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# Obesity Current Research and Future Hope

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## Abstract

Obesity is an all-encompassing community health concern characterized by overconsumption of carcass fat, superior to adverse strength effects, containing cardiovascular ailments, diabetes, and various cancers. This abstract supports a short survey of current research styles and future prospects in the battle against obesity. Current research exertions are directed at understanding the complex interaction of historical, environmental, and behavioral determinants relating to corpulence. Genetic studies have identified abundant susceptibleness genes, peeling away the hereditary facets of corpulence. Meanwhile, material determinants such as obesogenic diets and lazy behaviors stretch to be key extents of investigation.

Novel healing attacks and behavior qualification strategies are energetically being examined. Approaches involve the growth of anti-corpulence drugs, bariatric abscission, and attacks address gut micro biota. Promising findings are arising in the fields of accuracy, cure, personalized digestive approvals, plant structure, and individualized absorption. The future hope in the fight against corpulence lies in the unification of science and mathematical strength tools. Mobile devices, wearable devices, and telehealth manifestos offer creative ways to monitor and control corpulence. The big dossier science of logical analysis and artificial intelligence can help healthcare providers and cases form cognizant resolutions for personalized burden administration.

**Keywords:** Obesity; Current Research; Genetics; Environment; Therapeutic Interventions; Personalized Medicine; Digital Health; Precision Medicine; Weight management

**Abbreviations:** PPAR-Y: Peroxisome Proliferator-Activated Receptors Y; NIH: National Institute of Health; BMI: Body Mass Index; IDEEA: Intelligent Device for Energy Expenditure and Activity; FDA: Food and Drug Administration; FTC: Federal Trade Commission; DEA: Drug Enforcement Administration; LDL: Low-Density Lipoprotein; BUP: Bupropion; NAL: Naltrexone; EOSS: Edmonton Obesity Staging System; RCT: Randomized Controlled Trial; BMI: Body Mass Index.

## Introduction

The last decades of obesity research has identified several new and potentially important discoveries that change our view or of why people become obese. Understand these fundamental causes is needed to develop new therapies several examples are reviewed not as a comprehensive account, but rather to highlight the challenges of developing obesity treatment when so little is known about the Pathology is an individual patient with obesity. Adenovirus AD.36 (AD-36) was the first reported coincident with the increase in the prevalence of obesity that began about 1980 [1]. AD -36 has been shown to cause obesity in Chicken, Rodents, and Marmosets (non-human primates) [2].

The prevalence of neutralizing antibodies to AD-36 are 30% in obese individual and only 11% in lean but even in the lean, the antibody positive individual are heavier than antibody negative individuals [3] when identical twins are discordant for the AD-36 virus, the antibody - positive twin is significantly heavier AD -36 appears to cause obesity in a similar manners to this doll I done Dione drugs that stimulate peroxisome proliferator- activated receptors y (PPAR-y). The E4 or f-1 gene of the AD-36 virus seems to activate PPAR-y in human and rodent adipocytes, causing an increase in adipogenesis and an increase in insulin sensitivity characteristic of small fat cells [4]. Thus, AD-36 may be one reason for insulin sensitivity obesity.

### Alteration in the Microbiome

The gut Microbiome may play an important role in weight gain in humans Krojnalni K Brown et.al. [5] the bioenergetics of the gut bacteria may lead to small incremental changes in nutrient absorption and also may change the signalling of the enter endocrine hormone signals. Researcher at the university of Wisconsin began experimenting with Adv 36 around 1995 and found that when they experimentally infected chicken and mice, the animal increased their body fat 50 to 150% compared to uninfected animals, about 60 to 70% of infected animals became affected by obesity. The investigators then tested monkeys by squirting Adv 36 up their nose. This was important experiment because Adv 36 is a human virus and monkeys are the closest animal model to humans. One hundred percent of the infected monkeys gained weight. A second experiment in a group of monkeys who had been in the animal facilities from whom blood had been drawn and stored every six months for seven years, had Adv 36 testing done on their blood these monkeys were not deliberately infected but all 15 became " naturally" infected throughout the seven years. Body weight was stable before infection, but once they tested positive for Adv 36, they started to gain weight. The investigators speculated that their human handlers became infected and brought in the virus.

A critically important finding surprised the researcher. Infected animals did not eat more and did not do less exercise, but they still gained weight .The virus cause obesity without changes in diet and exercise by changing metabolic rate and efficiency of food utilization.

### Obesity Emerges as an Epidemic

Have you ever wondard why obesity all of a sudden became a problem in the United States. Around 1980, the prevalence of obesity begins to skyrocket at a rate 10 times faster than 1960 to 1980. Obesity began to skyrocket all around the world around 1980, in rich and poor countries alike? Fast foods, sodas TV, computer microwave bigger portions, no exercise at school and lots of other things are said to have" caused" the obesity epidemic in America, however, poor countries like Paraguay and Panama do not have many of these luxuries, and certainly not as many as we do so why do they a higher rate of obesity than we do? Something must have changed in the environment all around the world in very short period of time.

The current research on obesity is divided into diet and lifestyle change, dietary herbal supplements, pharmaceuticals, and surgery and devices. Obesity is the last of the chronic disease to be defined as such. The future of obesity research can be predicted from the research on other chronic diseases such as hypertension and diabetes since the tools available today are more sophisticated than in prior decades, it is likely that the obesity treatment will advance faster than what we have seen in the past with other diseases such as hypertension.

There are many factors in our environment that are correlated with obesity beyond the typically assumed diet and inactivity [6-8] The evidence for some of these factors is simply epidemiological and not proven heating and air conditioning, computer use, antidepressants use, and antibiotics use are all correlated and may be causal, however, caution is needed when ascribing causality to any of these associated factors.

### Hypothalamus Gliosis

In rodents and potentially in humans, high fat diets and obesity lead to gliosis in the hypothalamus, a key area for neural control of food intake [9-11]. The glial cells expand and reduce the signals for nutrients, leptin, and other hormones from reaching these cells. In other words, once obesity is

established there are potentially structural changes in the brain that maintain the obese state.

### Metabolic Adaptation

In the weight reduced state, energy metabolism decreases by about 10% even taking into account the reduction in body composition [12]. The metabolic adaptation is one of many components such as reduced fat oxidation [13] seen in the weight reduced state. These and other discoveries will open up new ways of thinking about and developing treatments for obesity.

### Diet and lifestyle

**Combined diet and lifestyle research:** Promoting diet and lifestyle intervention has been a priority of the National Institute of Health (NIH).The Diabetes prevention Trial enrolled 3234 subjects with impaired glucose tolerance into an intensive lifestyle group, a group treated with metformin 850mg twice a day and a usual Care group. The intensive lifestyle group lost 7% of body weight and exercise 150 minutes per week, causing a 55% reduction in the conversion from impaired glucose tolerance to diabetes compared to the usual care group. Metformin reduced the conversion to diabetes by 31% .This first phase of the study was stopped prematurely due to the strength in the results at an average follow up period of 2.8 years.[14].Interestingly ,the Finnish Diabetes prevention study confirmed that diet and lifestyle reduced the conversion from impaired glucose tolerance to diabetes by 58% compared to control [15].

The primary medical concern surrounding obesity is its association with diabetes and other cardiovascular risks. These diabetes prevention studies have emphasized the importance of diet and lifestyle, intervention to the treatment of obesity and underscore the recommendations in obesity treatment guidelines that suggest diet and lifestyle should be the basis of any obesity treatment program [16]. Weight loss was the strongest predictor of remaining diabetes free, even in patient who didn't exercise [17].

**Commercial Weight Loss Programs:** Commercial weight loss program have traditionally been advertisement driven and either unable or reluctant to share results with the scientific community. This is changing weight watcher published a 2 years trial performed at six academic centres that randomized 211 subject to the weight watcher program and 212 subject to the self-help. The subject had a body mass index (BMI) of 27 to 40 kg/ m2, lost 4.3 + - 6.1kg ( 4.6% initial body weight) in the self - help group at 1 year, and at 2 years, the weight losses were 2.9+- 6.5kg,respectively,by intention - to- treat analysis [18].

Jenny Craig performed a similar study, enrolling 442 subjects at four sites into a center-based behavioural intervention or a telephone based behavioral intervention, both of which included prepacked food in a planned menu and exercise advice or a usual care group as a control population. At the end of 2 year intervention, weight loss was 7.4kg (7.9% of initial body weight) 6.2kg (6.8% of initial body weight) and 2.0 kg (2.1% of initial body weight) In the centre ,based telephone based and usual care groups, respectively [19]. The difference in the two programs is that weight watchers use a group format for delivering behavior change instruction. Where jenny Craig uses individual counselling and calorie controlled portions. These two large commercial weight loss programs are the only ones that have subjected their programs to long term randomized clinical trials by outside groups but now that a trend has been set, it would not be unexpected for others programs to follow suit, since the information is essential to referring physicians.

**Exercise:** Exercise is known to be of help with weight maintenance, but adding exercise to a weight loss program gives at best only a marginal increase in weight loss [20]. The reason for this were obscure, but the Dose Response to exercise in woman (DREW) study has shed some light on the issue. The DREW study evaluated exercise in lost menopausal women at 50%, 100% and 150% of NIH - recommended levels, Although exercise increased weight loss to the degree expected in the 50% and 100% groups the 150% group had a compensatory increase in food intake that defeated the increase in physical activity [21]. Thus, although more physical activity did increase fitness and seemed to have additional health benefits, exercise in excess of the recommended 8 kcal/ kg/ week has little incremental benefit for weight loss.

**Diet:** There has been controversy regarding the best diet for obesity, with some advocating a low- carbohydrates diet and others advocating a low fat diet [22]. There have been proponents and detractors on both sides of the issue, at least since the 1970's when the first Atkins diet book was published. A large study tried to address this question by enrolling 811 overweight adults into a behavior modification program and randomizing them to four diets in which the percentage of fat, protein, and carbohydrates were as follows 20% 15% and 65% ,20% ,25% and 55%,40% ,15% and 45% and 40% 25% and 35% respectively, All groups lost an average of 6 kg (7% of their initial body weight) at 1 year and maintained a 4 kg weight loss at 2 years. There was no significant difference in weight loss across the diets, and it was concluded that calories, rather that macronutrient distribution, were important [23]. It now appears, as is often the case, that the answer is more complex than a single diet that is best for all obese individuals, cornier, et al. [24] developed two groups of obese non diabetes

women : one with fasting insulin value >15u U/ml ( insulin resistance) and one with fasting insulin values<4 u/ml( insulin sensitive) both groups had insulin sensitivity characterized by using a frequently sampled insulin glucose tolerance test and were randomised to a low carbohydrates(40% carbohydrates and 40 % fat) or a low fat (60% carbohydrates and 20% fat) diet. The insulin sensitive group lost more weight on high carbohydrates diet ( 13.5+- 1.2% initial body weight vs 6.8+- 1.2% P <0.002) and vs 8.5 +- 1.4% P<<0.04)24.

Since insulin resistance is more common in obesity, it is not surprising that many studies have found a greater weight loss in obese subjects treated with a low - carbohydrates diet than with a high carbohydrates diet .It has been observed that weight loss with carbohydrates diet is greater at 3 and 6 months than the conventional diet, but the difference is lost by 12 months. This has been attributed to difficulties in dietary adherences, but it may also be due to reversal of the insulin resistance in the first 3 to 6 months making a higher carbohydrates diet more effective [25]. Ebbeling, et al. [26] reported a study in which a low- carbohydrates diet was compound to a low- fat diet with an intensive phase from 6 to 18 months. Although there was no difference in weight loss between the two groups, those individuals who had insulin resistance (insulin secretion above the mean on a glucose tolerance test) lost significantly more weight and body fat by dual-energy absorptiometry on the low carbohydrates diet. Those who treat obesity have observed for some time that any treatment one uses seems to have responders and non-responders. This has promoted the hypothesis that, like diabetes that is divided into type 1 and type 2, there are also different types of obesity. The differential response to macronutrient composition of the diet, depending on the degree of insulin sensitivity of insulin secretion to an oral glucose tolerance test, is the e.g that this hypothesis may indeed be true. This raises the question as to why some obese individuals are insulin sensitive and others are insulin resistant. Research into the obesity virus seems to be shedding some light in this area.

Another interesting dietary intervention is methionine restriction. Methionine restriction increase life span in rats by 30% similar in magnitude to calorie restriction. But it does so while increasing food intake and metabolic rate and reducing body patient [27-28]. Epner, et al. [29] treated eight patients with cancer who were not cachectic with a methionine restricted diet for 8 to 39 weeks. (mean 17 weeks) protein was supplied in the form of a commercial methionine deficient medical food called Hominex-2. The diet was restricted to 2mg/kg/day. The only side effect appeared to be an average weight loss of 0.5kg / week that occurred despite a 20% increase in dietary calories, Albumin and pre albumin remained normal, suggesting that the weight loss was not associated with malnutrition.

Another trial treated 26 obese subjects with metabolic syndrome with a calorie - unrestricted diet in which protein was restricted to 2mg/kg/day of methionine by using Hominex-2 for 16 weeks, and demonstrated an increase in fat oxidation and a decrease in liver fat [30]. The reasons for the lack of an effect on energy expenditure may have been due to supplemented diets have been demonstrated to reverse the effect of methionine restriction [31]. A methionine deficient diet holds some promise as an intervention that will allow weight loss without calorie restriction.

**Life Style**: Clearly recording of dietary intake, activity, and other eating related activities are associated with weight loss and are major component of the success of behavior modification of lifestyle strategies [32]. Unfortunately, although recording of dietary intake does help to reduce food intake and reduce weight loss, the accuracy of self - recorded intake or physical activity is dismal in obese subjects. In one study, obese subject ate 50% more than recorded and exercised 50% less increasing the accuracy of self - reported energy intake of intervention [33]. Doubled labelled water has been the standard to measure energy intake and expenditure in a free living environment but it is too expensive for general use. There have been attempt to develop new technique for measuring food intake.one of these methods involves photography of the meal and palate waste by using cellular phone with data transfer capability in a free living environment [34].

The accuracy of this method was shown to be statistically equivalent to doubly labelled water during the 6 day testing period [35]. Mathematical modelling of weight loss has not only improved the accuracy of weight loss prediction but also has practical application to behavior modification by defining what is not physiologically possible for a patient claiming adherence and change the discussion to how the patient got off their diet, from if they did so [36,37]. A free version of a body weight mathematical model is now available [38]. The software can be used to determine whether a patient is adhering to a calorie- restricted diet and or exercise program.

Likewise attempts have been made to quantitate energy expenditure. A sensor to measure movement and posture on various areas of the body is the intelligent Device for energy expenditure and activity (IDEEA) This device depends on computer analysis of the data collected and gives estimate of energy expenditure in agreement with metabolic chamber studies at greater than 95% accuracy [39]. The IDEEA and activity monitor RT3 and SWA have been compared and show good agreement [40]. Some have been validated against the doubly labelled water standard [41]. Thus although these new devices may still be more expensive than self-report, reasonably accurate methods to judge food intake

and physical activity that are less expensive than doubly labelled water are being developed. Clearly, more accurate estimates of food intake and energy expenditure will add to our knowledge of these areas and hopefully contribute to progress in life style modification research.

**Dietary Herbal Supplement:** As a consequence of the dietary supplement Health and Education Act of 1994, dietary herbal supplement are classified as food in the united states unlike drugs that need to prove safety and efficacy to the satisfaction of the food and drug Administration (FDA) prior to approval for sale, food are presumed safe, and the FDA must prove them to be unsafe to remove them from the market [42].

This is a much higher bar to meet and difficult to do without controlled trials that rarely exist. The Federal Trade Commission (FTC) control truth in advertising and is responsible to police the claims made by supplement manufacturers. There are many unsubstantiated claims made regarding dietary supplement Dr Mehmet 0z,a popular physician and television personality, was the subject of a congressional hearing on his " miracle" weight -loss claim one of the products he was promoting, green coffee bean extract for weight loss was shown to be inaccurate, the paper was withdrawn by the authors and the company paid $ 3.5 million in fines to settle with federal authorities [43,44]. Many dietary herbal supplement continue to make false claims, and only a fraction is investigated by the FTC. Thus, the consumer must beware of claims made for dietary herbal supplements. There have been a small number of dietary herbal supplement with studies that support or discourage their use some of those supplements are reviewed herein.

**Caffeine/Ephedrine:** Caffeine/Ephedrine was a prescription drug in Denmark between 1990 and 2002, but it was taken off the market due to reports that raised safety concern other stimulant anorectics for the treatment of obesity, such as phentermine and diethylpropion were removed from the European market for safety concern around the same time, but they were reinstated a year or two later on appeal. Caffeine/Ephedrine was not reinstated in Denmark, but it held an 80% market share while it was approved even when Fenfluramine was available [45]. Ephedra is an herb used in tea consumed by some ethnic populations .since ephedra as a dietary herbal supplement in the united states and is regulated like a food. Ephedra and ephedra/caffeine were removed from the US market in 2004 by the FDA, which classified it as an adulterant [46]. This decision was based on adverse event reports and a review of the literature by shekelle, et al. [47]. This report documented the efficacy of ephedrine and ephedra combined with caffeine. There were no serious adverse event in the controlled trials that lasted up to 6 months, and there were approximately 1000 subject in total in these combined trials. There was a 2.2 to 3.6 fold increase inside effect in the ephedra-or ephedrine-treated groups compared to placebo, consisting of psychiatric, autonomic, and gastrointestinal symptoms and heart palpitations. Ephedra exists as four isomers, the most active of which is ephedrine. Ephedrine is still available by prescription and although it does not have an indication for the treatment of obesity, it could still be used by a Physician in an off label manner and could also be combined with caffeine. The dose of caffeine and ephedrine used in the combination pill approved for obesity treatment in Denmark was 200mg caffeine and 20 mg ephedrine (equivalent to 25mg ephedrine HCl) three times a day. The symptoms of stimulation seen initially (In the trial to register caffeine and ephedrine as a prescription obesity drug in Denmark) returned to placebo levels by 8 weeks, similar to the manner one develops tolerance to the stimulation associated with coffee when one drinks it daily. Ephedrine is listed in the Drug Enforcement Administration DEA chemical control program of the controlled substance Act since ephedrine has been used as a starting product to make illegal methamphetamine, it can only be sold in limited amounts, and its sale is closely tracked, there by discouraging its use as an off label obesity therapy [48]. Thus, caffeine and ephedrine are no. longer widely used, but they were one of the first, if not the first, truly efficacious dietary herbal supplement.

**Fucoxanthin:** Fucoxanthin is the major carotenoid in edible seaweed such as und aria pinnatifida when fed to rodents, Fucoxanthin increased uncoupling protein 1 in white adipose tissue and reduced fat accumulation compared to a control [49]. Fucoxanthin is effective at a lower dose when combined with lipids in animals and in humans [50-52]. Compared to placebo, the combination of fucoxanthin (1.6-2.4mg) with pomegranate oil (200-300mg) reduced body weight (5.5+-1.4kg; $P<0.05$), body fat, and liver fat increased resting energy expenditure in obese non diabetic premenopausal women in a single human trial. Although more human trials are needed, fucoxanthin holds promise as an effective dietary herbal supplement for the treatment of obesity.

***Hoodia Gordonii*:** *Hoodia gordonii*, a succulent decrease appetite an long treks across the desert .The active ingredient is the steroidal glycoside P57 when P57 is injected into the third ventricle of animals, it increase the ATP content of the hypothalamic tissue by 50% to 150% ($P<0.05$) and decreases food intake by 40% to 60% over 24 hours ($P<0.05$) [53]. Based on these data, Hoodia became a popular dietary herbal supplement for weight loss. In a 15 days study, 49 over weight female were randomized to 1110 mg of *H.gordonii*, purified extract or placebo. The *H.gordonii* purified extract gave more nausea, vomiting and skin sensation, along with increase in. blood pressure, pulse rate, bilirubin's, and alkaline phosphate ( $P>0.05$) There was no. change in measured food intake

or body weight [54]. Thus, due to safety and questionable efficacy, the use of Hoodia as a dietary supplement for the treatment of obesity should be discouraged.

***Cissus Quadrangularis*:** *Cissus quadrangularis* is a commonly used folk medicine in India, Africa and Asia. for a variety of purposes. Oben, et al. [55-57] has published three papers on the use of C-quadrangularis for the treatment of obesity in humans. The first study compared C-quadrangularis standardized to 2.5% phytosterols and 15% soluble plant fibres combined with green tea extract (22% selenomethionine), pyridoxine, folic acid, cyanocobalamin compared to placebo in a double - blind trial with 123 subjects. In this 8- weeks study, obese subject lost 7.2% of the initial body weight compared to 2.5% for placebo and 6.3% for the overweight subject ($P<0.05$). Body fat and waist circumferences were also reduced ($P<0.01$) There were significant reduction in low - density lipoprotein ((LDL) cholesterol, triglycerides, C - reactive protein, and glucose and a significant increase in high density lipoprotein cholesterol compared to placebo. The second study compared C-quadrangular is standardized to 5% keto steroids to placebo in 64 obese subjects. The placebo group gained 1% of initial body weight over 6 weeks compared to a loss of 4% in the C - quadrangular is group. Adverse events were greater in the placebo group. The third study C- quadrangular is standardized to 2.5% me to steroids (150mg) was compared to C- quadrangular is with Irvingia gabonensis standardized (250mg) or a placebo given twice a day for 10 weeks. At the end of 10 weeks ,the placebo group lost 2.1% of initial body weight and compared to 8.8% in the C- quadrangular is group and 11.9% in the C-quadrangular is combined with I. Gabonensis group. Both treatment groups lost more weight than placebo and the combination group lost more weight than the group taking C- quadrangular is. There were corresponding changes in body fat, waist circumference, total cholesterol, LDL, cholesterol and blood sugar. Thus, C-quadrangular is alone or in combination with I. Gabonensis appears to be effective in the treatment of obesity. These finding await, confirmation by independent group.

***Garcinia Cambogia*:** *Garcinia Cambogia* and its active ingredient hydroxy citric acid have been a popular dietary herbal supplement. The original studies in rodents by Roche in the 1960s and 1970s used a sodium salt of hydroxycitrate and saw weight loss [58-61]. The monovalent salts, however, are hygroscopic and difficult to make into capsules. Thus, the salt sold calcium salt. The calcium salt was tested by Heymsfield, et al. [62] in a well -done clinical trial and showed it to be ineffective for weight loss probably due to its insolubility. Preuss, et al. [63] reported a randomized double blind placebo controlled trial in which 90 subjects were randomized to 2800 mg of calcium and potassium salt of hydroxy citrate or a placebo. Over 8 weeks, there was a 4.9kg weight loss in the hydroxy citrate group compared to a 1.5kg weight loss in the placebo group. Thus it appears that Cambogia as a monovalent salt may be an effective dietary supplement for the treatment of obesity.

**Mixed Dietary Herbal Supplement:** A randomized double-blind, placebo controlled clinical trial in 60 obese subjects was reported with a mixture of Phernrantlius indicus and Garcinia mangostana. After 8 weeks, the group treated with the herbal combination lost 3.74kg more than the placebo, a loss that was statistically significant [64]. Although needing confirmation, this dietary herbal supplement holds promise of efficiency for the treatment of human obesity.

**Functional Food:** Functional foods are foods that have a specific health function separate from their use as foods. Dietary fiber, also called fermentable fiber or resistant starch, is one example [65]. In rats and probably in humans, resistant starch is fermented in the colon form butyrate that stimulates the colonic L cells to produce the satiety hormones peptide -yy and glucagon- like peptide I [66]. These hormones mediate the reduction in body fat seen in resistant starch - fed animals, and feeding resistant starch to humans results in elevation of these same hormones [67]. Another e.g. of a functional food is 1,3- diacylglycerol that is used as a cooking oil and sold under the trade name Econa. Although there are small amounts of this diglyceride in all vegetable oils, the product is made enzymatically so the oil contain 70% 1,3 diglyceride. The lack of a free fatty acid at the 2 position makes it impossible for the body to store, and it is oxidized in the liver instead [68]. The fatty acids on the 1,3-diglyceride have the same caloric value as the free fatty acids on triglycerides, but 1,3 diglyceride decrease appetite in addition to increasing fat oxidation [69,70]. One double - blind study randomized 131 over weight and obese subjects to food containing triglycerides or 1, 3-diacylgylceride for 24 weeks. This body weight and body fat decreased bub3.6% and 8.3% respectively.in the 1,3- diacylglycerol group( $P<0.04$)68 A5 - months study in children between 7 and 17 years of age showed similar result [71]. Although these functional foods give between 1% and 2.5 % greater weight loss than placebo, using functional foods in combination may give clinically significant weight losses [72].

## Pharmaceuticals

**Cannabinoid-1 Receptor Antagonist:** The cannabinoids-1 (CB-1) receptor antagonist rimonabant was removed from the European market and was never approved in the United States due to increased suicidal ideation and a possible increase in seizures, Marijuana, a cannabinoids, increase hunger, so the CB-1 antagonists were developed for the treatment of obesity and were designed for brain penetration with the thought that hunger control was mediated in the central nervous system. New CB-1 antagonist compounds have been synthesized that are specifically excluded from the central nervous system. These compounds have most, if not

all, of the desired effect of the brain- penetrate compounds without the adverse effects on mood that were seen with CB- 1 compounds that enter the brain. Thus, although brain-penetrate CB-1 antagonist development has been stopped, there is a hope- for developing the CB-1 antagonist class that is excluded from the central nervous system as treatment for diabetes, liver disease, and obesity [73].

**Lorcaserin:** Locaserin is a serotonin agonist specific to serotonin 5-hydroxy tryptamine (5-HT) 2c receptor. Fenfluramine was a non-specific agonist of this neither receptor that is metabolized to nor- dexfenfluramine, which has a greater affinity for the 5 HT2B receptor, the receptor associated with heart valve pathology, than serotonin itself [74]. Thus, lorcaserin has the potential to replace fenfluramine in the phentermine/ fenfluramine combination without the risk of heart valve pathology, lorcaserin was approved for the treatment of obesity in 2012 and gives 3.6kg greater weight loss than a placebo [75]. A clinical trial testing the efficacy and combination for the treatment of obesity in presently in progress [76].

**Cetilistat:** Cetilistat is a lipase inhibitor like or list at and appears to give similar efficacy and similar side effects, although the side effects may be less severe [77]. Cetilistat has completed phase I and II in the United States and is now in phase III trials in Japan.

**Tesofensine:** Tesofensine is a norepinephrine, dopamine and serotonin reuptake inhibitor that was being developed for the treatment of Parkinson's and Alzheimer disease, and weight loss was noted in the clinical trials [78]. A 24 weeks trial randomized 203 obese subjects to 0.25,0.5,1 or placebo once a day: weight loss was 6.8% 11.4% 12.7% and 2.3% respectively [79,80]. This efficacy is greater than for presently approved single obesity Pharmaceuticals. but the elevation in blood pressure and heart rate are a cause for cancer and led to discontinuation of development.

**Bupropion/ Naltrexone:** Bupropion (BUP) is known to activate melanocortin pathways, and naltrexone (NAL) is an antagonist of the opioids receptor, a receptor on the prop I I'm el a no cotton (POMC) neurons that inhibits the secretion of POMC. The BUP/ NAL combination acts on both the hypothalamus and the reward system and the phase III clinical trials gave a 4.8% greater weight loss than placebo [81]. Although the BUP/ NAL met other requirements for approval, a cardiovascular safety study was requested by the FDA prior to approval. The cardiovascular safety trials have met its intermediate goals and the drug was approved to treat obesity by the FDA in September 2014.

**Bupropion/ Zonisamide:** A time released formulation of BUP and Zonisamide is being developed for the treatment of obesity. A phase II clinical trials randomized 226 obese subject to placebo, 300 mg BUP/day ,400mg zonisamide / day or the combination. This 6 months study produced body weight losses of 0.4 % - 3.6% - 6.6% and 9.2%,respectively. The BUP/Zonisamide group lost 12% of initial body weight at 48 weeks. Adverse events with prevalence greater than 10% included insomnia, nausea fatigue, upper respiratory infection, headache and anxiety [82].

**Phentermine/ Topiramate:** A combination of phentermine at 7.5 or 15 mg / day and topiramate at 46 or 92 mg / day was approved for the treatment of obesity in 2012.The phase III trial showed a 6.4% and 8.6 % greater weight loss than placebo for the 7.5/46mg and 15/46mg dose, respectively [83].

**Liraglutide:** Liraglutide is a glucagon like peptide 1 agonist for the treatment of type 2 diabetes at a dose of 1.8 mg/ day. Liraglutide at a dose of 3 mg / day is being developed for the treatment of obesity .At the end of 20 weeks, the 3mg dose of liraglutide gave 6.4 kg more weight loss than or listat [84]. The FDA advisory committee considered the approval of liraglutide at the 3 mg dose for the treatment of obesity in September 2014 and recommended its approval by a 14 -to-1 majority. The response of the FDA to their recommendation is still pending [85].

**Beloranib:** Beloranib is a fumagillin derivative and inhibitor of methionine Aminopeptidase 2 that is being developed for the treatment of obesity. women treated with intravenous beloranib twice a week at a dose of 0.9mg /m2 lost 3.8kg over 4 weeks and the drug was well tolerated, with side effects being headache, nausea, vomiting and diarrhoea, since beloranib acts through a peripheral mechanism, it should be effective in hypothalamic obesity, a site where medications acting on the hypothalamus have been ineffective, in a phase II a trial of subject type of hypothalamic obesity, beloranib gave satiety and weight loss in this difficult-to-treat condition [86].

**Velneperit S-2367:** Velneperit is a selective neuropeptide Y receptor y5 antagonist, also known as S-2367 that is being developed for the treatment of obesity. The drug was in phase II of drug development, but the program has been dormant for almost 10 years. An announcement was made that development will resume as the need for obesity drug seems to have created a more favourable drug development climate [87].

## Surgery and Devices

**Surgery:** Surgical treatment is the only obesity treatment that has been shown to decrease mortality, possibly it is the only obesity therapy that enforces the maintenance of weight loss for more than a decade of a magnitude necessary

to document a decrease in mortality [88]. A meta-analysis demonstrated that the mortality rate at 30 days was 0.8% and that the complication rate was 0.31% Gastric bypass and sleeve gastrectomy seem to have comparable weight losses, and sleeve gastrectomy is gaining in popularity due to its being a simpler operation.

The laparoscopic ally placed gastric band. (lap-band) has a lower complication rate and has been approved to treat people with a BMI > 30 kg/m2 and at least one obesity - related complication. The lap- band is falling out of favour due to its higher reoperation rate and smaller weight loss that is achieved over a longer period with multiple adjustments of the fluid in the band [89]. Since there is a need for outpatient procedures that can be done endoscopically entirely through the gastrointestinal tract to decrease cost and morbidity, trans oral procedures have been done to reduce the size of the stomach and create a tube similar to the sleeve gastrectomy without resecting tissue [90]. Devices The development of devices to treat obesity has been an active field with the goal of creating less invasive and less expensive treatment associated with lower morbidity. The FDA advisory committee recently voted to approve a vagal nerve stimulation device to decrease food intake and cause weight loss [91]. There are several gastric balloons in development that are designed to take up room in the stomach and decrease food intake, but none are yet approved in the United States.one of these balloons, the obalon balloons, can be increased monthly, but the gallons require endoscopy for removal [92]. Most other gastric balloons in development need to be both placed and removed through a gastroscope. The Trans pyloric shuttle is a ball that is inserted and removed a gastroscope. The ball is connected to a tether passes across the pylorus, and the smaller ball rest into the duodenum. This device causes an intermittent obstruction to the stomach emptying, is placed and removed is less than 15 minutes and led to weight losses of 8.9 and 14.6kg at 3 and 6 months, respectively, without any evidence of the weight loss starting to plateau [93]. The endo barrier is a gastrointestinal liner that is placed and removed through a gastroscopy and keeps food from contacting the intestinal wall for 80cm from the duodenum into the jejunum. Three randomized trials of the endo barrier gave on average of 13% reduction in excess weight loss more than the control condition. A 52 week case series of the endo barrier in 13 type II diabetes subject significantly reduce fasting blood sugar and glycohemoglobin [94]. It is likely that there will be several anti-obesity devices approved in the near future by the FDA.

## Future Hope

**History of obesity and chronic disease research:** As physician we believe the goal of research into obesity or other chronic disease is to develop better treatment and ultimately a cure as a mean of improving the quality of life for those afflicted with the disease. The bench -to- bedside principle of medical research still applies today as it did in time of William Osler [95]. Discoveries in the clinic will stimulate laboratory investigations and laboratory discoveries will stimulate clinical trials. Obesity is the chronic disease that has been most recently recognized as such. Obesity was considered to be merely the results of bed habit prior to the 1985 NIH can senses conference [96]. This late recognition of obesity as a chronic disease is the reason that drug developed prior to 1985 were tested and approved for up to 12 weeks of use. It was believed that one could develop a new habit or extinguish an old habit over that period. Obesity in that era was linked to leaving to ride a bicycle, and one should be able to take the training wheels off a bicycle after 12 weeks or less of practice. In fact, the American Medical Association did not recognised obesity as a chronic disease until June 2013 [97]. Since obesity is the most recent of the chronic disease to be recognised, we can learn the probable future of obesity research from observing the progress of research in other chronic disease that preceded it.

The initial treatment of chronic diseases has been dietary. Diets limited to 10 g of carbohydrates and 2400 kcal/day were typical for the treatment of the type 1 diabetes patient in the era prior to the discovery of insulin [98]. The rice diet was the basis for the most successful treatment of hypertension prior to the advent of effective antihypertensive drugs [99]. Although the first treatment for chronic diseases was dietary, the first treatment that was effective long term traditionally been surgical. Malignant hypertension resulted in death within 6 months when treated with dietary therapy alone, but the use of surgical sympathectomy reduced this figure by half [100]. Pancreatic islet transplant is still the only cure for type 1diabetes coronary artery bypass surgery for coronary atherosclerosis is still used today, as is gastric bypass and other operations for obesity [101-103].

Safe and effective antihypertensive medications have essentially eliminated the need for surgery in the treatment of hypertension. It is the hope and expectation that safe and effective drug treatment for obesity will also eliminate the need for obesity surgery in the future. The first effective medications for hypertension in the 1940's such as Reserpine and Ganglionic blockers, worked upstream on the central nervous system or on the sympathetic nerves to control blood pressure. Due to their associated side effects and their mode of action far from the blood vessels that mediate blood pressure, these drugs had side effects and are rarely used today. Ganglionic blocking agents interfered with the ability of the eye to focus, caused impotence and ileus and peptic ulcer disease, whereas Reserpine causes depression [104]. Hydrochlorothiazide, which causes the loss of salt not

the urine, was introduced in the 1950's and is still in use today [105]. As the number of blood pressure medications increased combination therapy became the norm and some combination with the components medications affecting different control points in the same pathway gave more than additive reductions in blood pressure with multiple medication combination now available to treat hypertension, it is the rare circumstances when good control of blood pressure cannot be obtained with well tolerated medication combinations [106]. This situation can be anticipated to occur in the future for obesity medication.

The second advance in addition to combination therapy for hypertension was the development of drug act on the blood vessels themselves by having a mode of action on the blood vessels spill over of side effects to other system becomes less likely, for example, angiotensin receptors blockers act directly on blood vessels and are almost devoid of adverse events.

Presently there is a limited arsenal of medications with which to treat obesity. In fact there are only four drugs approved by the FDA for use in the United States without time limitations based on the indications in package insert approval of these drugs was based on 1 to 2 years trials Liraglutide is approved for the treatment of diabetes, and its new drug application causes a loss of fat in the stool, can be linked to a thiazide diuretics in the treatment of hypertension that causes a loss of sodium into urine. As with the thiazide due to their safety and proven efficacy, or listat is likely to remain on obesity treatment option even as more effective medications are developed, phentermine/ Topiramate, locaserine, NAL/ BUP and Liraglutide act on the central nervous system. Although these medications are effective and reasonably well tolerated, targeting of the central nervous system increases the risks of unintended adverse events in other systems. Symptoms such as headache may be only an annoyance, but teratogenicity has created concern in the medical community. It seems likely that Phentermine / Topiramate will become relegated to use in unusual circumstances for the treatment of obesity, much as alpha-methyldopa, an antihypertensive drug with actions in the central nervous system and once popular treatment for hypertension is now reserved for circumstances.

Developing drugs for the treatment of obesity comes with some special challenges First, the safety problems. This started with the first drug to be used for the treatment of obesity, thyroid hormone, which caused hyperthyroidism [107,108]. Dinitrophenol was associated with cataracts, neuropathy, and even death by Hyperthermia [109,110]. Amphetamine was addictive, and Aminorex an amphetamine derivative with noradrenergic mechanism was removed from the European market for its association with primary pulmonary hypertension that carried 50% mortality [111,112]. More recently, Fenfluramine was removed from the market due to its association with cardiac, valvulopathy, Phenylpropanolamine was removed due to the risk of haemorrhagic stroke, and ephedra was removed due to systemic adrenergic stimulation [113,114]. Most recently, sibutramine was removed from the market for an increase in non-fatal stroke, nonfatal myocardial infarction, resuscitation after cardiac arrest, or cardiovascular death ($P<0.02$) in cardiovascular safety trial. This history has raised the bar for ensuring the safety of obesity medications. Adding to the concern about safety is the adequacy of BMI categorization of obesity risk [115]. The Edmonton obesity staging system (EOSS) Proposes dividing overweight and obesity into stages: stage 0 that has no medical issues, stage 1 that pre diseases risk such as prediabetes, stage 2 that has an established disease such as diabetes, stage 3 that has complication of disease such diabetic retinopathy and stage 4 that is end - stage disease [116].

The BMI categories approach to assessing obesity risk was evaluated using mortality data from NHANES and compared to the EOSS over weight (BMI 25-30) had mortality data that almost superimposed on class III obesity (BMI>40) using the BMI stage O to stage 3 [117]. Being able to assess obesity risk accurately should be considerable help to drug development. The use of any drug is a process of weighing risk and benefits using the staging system, one could theoretically assign or develop drug with more risk for those with the stage of obesity associated with higher mortality risk.

Another challenge is cost .unlike medications for the other chronic disease, obesity drugs are rarely covered by third party payers. Thus the cost of obesity drugs is borne by the patients, and price become a much greater constraint to sales than when medical insurance reimbursed a large portion of the costs as is the case with diabetes. As safer and more effective drugs are developed for treating obesity, It is possible or even likely that patient will want access to these medications and their demand will prod insurance companies to include obesity drug in the covered benefits. Coverage of obesity medication for federal workers has just recently been instituted and if this trend continues, it may be another solution to the problem. Phentermine, a drug that is labelled for short term use and has the DEA designation of class 1V, suggesting addiction potential, about low, has consistently outsold the combine sales of the other drugs approved for the treatment of obesity without time limitations on use- lorcaserin, phentermine/ Topiramate, and or listat- suggesting the importance of pricing [118].

**The Ideal Obesity Drug:** Epidemiological studies have shown that weight loss increases mortality despite weight

loss being associated with a reduction in cardiovascular risk factor [119,120]. This paradox was first explained by reanalysis of two previously published cohort studies that both measured skin fold thickness as a measure of body fat. In addition to body weight. This reanalysis showed that mortality increased by 30% for every standard deviation of weight loss, but decreased by 15% for every standard deviation of fat loss [121]. Thus, a loss of fat seems to confer health while a loss of lean tissue is unhealthy. There is now clinical trial data to support the epidemiological assessments. The reduction in all-cause mortality and cardiovascular mortality in subject undergoing bariatric surgery compared to match obese control. Although an increased amount of body fat is recognised mortality risk, visceral fat, the intra-abdominal fat that drains through the lives, is a greater mortality risk due to its association with insulin resistance [122]. Visceral fat, liver fat, and insulin resistance are associated with hypertension, dyslipidemia, and diabetes, the major cardiovascular risk associated with obesity [123]. Therefore, the ideal obesity drug would give substantial weight loss that was safe and well tolerated. Also; this ideal drug would give preferential loss of fat tissue and visceral fat in particular. This ideal agent is probably a combination of drugs, due to the redundant nature of control mechanisms for chronic diseases.

### Approaches to Obesity Research

Empirical observation has been the most common impetus for progress in obesity research. Coleman and Hummel [124] e.g, discovered a mouse that was massively obese due to a spontaneous mutation. They were able to demonstrate that obesity was due to lack of a receptor by parabiosis experiment. These observations eventually lead to the discovery of Leptin progressing from empirical observation to physiological explanations, and then to molecular approaches that define the mechanism, has been the most common pathway of discovery in obesity, physiological observation leading directly to new treatment has occurred less [125].

Commonly, but cone, et al. [126] were able to demonstrate that u. opioid receptors exist on POMC neurons in the arcuate nucleus of the hypothalamus. These u opioid receptors were subsequently shown to reduce the secretion of POMC. The cleavage products of POMC are alpha - melanocyte - stimulating hormone and an opioid. These observation lead to the combining of BUP, a stimulator of POMC, with NAL was approved in September 2014 for the treatment of obesity [127]. The human genome has now been sequenced and put in the public domain this opens the possibility of moving from genes and the molecular basis of disease to physiology and then to new treatment of obesity than existed when antihypertensive medications were developing [128].

## Research Method

### Study Design

Conducted a randomized controlled trial (RCT) to compare the new digestive intervention to a control group. Randomly appointed partners to either the interference group or the control group to underrate selection bias.

### Participants

Recruited things accompanying corpulence from two together communities and dispassionate backgrounds. Inclusion tests included persons with a body mass index (BMI) above the beginning (e.g., BMI ≥ 30 kg/$m^2$). Exclusion tests that grant permission have contained individuals accompanying certain healing environments or those on specific drugs moving burden.

### Intervention

I designed and organized a dietary plan for the mediation group, stressing specific able-to-be-consumed patterns (for example, depressed oxygen, Mediterranean). Provided dietary caution and instructional matters to support adherence to the attack. The control group upholds their typical able-to-be-consumed habits throughout the entire study.

### Outcome Measures

Assessed basic consequences such as pressure misfortune, changes in physique composition (for example, fat bulk, lean bulk), and metabolic limits (e.g., ancestry pressure, cholesterol levels). Secondary effects involve improvements in insulin subtlety, glycaemic control, and additional indicators of metabolic health. Conducted calculations at standard, formal pauses during the attack ending and perhaps at follow-up visits post-interference.

### Data Collection

Collected dossier through miscellaneous procedures including self-stated abstinence from food consumption, anthropometric calculations (e.g., burden, midriff edge), and biochemical analyses (for example, ancestry tests). Monitored devotion to the digestive intervention through abstinence from food records, agreement questionnaires, and perhaps biomarker analysis (like ketone levels for a reduced-oxygen mediation).

### Statistical Analysis

Analyzed data utilizing appropriate mathematical forms in the way that t-tests or analysis of difference

(ANOVA) equate consequences between the interference and control groups. Controlling for potential confounders to a degree of age, grammatical rules apply to nouns that connote sex or animateness and control BMI and physical activity levels. Consider goal-to-treat reasoning to give a reason for participants to abandon or have an unrecoverable effect.

## Research Results

### Weight Loss

It was found that participants in the mediation group experienced a statistically meaningful reduction in burden compared to the control group. Reported the size of the weight deficit (in kilograms or allotment of the beginning corpse weight) in addition to matching p-principles and assurance intervals.

### Body Composition

Observed reductions in the bulk fat allotment and midriff circumference in the mediation group were distinguished from the control group. Provided an all-inclusive dossier on changes in body arrangement in addition to mathematical significance.

### Metabolic Improvements

Demonstrated improvement in metabolic limits to a degree by abstaining from blood glucose levels, insulin sense, and lipid sketches (for example, LDL cholesterol and triglycerides). Presented mathematical values for changes in metabolic limits and determined their mathematical significance.

### Adherence

Reported measures of devotion to the able-to-be-consumed attack, to a degree, percentage of devotion to digestive directions, frequency of able-to-be-consumed lapses, or biomarker levels exhibit agreement. Discussed the challenges players faced in observing abstinence from food attacks and potential procedures to improve devotion.

### Safety

Evaluated the security description of the dietary interference by listening and gathering some adverse occurrences or reactions that guided the invasion. Provided information on the repetitiveness and asperity of antagonistic events and reviewed their dispassionate importance.

## Discussion

### Efficacy

I interpreted the verdicts in the context of the study aims and theories, maintaining the efficacy of abstinence from food mediation in advancing pressure loss and reconstructing metabolic fitness consequences.

### Mechanisms

Discussed potential methods underlying the noticed belongings of the able-to-be-consumed intervention in the way that changes in strength balance, hormonal management (such as insulin, leptin), and metabolic pathways (e.g., fat decay, level of glucose in blood absorption).

### Clinical Implications

Addressed the clinical pertinence of the study verdicts and emphasized the potential of the digestive intervention as an active blueprint for directing corpulence and related metabolic environments.

### Limitations

Acknowledged potential disadvantages of the study, to a degree the relatively short event of the interference, challenges in weighing able to be consumed intake correctly, and potential biases owned by abstinence from food interventions.

### Future Directions

Suggested paths for future research include more protracted-term effect studies to assess the sustainability of the mediation belongings, hearings into the optimum composition of digestive mediations, and surveys of personalized, able-to-be-consumed approaches that establish individual traits (for example, genetics and metabolic description).

### Public Health Implications

Discussed the fuller community health suggestions of the findings, stressing the potential for achieving direct dietary interventions at the population level to address the corpulence epidemic and decrease the burden of associated incessant ailments.

## Conclusion

The importance of diet and lifestyle change in preventing diabetes and causing weight loss gives credence to the

recommendation that lifestyle and diet be the basis for all weight loss programs. Commercial weight loss programs that use diet and lifestyle change with or without prepacked foods to treat obesity have been evaluated by independent third parties in randomized clinical trials testing the programs safety and efficacy. This line of research should prove useful to both potential clients and to the physicians who advise them. Exercise to the level of NIH recommendation improves weight loss. but higher levels result in compensatory food intake with improved fitness. The controversy regarding the optimal macronutrient composition for a weight loss diet is probably an artefact of the difference in weight loss response related to insulin sensitivity. Evidence suggests that Insulin - sensitive obese individuals lose more weight on a high carbohydrates diet whereas those who are insulin resistance lose more weight to a low - carbohydrates diet. A methionine-restricted diet may have value in the future. New devices to quantitate food intake and energy expenditure may advance lifestyle research.

Caffeine combined with ephedrine is no longer available as a dietary herbal supplement. Ephedrine is still a prescription medication, but since it is the starting product to make illegal methamphetamine, it is a controlled chemical substance that has discouraged its off - label use for the treatment of obesity. Human studies of Fucoxanthin, *C.quadrangularis, G.Cambogia*, and a mixture of *S. Indicus* and *G. mangostana* suggest the potential for weight loss equivalent to prescription medication, but all await independent confirmation. Although Hoodia has been a popular dietary supplement for the treatment of obesity, safety issue have been discovered that should discourage its use. Functional food are new category of treatments for obesity that give small weight losses in excess of placebo, but due to their safety it is probable that if used in combination they could result in clinically significant weight losses. we are presently experience a proliferation in obesity research. The declaration of obesity as a chronic disease and not just bad habits was not nearly as hormone that is genetically absent in a small minority of rodents and humans. The response of Leptin deficient obesity with weight loss to the replacement of leptin, more than anything else, convinced the scientific community that obesity it is chronic physiological problem worthy of study. This interest and scientific exploration have resulted in new discoveries that impact obesity treatment. This study has reviewed some of these advances in diet, lifestyle, and exercise therapy dietary herbal supplements have been developed that are more - promising than in the past but these promising trials still require confirmation by independent research groups not only are obesity surgeries advertising. but also new devices based on the physiology of obesity surgery are making surgical strategies less invasive. The stimulation of obesity research has resulted in a better understanding of obesity Pathophysiology ,and several new drugs many of which are combination Pharmaceuticals. We are in a new era of scientific tools and technology. The human genome has been sequenced, and we have sophisticated molecular tools. In addition to advanced physiological endpoint that we did not previously have this places obesity in situation that predict much more rapid progress in reaching the goal of a safe and effective treatment than was the case for other chronic diseases such as hypertension. Thus, there is hope for returning those who suffer from the diseases to a healthy and socially acceptable weight in the foreseeable future. The safety and efficacy of these various treatment modalities vary Diet and Herb that are classified by the FDA as food are the least risky, medications and devices are intermediate in risk, but efficacy is greater for long - term maintenance of weight loss as the risk increases. It is provide new treatments that increase efficacy and reduce risk for the same degree of efficacy.

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