjab, India
2Gautam Allahbadia, (Obstt&Gynae), D.N.B Scientific Director Rotunda-A Centre For Human Reproduction 672, Kalpak Garden, Perry Cross Road, Near Otter’s Club, Bandra (W)-400040 Mumbai, India
3Mandeep Singh M.D.DM.(Std) (Neurology) Consultant Neurologist Swami Satyanand Hospital Near Nawi Kachehri, Baradri, Ladowali Road, Jalandhar Punjab India

*Corresponding author: Kulvinder Kaur, Centre For Human Reproduction 721, G.T.B. Nagar Jalandhar-144001 Punjab, India Tel: 91-181-9501358180/91-181-4613422 Fax: 91-181-4613422; E-mail: kulvinder.dr@gmail.com

Rec Date: January 2, 2017, Acc Date: January 10, 2017, Pub Date: January 11, 2017.


Copyright: © 2017 Kulvinder Kochar Kaur, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
show novel genes/loci and biology associated with treatment response. Randomized Control Trials of lifestyle interventions for behavioral weight loss, produce Initial losses of 7% or more consistently=>clinical important health benefits [24,25].

Two of the biggest treatment RCT’s have concentrated on energy intake, dietary fat and physical activity for supporting weight loss aims.3234 cases were randomized in the diabetes prevention program (DPP), with obesity or overweight with risk for DM to Metformin treatment, lifestyle intervention or a placebo control arm [24,26]. While 5145 individuals in Look AHEAD (Action for health in Diabetes) trial were randomized to intensive lifestyle interventions (ILI), or a diabetes support and education (DSE) control without an active weight loss programme [27]. Significant weight losses were produced in both intervention programmes, in contrast to control groups (e.g Look AHEAD Year 1 percent weight change ILI:-8.6%+6.9%DSE:0.7%+4.8% [8]; Partial weight regain was common (e.g. Look AHEAD, Year 4, percent weight changesILI-6.15%vs DSE3.5% [25,28].

The biggest study till date addresses the role of genetic variation in weight loss response examined the association between 91 established predisposing loci which was obtained from the comprehensive results of GWAS available in 2015 [17] and weight loss weight regain in the DPP and Look AHEAD cohorts [29]. The combined genetic samples included 5730 participants randomly assigned to behavioral weight loss treatment or control. Of the 91 loci one was constantly associated with a weight loss over 4 years in a meta analysis. Each copy of the minor G allele for the rs1885988 variant at MTIF3 was markedly related to a mean 1.14kg lower weight in the lifestyle arm vs. a non significant greater weight of 0.33kg in the comparison arm. These effects produced statistical intervention of gene treatment arm reaching experiment-wide significance at year 3 and nominal significance across the 4 year.

No other obesity association loci could predict weight loss or weight regain. The MTIF3 gene encodes a protein which is essential for ATP synthesis and energy balance in the mitochondria [30]. The minor G allele has previously been associated with >BMI [31,32] and hip circumference [33]. Therefore those carrying the MTIF3 obesity inducing allele seems to get greater benefit from ILI’s as compared to non carriers. Thus this locus has started emerging in epidemiological gene environment interaction studies of BMI, with MTIF3 genotype associated more strongly with BMI for those eating a healthy dietary intake pattern compared with those in the non healthy diet group [34].

No studies have searched for novel genetic loci associated with behavioral weight loss using a genome wide association. Only study till date comes from Look AHEAD in which single nucleotide polymorphism (SNP) variations across the IBC chip (Illumina, San Diego CA), a gene centric assay of roughly 30,000 SNP’s covering early candidate genes for CVS disease, was examined in relation to magnitude of weight loss after 1yr [35]. The novel regions of significant array-wide association with year 1 weight loss in ILI were identified. ABCB11/G6PC rs484066 was

Obesity Treatment Response-Genetic Predictors

Only small effects of BMI loci have been found till date. It is possible that genetic effects maybe more closely aligned with dynamic, as compared to static phenotypes. Recent GWAS of weight change trajectories from age 1-17 year a novel variant in the FAM120AOS gene was found by Warrington et al. [23] and they confirmed three known adult BMI associated loci (FTO, Mc4R and ADC43) and one childhood obesity locus (OLF4M4) with significant GWA ($P_{val} < 1.13 \times 10^{-8}$) with BMI at 8yr and/or change overtime. This short term change secondary to weight loss interventions may
associated with 1.16kg less wt loss per minor allele at year 1 whereas TNFRSF11A, or RANK, rs17069904 was associated with 1.70kg > wt loss/allele at y1 ABCB11 or BSEP, a bile salt export pump and the primary mediator of bile salt secretion and fat transport from the gut. G6PC is a primary regulator of glucose homeostasis, with mutations related to hypoglycemia; this locus has been identified as a predictor of HDL cholesterol and glucose in GWAS [36,37]. RANK along with the RANK ligand are members of the TNF family of genes and are expressed in AT [38]. Although provocative these exploratory analysis await confirmation in independent samples. Smaller trials have tested whether genetic variants may predict differential response to diets varying in macronutrients compounds [39]. For e.g. Pounds Lost Trial [40] found individuals carrying obesity associated alleles at the FTO locus to differentially benefit from a high protein calorie restricted diet in losing weight. Variations in the FTO locus has also been shown to be associated with weight loss for bariatric surgery [41,42]. This awaits further replication.

To summarize evidence indicates genetic variation may affect the efficiency of behavioral weight loss interventions. Early results suggest that agonistic genetic association studies focused on treatment response might give newer insights into genetic predictors of weight loss, but larger trials will be required to get the larger samples size necessary for testing these hypothesis with statistical surety.

Effects of Epigenetic in Energy Homeostasis-Obesity

Environmental interactions and the genome which modulate the risk for obesity may occur through direct chemical changes, which include DNA methylation and histone modification [43]. Methylation which can positively and negatively regulate gene expression plays a critical role in altering the many cell specific and tissue specific functions. Some epigenetic modifications of DNA may also occur in response to changes in the environment, which includes nutrition and exercise, which can change gene expression in a stable and heritable manner which can influence metabolism, behavior and ultimately overall health.

Recent epigenome wide association studies reported that physical activity and high fat diets may change the DNA methylation pattern in tissues importance for energy homeostasis like skeletal muscle and AT [44-46]; these epigenetic changes may affect weight loss or weight gain. To support this hypothesis 6 months exercise intervention was associated with altered DNA methylation patterns of numerous candidate genes for obesity such as FTO, GRBM and TUB in AT, as well as of genes regulating adipogenesis and was associated with reduced waist circumference in sedentary middle aged men [44]. Additionally, obesity has been associated with decreased altered DNA methylation as compared to individuals without obesity in numerous human studies [43,47]. HIF3A has shown consistent differential DNA methylation in relation to obesity in several studies [48,49]. These epigenetic changes may also affect an individual response to weight increase, weight loss and maintenance by controlling genes which regulated energy homeostasis. e.g. Demerah et al. [50] found that the degree of methylation of 8 different CpG sites including one site near CPT1A, was associated with a change in BMI in participants who gained wt over a 30yr period. Additionally when Dohlmanetal [51] compared the methylome in adipocytes from women who had obesity formerly and had lost weight by gastric bypass surgery and women who had never had obesity. They found differential DNA methylation of genes involved in adipogenesis.

Recently it was shown that weight loss with roux-en‐Y gastric bypass surgery, commonly used for treating morbid obesity changed the epigenome in skeletal muscle, AT and blood [52,53]. Maternal weight loss by gastric bypass surgery also influenced methylation pattern of offspring born after, versus before weight loss [54]. Nicoletti et al. [55], compared epigenetic changes in relation to two different weight loss strategies; an energy restricted diet and gastric bypass surgery and they found that baseline methylation of SERPINE1 may predict weight loss after gastric bypass surgery. Thus these studies summarize role of epigenetic changes in controlling energy homeostasis and obesity. Still further studies are needed to get the full role of epigenetic.

Similarly Benton et al. investigated DNA methylation in AT in obese women before and after gastric bypass and significant weight loss. In total 485577 CpG sites were profiled in matched before and after weight loss subcutaneous (s/c) and omental AT. A paired analysis revealed significant differential methylationin omental and s/c AT.A greater proportion of CpG's were hyper methylated before weight loss and increased methylation was observed in 3 untranslated region and gene bodies relative to promoter regions like CETP, FOXP2, HDAC4, DNMT3BKCNQ1&HOX clusters. They identified robust correlations between changes in methylation and clinical trials in clustering association between glucose and HDAC4, SLC37A3 and DENND1C in s/c AT. Genes investigated with differential promoter methylation all show significant different levels of mRNA before and after gastric bypass. They thus concluded that this was the first study reporting global demethylation profiling of AT before and after Gastric bypass and associated weight loss. It gave a strong basis for future work and gives additional evidence for the role of DNA methylation of AT in obesity. [56] (Benton 2015).

Lim et al. performed reduced representation bisulfate sequencing (RRBS) and RNA seq to depict a genome wide integration of the DNA methylome and transcriptome during brown and white adipogenesis.

On analysis it was shown that DNA methylation is a stable epigenetic signature for brown and white cell lineage before, during and after differentiation. They identified 31 genes where promoters were significantly differentially methylated between white and brown adipocytes at all points of differentiation. Among them 5 genes belong to the Hox family; their expression levels were anti correlated most with promoter methylation, which suggests a regulatory role of DNA methylation in transcription. Blocking DNA methylation with 5- Aza-cytidine increased the expression
of these genes, with the most prominent effect on Hoxc 10, a repressor of BAT marker expression. Thus they concluded that DNA methylation may play an important role in lineage specific development in adipocytes [57] (lim2016).

**Weight Change-Microbiome**

A major role is played in the etiopathogenesis of obesity in both humans along with animal models by the human microbiome [58]. Hosted in the GIT, the gut microbiome is part of a large endocrine organ which regulates not only nutrient sensing, metabolism, but comprising also satiety and energy homeostasis. There are millions of microorganisms which comprise the complex intestinal “superorganism” which performs lot of function for the host health, which include food processes of breakdown and metabolism of individual nutrients, pathogen displacement, synthesis of vitamins and control of body weight [59]. How important role they play is exemplified by microbiota disruption in early life can have long lasting effects on body weight in adulthood [60]. The host bacterial composition has been adapted to respond to dietary factors and in response to weight loss. Diet or surgically induced weight loss promotes changes in the gut, which can impact the efficacy of treatment strategies [61,62]. Specific bacterial species can have influence by themselves e.g the Methane brevibacterium Smithii has an enhanced activity to metabolize dietary substrates or end products of the metabolism of other bacteria, thereby increasing host energy initiated weight gain [63]. In animal models especially rodents show specific reproducible changes in microbiota, because of the ability to control factors like genetics, diet and environment. However in humans these effects have been less consistently shown with weight loss, there is a decrease in the ratio of Firmicutes to Bacteroides phyla [62]. Damms-Machado et al. [64] demonstrated that weight loss obtained by surgical means like laparoscopic sleeve gastrectomy seems to improve the obesity associated gut microbiota towards a lean microbiome phenotype. They showed that a decrease of the energy reabsorbing potential of the gut microbiota following surgery is indicated by the Firmicutes/Bacteroides ratio. The interaction of a community depends on a balanced microbial diversity and each group has different tasks and different qualities which together compose a healthy microbiome [65]. Manipulation of gut microbiota could reduce intestinal low grade inflammation and improve gut barrier, integrity, adjusting metabolic balance and initiating weight loss [65]. Manipulation of gut microbiota could reduce intestinal low grade inflammation and improve gut barrier integrity, adjusting metabolic balance and initiating weight loss [65]. Use of prebiotics and probiotics as potential aids in weight loss/gain interventions has great potential but needs further work.

**Methods of Abdominal Fat Assessment**

It is important to have certain fat measures by using noninvasive methods of body fat to divide patients and study how various therapies are working. In obese people there is an alteration in body composition, which is different from that of normal weight individuals. Specially an increase in total body hydration and a relative increase of the extracellular compartment which is typical of obesity. Different techniques can be used for assessing body fat with a different validity in obesity and specific populations; the strengths and limitations being related to accuracy, safety, cost, portability of the device.

Anthropometry is the most frequent method used in research and clinical practice. Others are hydro densitometry and dual X-ray absorptiometry (DXA). These all are indirect methods which measure body density or resistance with body fat percentage derived from specific equations [reviewed in ref [66-68]]. They cannot make a difference between SAT and VAT or identify ectopic fat in the liver, muscle epicardial, perirenal tissue etc.

Anthropometry is the least expensive with BMI being the commonest used index in epidemiological studies. BMI is a surrogate index of total adiposity and many studies have shown how it can determine body fatness in age, sex and ethnic matched populations along with disease risk and mortality. In obesity BMI does not show a good relation with body fat, thus the need for use of corrections like leptin concentrations to improve the accuracy of BMI [69]. ii) BMI does not differentiate fat compartments especially VAT [68]. Waist circumference, hip circumference, waist to hip ratio and waist to height ratio are indirect indices for VAT and SAT. Of these the first two have been validated against the measures derived from DXA, CT scan and magnetic resonance imaging (MRI) [68,70,71]. It is considered that waist circumference represents VAT and SAT, in contrast to hip circumference reflecting SAT only, whose biological significance is not clear [72]. The correlations, with fat mass vary by sex, ethnicity, life changes, along with other yet unknown factors [73]. Waist to hip ratio provides no advantage as compared to waist circumference alone [68]. Further the accuracy of these measurements is low, based on the training of the person taking these measurements with a lot of variability based on intra or inter individual differences seen. Fat distribution value measurements have additional value for predicting morbidity along with mortality in subjects who are normal weight, or those being moderately overweight, but not in the ones who are obese, specially the morbidly obese. The waist to hip ratio is adjusted for frame size (which is represented by height) and is easy to use. Although this does not indicate that it can predict morbidity or mortality in a better way than waist circumference or waist to hip ratio, and since it comprises of two variables its interpretation is very complicated. For these measurements corrections using blood biomarkers to predict the VAT or SAT and stratification of patients is being done [74].

CT and MRI are the most accurate methods available regarding measurement of fat compartments, however they are very expensive, and not portable. Both give a high resolution cross sectional states of selected tissues/ organs and can be of use in measuring volume, along with distribution of SAT, VAT, muscle mass along with organ composition, which includes ectopic fat. A CT Scan uses x-rays along with reconstruction of total body mass and separate organ masses, which is based on the scans of length of the body at 10cm intervals and has been shown to have great accuracy along with precision(<1% for both) [66,75]. Though single slice images
are often used in research studies for predicting whole body compartments to reduce costs, besides radiation exposure, they are less accurate than the multi slice ones because soft structures are moving continuously, which may negatively affect the dependency of the VAT measurements. Moreover intra subject variation and that fat loss in abdomen is not uniform, decreases the accuracy of single slice images [66,68,76]. A computer aided non contrast CT scan can measure pericardial and thoracic fat [77]. Because of too much radiation exposure, CT scans are limited in research studies and hence not recommended on ethical grounds.

On the other hand MRI, does not use x-rays and is safe as such and applicable to populations, including neonates. Multislice volume MRI is considered the gold standard for measuring total as well as regional AT depots, as shown by a comparison with dissection of cadavers [78]. Single slice image has the same limitations as for CT Scan. Though x-ray free, MRI cannot be used for people suffering from claustrophobia/those who are morbidly obese (BMI > 40KG/m²) and can’t fit within the field of view. Same is the problem in CT Scan.

Newer techniques have been developed and are being validated. They include chemical shift imaging and magnetic resonance spectroscopy, which separate water and fat signals and are applied to a MRI. They help in detecting ectopic fat and integrate MRI information on body fat distribution [79]. Although expensive, they give better perspectives for exploring body fat compartments in relation to diseases and biomarkers. Recently quantitative MRI has been constructed to assess body composition assessment in humans, after testing in animals. It is able to detect small changes in fat mass and is superior to other methods, though there are few differences with regards to gold standards. It is also very fast (<3') and overall seems promising [68,80]. Besides these methods studies validate USG techniques for measurement of SAT and VAT in the abdomen, along with for muscle thickness, which are ongoing [81]. New devices with specific software are needed for increasing their accuracy and decrease operator variability to give a method which is reliable in both clinical studies as well as epidemiological ones.

**Role Of Transcriptomics To Study Accurate Neurons**

Molecular and cellular processes in neurons are critical for sensing and responding to energy deficit states such as during weight loss. AGRP expressing neurons are a key hypothalamic population (fig1), which is activated during energy deficit and increases appetite and weight gain. Cell type specific transcriptomics can be used to find pathways which counteract weight loss. Henry et al reported high quality gene expression profiles of AGRP neurons from well fed and food deprived young adult mice. Simultaneously they analyzed proopiomelanocortin (POMC) expressing neurons for comparison, which are an intermingled population, which suppresses appetite and body weight. They found that AGRP neurons are much more sensitive to energy deficits than POMC neurons. They further identified cell type specific pathways, which involve endoplasmic reticulum stress-circadian signaling, ion channel, neuropeptides and receptors. They used methods to validate and manipulate these pathways and conclude these resources markedly enhanced molecular insights into neuronal regulation of body weight and maybe useful for devising therapeutic strategies for obesity and eating disorders [82].

**Role of Sympathetic Nervous System (SNS)**

SNS is involved in both cardiovascular and metabolic functions, thus disturbances of SNS are going to affect both CVS as well as metabolic health. With increased adiposity, specially with visceral fat accumulation SNS avitation is usually encountered. AT releases a lot of cytokines, adipokines and bioactive mediators which can stimulate the SNS. This activation of the SNS and its interaction with AT may lead to development of hypertension and end organ damage, which includes cardiac, vascular and renal impairment, besides causing metabolic abnormalities like insulin resistance. With lifestyle changes like weight loss and exercise programs there is marked improvement in both cardiovascular and metabolic abnormalities in patients having obesity, but mostly weight loss is difficult to sustain Pharmacological and device based approaches to directly and indirectly target the activation of the SNS may offer in decreasing the cardio metabolic consequences of obesity. Although initial results are encouraging, more trials are needed to study if sympathtic inhibition could be used in obesity to reverse or prevent cardio metabolic disease development .Lambert et al. reviewed how SNS affects obesity and how sympathetic inhibition may be used to prevent the side effects of obesity [83].

**Novel Methods of Anti Obesity Treatment**

Mc4 receptors have been thought to be the initial targets for efficacious therapy in monitoring Obesity [84,85] Various Mc4 receptor agonists were described, which produced mark decrease in adiposity in humans and monkey [86-88]. Yet Mc4 receptor agonists are not used in normal therapeutic arena because of
potential side effects, especially those affecting the autonomic nervous system. E.g. Mc4 receptor agonists like Melatonin II may => hypertension and priapism [89,90]. These side effects are caused by the stimulation of preganglionic autonomic neurons expressing Mc4 receptors [91]. Still all Mc4 receptor agonists may not similarly change autonomic function. A small peptideRM-493 has been as shown to effectively induce weight loss in nonhuman primates as well as humans, with no marked effect on cardiovascular function [87]. It is in clinical trials for genetic obesity. Mc4 receptors may also be modulated by the melanocortin receptor accessory proteins (Mrap1 and Mrap2) [92,93]. These Mraps may give something to differentially target the beneficial effects of Mc4 receptors actively on energy expenditure, glucose utilization and other metabolic parameters, while minimizing the adverse side effects. Recent work has also highlighted a potential role for the melanocortin system to control BAT thermo genesis along with browning/beiging of WAT [94-98]. It is not clear how much this thermo genesis aids in regulation of body composition and glucose homeostasis, yet this data may help in the development of Mc4 receptor agonists to fight obesity and DM.

Current newer ways of increasing the efficiency of the available appetite suppressants specially leptin is being worked on. Because obesity is accompanied by hyperleptinemia [99] and not leptin deficiency, in most of morbidly obese people leptin monotherapy is not efficacious in decreasing the food intake or body weight. Since normal fall of leptin which accompanies weight loss is picked up by the brain as starvation signal [100] it has been suggested that giving leptin during the course of dieting may further enhance weight loss and increase compliance [101].

Different gut peptides have been shown to increase or restore leptin sensitivity in diet induced obesity. Amylin, a pancreatic derived small peptide has been shown to successfully increase the effects of leptin administration on energy balance in obese rodents as well as in humans [102,103], 2) Additionally recent synthesis of peptides having co agonistic properties have helped in the development of a new generation of anti obesity molecules. Included in this area GLP1:: glucagon unimolecular coagonist [104]. This molecule reduced body weight in obese animals to almost 30% of initial body weight in only one month ii) Leptin induces body weight loss has also been shown to be considerably potentiated by the GLP1::glucagon coagonist [105]. Chronic co administration of leptin and GLP1::glucagon give a 50% weight loss in obese mice over one month along with normalizing glucose intolerance

3) A different co agonist or dual peptide strategy is administering peptide agonist with an attached (linker) small molecule. By this one can deliver selectively complex molecules to special target cells [106]. Using this method researchers benefitted on the mono agonistic properties of the GLP1 and the sex steroid hormone E2, to improve metabolic parameters of obesity and T2DM. A fully active GLP1 agonist stably linked to estrogen consistently proved to be more effective in reducing body weight than either molecule alone. These effects of the GLP1:: Estrogen conjugate were independent of gynecological side effects and on cogenic outcomes. This method uniquely combines potency and specificity; however the molecular mechanism of their beneficial effects remains to be elucidated. These co agonists data suggest that the maximally achievable and sustainable body weight loss of 10% observed to available pharmaceutics may not reflect an insurmountable physiological barrier [104]. Hence co agonistic pharmacotherapy along with varied leptin sensitizers and new classes of chemical compounds hold promise as an efficacious approach in the obesity management.

The GLP1 system is used for diabetes as well as reduction in food intake. It is well known that the anorexogenic effects of GLP1 can be obtained through the hypothalamic as well as brain stem circuits implicated in homeostatic feeding. Dickson et al. studying the role of extendin-r4 on food reward which are mediated at the level of meso limbic reward system. They assessed the impact of peripheral, central and intra meso limbic Ex4 on 2 models of food reward; conditioned place preference (CPP) and progressive ratio operant conditioning. Food reward behavior was reduced in the CPP test by Ex 4 as rats no longer preferred an environment previously paired to chocolate pellets. Ex 4 also decreased motivated behavior for sucrose in a progressive ratio operant conditioning paradigm, when administered peripherally. They showed that this effect is mediated centrally via GLP1 Receptors (GLP1R). GLP1R's are expressed in key nodes of the mesolimbic reward system however their function remains unexplored. Thus they sought to determine the neurobiological substrates underlying the food reward could be driven from two key meso limbic strutures-ventral segmental area (VTA) and nucleus accumbens- without inducing malaise or locomotor impairment. These findings that activation of central GLP1R's suppresses food reward /motivation by interacting with the meso limbic system indicates a novel mechanism by which GLP1R's stimulation affects feeding oriented behavior [107].

Lastly novel centrally acting molecules which require metabolism are being described. FGF21 was shown to be a very effective anti obesity factor, which mainly affected energy expenditure [108-110] and in humans they showed a great lipid lowering effect [111]. Based on genetic studies in rodents the antiobesity actions of FGF21 have been ascribed to its direct action on the nervous system [108-110]. Yet current data indicate that the AT in contrast to nervous system is needed for FGF21 anti obesity actions [112]. The regulation of glucose metabolism by FGF21 has also been attributed to direct actions on the liver [112]. More work will give the detailed way FGF21 works.

Device Assisted Neuro modulatory Techniques

Device Assisted Neuro modulator is the delivery of an electric current to either a specific nerve or a specific brain region to influence the brain activity and autonomic outflow. Devices include but are not limited to stimulators of the spinal cord. Though most of these devices have not been approved by FDA for the treatment of metabolic disorders, accumulating evidence suggests that modulation of targeted brain sites or peripheral nerves activity by device assisted means is a valuable tool in the treatment of many chronic diseases [113]. Idea of targeting a particular brain site is attractive considering the unwanted side effects of several
Peripheral nerves are being shown to play main role in metabolic functions [114,115]. Vagus nerve is a mixed (sensory and motor nerve), which innervates most of thoracic as well as abdominal viscera which include entire GIT, pancreas and liver [116]. Vagal sensory neurons transmit a wide range of signals that originate from the GIT, which include mechanical stretch, changing levels of nutrients, lipids, immune signals and gut peptides [117]. Experimentally it has been shown vagal afferents ability of responding to dietary as well as endogenous metabolic signals is decreased in animals fed a high fat diets [118]. From these it is clear that the vagus nerve acts as a critical link between the gut and the brain and the link is impaired in obesity. On the basis of above facts stimulation of vagal afferents has been suggested to be a promising anti obesity approach along with an alternative to bariatric surgery [115]. Preclinical studies in large animals along with humans suggest that vagus nerve stimulation (VNS) may show decreased food craving and weight gain [119,120]. Similarly a technique of vagal blocking has also been tested in preclinical studies (VBLOC), along with getting approved by the FDA recently as a weight loss treatment device in obese people. This technique targets the nerve pathway between the brain and stomach by stimulating the vagal trunks at high frequency, and thereby interfering with normal gastric functions and ultimately resulting in early satiation [121]. Yet contradictory results have been obtained as the benefits of this novel weight loss approach in obese individuals, with a couple of studies illustrating a significant weight loss and decreased food craving [121,122], while others finding no significant benefits [123,124].

Central neuro modulatory techniques may also be of interest in the treatment of obesity. High frequency deep brain stimulation (hfDBS) has been effective in treatment of symptoms related to Parkinson’s disease along with other disabling neurological disorders by normalizing pathological patterns of neuronal activity [125]. This involved the chronic implantation by stereotaxic surgery of stimulation electrodes in a targeted brain site. Electric current is given to electrodes connected to a pulse generator similar to a pacemaker. Stimulation of the hypothalamus is possible and has been used recently in morbidly obese humans to target the LHA [126]. LHA stimulation succeeded in increasing resting metabolic rate, which caused reduced binge eating scores and or body weight in all 3 test subjects. Similar results were obtained in a rat model, which supports this method to be considered as an alternative technique for obesity treatment [127].

Brain surgery has inherent risks of hemorrhage, infection and post surgical complications. Thus less invasive techniques which target the activity of subpopulation of neurons may pose fewer concerns. Specially transcranial direct current stimulation (tDCS) is emerging as a promising technique for noninvasive modulation in a variety of clinical conditions [128]. By this neuronal excitability gets modulated in regions involved-positions in particular behaviors by delivering a weak current through the scalp [128]. Thus this tDCS is suited for cortical targets specially lateral and dorsomedial sectors of prefrontal cortex which contribute to cognitive control. This technique has shown that food craving gets reduced acutely [129,130] and hence maybe suitable for obese people. More novel technologies are needed in the field to aid therapeutic opportunities in this field.

**Conclusions**

Thus since current mono therapeutic approaches (lorcaserin) in the treatment of obesity are not optimally effective, combination therapies have been more efficacious like phentermine/Topiramate (Qsymia) and Bupropion /naltrexone (Contrave) both approved by FDA in 2012 and 2014 respectively, former for treatment of various neurological disorders. Besides another combination of zonisamide and bupropion (emericit)is in phase 2 trial. The details have been reviewed in ref 7 in our previous article, besides advantage and disadvantages of bariatric surgery, which gives a better loss than these medical therapies giving 8-10% of initial body weight [31]. Liraglutide a GLP1 agonist is slightly more efficacious acting both on homeostatic feeding centers as well as hedonic meso limbic area, approved in 2012 and the most effective dose being 3mg, is used both for diabetes as well as treatment of obesity. However most of the medical drugs give much smaller weight losses vis a vis bariatric surgery hence a need to follow newer strategies has been discussed, with the aim of replacing bariatric surgery in the future. The impact of genetics has further been exemplified in various strategies to explain the individual differences in weight reduction.

**References**


