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# Artificial Sweeteners and Weight Gain: Fighting or Feeding the Obesity Epidemic?

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## Abstract

Our world has developed an obsession with weight control and, as a result, has begun replacing high calorie foods with low-fat and non-caloric substitutes. Artificial sweeteners are a widely used solution to this growing problem. Though the intention when using artificial sweeteners is to lose weight, studies have shown that the opposite sometimes occurs. Researchers attempt to explain this surprising phenomenon with multiple hypotheses. Lack of appetite suppression and reward response may cause individuals to search for more food and to consume more calories. Artificial sweeteners can also have negative affects on biological mechanisms such as resting metabolic rate, as well as the gut microbial environment. These changes can cause improper energy absorption and storage, which leads to weight gain. Sociological effects of artificial sweeteners have lead consumers to enjoy products that are super sweet. They have also convinced consumers that they can eat more (food) but consume less (calories), a misconception that has left the world with a big "fat problem".

## Introduction

In a society plagued by obesity, diabetes and overeating, we search for ways to counteract these negative effects. Early research into these problems led to the assumption that the major cause of these maladies was over consumption of sugar. The food industry was taken by storm with the introduction of non-caloric artificial sweeteners (AS) such as saccharin, sucralose, and aspartame, which are widely used to replace sugar in the average western diet. However, are these sweeteners fighting or feeding the problems they were intended to combat?

Studies conducted in this area of science see a direct dose-response relationship between artificial sweetener use and weight gain. This relationship begs an explanation. Researchers propose that the weight gain caused by artificial sweetener can be due to natural circumstances, flawed gut microbial activity, or altered neurometabolic functions. Artificial sweeteners have been connected to both an increased appetite, and inefficient energy absorption. This combination can lead to weight gain and obesity.

## Methods

The studies and information in this paper were acquired through the PubMed government database and the Touro College Library databases such as J Store, Ebsco Host, and Proquest. To answer the present questions the articles and reviews have been read through; only the relevant information has been included.

## History of Artificial Sweeteners

The first sweetener to be discovered was saccharin. A scientist named Constantine Fahlberg stumbled upon it in 1879 at Johns Hopkins University. For nearly half a century saccharin was the only artificial sweetener on the market. Originally, it was for diabetics only, later it was used for anyone wanting to limit their sugar intake. Fifty years later, in the University of Illinois, Michal Sveda discovered Cyclamate. Combining cyclamate with saccharin improved the taste and soon became common practice. By 1969 the FDA banned cyclamate because of its link to cancer, while they deemed saccharin safe to use. Artificial Sweeteners

use went down in the general population until the new products surfaced. Aspartame was found in 1965 by James Schlatter at Searle while researching ulcer drugs. This was the first AS that could be metabolized, and the FDA approved it in 1981. Next came acesulfame potassium in 1967 and sucralose in 1979. Neotame was later approved for use is 2002 by the FDA.

In the years between 1999 and 2004 more than 6,000 new products have been created using artificial sweeteners. These sweeteners are most commonly used in carbonated drinks. Sucralose is the most widely used due to its close mimicry of real sucrose taste. The wide use of these sweeteners in countless products ensures that sweeteners affect most aspects of our dietary life (Yang, 2010).

## Discussion

Artificial Sweetener use and Weight Change:

The perpetual debate surrounding the effects of artificial sweeteners on the human body gave rise to a lengthy list of studies that attempt to determine the risks as well as the benefits. A controversial matter that has taken priority in these studies is the question regarding weight change in relation to artificial sweetener use. Due to their lack of calories, sweeteners have been used to control diseases such as diabetes as well as prevent diseases such as obesity. Yet, studies have found a substantial dose-response relationship between artificial sweetener use and weight gain. These studies range from 4 day studies to 10 year epidemiological events.

One of the largest scale studies performed was the San Antonio Heart Study (Fowler et al, 2008). The study included 5,158 Mexican and non-Hispanic white Americans between the ages of 25 and 64. All the members of the study lived in randomly selected homes in the San Antonio area. Consisting of 2 cohort studies, the first of which was from 1979 to 1982, the second was from 1984 to 1988. Of the 4,998 surviving individuals, took part in a follow-up study 7- 8 years later. This study focused on artificial sweetener consumption in beverages. Participants

were asked to answer a series of questions regarding amount of cans, bottles or cups of beverages, such as soft drinks, diet or regular, and coffee, sweetened with sugar or AS, they consumed per week. Based on their answers participants were placed in either a user or nonuser category. Dieting status and exercise frequency were recorded at baseline as well. Each participant was categorized by weight at baseline. A BMI of <25 was categorized as normal weight (NW), >25 but <30 was overweight (OW) and >30 was obese (OB). Incidence of OW/OB was defined as the percentage of originally NW participants who entered the OW/OB category by follow-up.

Results of the study show a strong dose-response relationship between AS beverage consumption and change in BMI. In Cohort 1 AS users had a 78% greater change in BMI than non-users and Cohort 2 experienced 74% and 83% greater change in BMIs in quartiles 3 and 4 respectively. The change in BMI followed a consistent pattern within the user subset. The more artificially sweetened beverages consumed per week the greater the change in BMI. Less than 3 ASBs consumed per week resulted in an average change of 1.2 kg/m<sup>2</sup> while 22+ ASB per week resulted in 2.0 kg/m<sup>2</sup> change and up. Participants who started out as users then chose to discontinue use experienced 58% lower BMIs than those who continued use. Once gender, ethnicity, weight category at baseline, diabetes, dieting status, exercise and cohort were factored in, change in BMIs were 47% higher in artificial sweetener users than non-users, suggesting greater gains, or smaller losses, for users versus non-users. Limitations of the study include a lack of sweetener specific study ability, fruit juices were not included, neither were artificial sweeteners consumed in products including food, other beverages, cosmetics and pharmaceuticals (which can contain aspartame) (Theodore, 2006).

The San Antonio Heart Study is far from the only one performed on this topic. Many studies have led to the same conclusion showing a relationship between artificial sweetener consumption and weight gain. The list is never ending. The American Cancer Society Study (Stellman, Garfunkel, 1986), which focused on 78,694 women, was conducted in the early 1980's. At a one-year follow-up 2.7% compared to 7.1% more AS users gained weight than non-users. The average difference in the amount gained was just shy of two pounds, nevertheless it was statistically significant. A third well known study was the Nurse's Health Study (Colditz et al, 1990) conducted between the years of 1976 and 1984. In this study 8 year weight gain was associated with saccharin use in 31,940 women.

Researchers such as Blundell (Blundell, Hill, 1986), Rogers (Rogers et al, 1988)(Rogers, Blundell, 1989), Tordoff (Tordoff, Alleva, 1990)(Tordoff, Friedman, 1989), and Lavin (Lavin et al,

1997), who have conducted studies attempting to find a reason for this phenomenon, have seen increased hunger, appetite, and food consumption as a result of AS users. However, reviews written by Rolls

(1991) and Malik et al, (2006), which consist of multiple short term studies, have seen either no weight gain, or even increased weight loss in users. A meta analysis of nine interventional studies summarized by De La Hunty (De La Hunty et al, 2006) saw significantly greater weight loss in aspartame users versus non users.

When researchers saw the incongruent results of these studies they chose to conduct a study of their own. In a 10-week study they tried to prove their claim that "short term studies are not very informative because appetite regulation and macronutrient balance probably do not correct for the missing energy and sucrose until the individual has consumed the diet for several days" (Raben et al, 2002). Their results, however, proved their hypothesis wrong. For 10 weeks overweight individuals were placed into either a sucrose group or an artificial sweetener group. The study found no increased hunger or appetite in the AS group compared to the sucrose group, and weight gain was observed in the sucrose group while weight loss occurred in the artificial sweetener group.

The lack of consistent results in these studies can obviously be due to the human components. The controlled short term studies consisted much more of restricting diets and exercise regimens. The long-term studies, spanning multiple years, thus allowing natural eating habits and appetites to develop, were more likely to see increased BMI amongst artificial sweetener users. There is a possibility that those using AS are those who are more susceptible to weight gain, and therefore, we see these results. But research doesn't stop with speculation. Scientists are now trying to understand how non-caloric sweeteners could lead to weight gain.

### **Biological Response to Sweet Taste Natural Sugars:**

Many different explanations have been suggested as to why artificial sweeteners would cause an increase in weight. The first is the suggestion of increased appetite or lack of appetite suppression. As stated previously, AS use has been continuously linked to hunger and overeating. The debate lies in how sweeteners can cause these biological reactions. In order to understand the specific way in which the body reacts with artificial sweeteners we must first understand how the body acts with natural sugars.

There are 2 pathways of glucose absorption (Mace et al, 2007). One is active transport through the Na<sup>+</sup> glucose co-transporter

SGLT1. This pathway reacts only with glucose and is thus unaffected by artificial sweeteners. The second route is known as the apical GLUT2 pathway. This pathway reacts at high concentrations of glucose and can have 3 to 5 times more rapid and precise absorption than the classic SGLT1. The GLUT2 route is mediated by  $\text{Ca}^{2+}$ . Depolarization of the apical membrane through glucose transport via SGLT1 allows  $\text{Ca}^{2+}$  to enter the L-type channel  $\text{Cav}1.3$ , this causes the terminal web to contract. This is essential for insertion. Little insertion occurs at low concentrations of glucose, in which case the SGLT1 transporter dominates. However, at 30 mM (millimoles) of glucose or more the GLUT2 pathway takes over as the main absorption pathway for unknown reasons.

The calcium concentration goes up as a result of the G-protein coupling receptor,  $\alpha$ -gustducin, activated phospholipase c  $\beta$ 2- dependent pathway. The GCPR is coupled with the TIR2 and TIR3 sweet taste receptor heterodimer. When these receptors, found in both lingual cells on the tongue and intestinal brush cells in the duodenum, sense sweet taste they release the  $\alpha$ -gustducin and set this reaction in motion.

The  $\alpha$ -gustducin also induces the secretion of glucagon-like peptide (GLP)-I and peptide YY from enteroendocrine L-cells (Ford et al, 2011). Both GLP-I and PYY have been observed to be satiety factors in humans (Flint et al, 1998, Gutzwiller et al, 1999). GLP-I is known to raise insulin sensitivity as well as increase leptin levels in the hypothalamus, thus increasing satiety in the brain. The sweet taste path continues eventually terminating in the insula/frontal operculum and the orbitofrontal cortex (Small, 2006). The mesolimbic system sends the feeling of satisfaction received for the good taste (Stice et al, 2008). The metabolic products of the ingested foods determine this post-ingestive effect. Therefore, when sugar enters the body it stimulates the sweet taste receptors, which activate both the absorption pathway and the satiety pathway, providing both an energy source for the body and a reward for the brain. The combination of these factors means the person is no longer in search for food; he is satisfied.

### Biological Response to Sweet Taste Artificial Sweeteners:

In 2010, Ford and Peters conducted an experiment to determine if artificial sweeteners invoke this same response as sugar does in the body (Ford et al, 2011). They conducted a signal blind, randomized, crossover study in eight healthy volunteers over a 4 day period. The volunteers consisted of seven females and one male ages 22-27, all in the normal body weight range.

The subjects were randomly selected to receive one of four solutions: 50ml of either water, sucralose, maltodextrin (a

non-sweet caloric substance, matched for the sweetness of sucralose in this experiment) or a modified sham-feeding protocol of sucralose (used to study oral stimulation of sweet taste receptors in the mouth versus those in the gastro-intestinal tract). The dose of sucralose used was based on the observed average intake of sucralose per day. Observations were made on four separate days with a minimum of three days left in between each solution study. Participants initial blood work was taken on arrival, they then ingested one of the first three solutions followed by the MSF of the solution that they had swallowed. Blood samples were taken -15 minutes and 0 minutes prior to ingestion and then 15, 30, 45, 60, 90, and 120 min after ingestion. To analyze cephalic phase insulin response as well as GLP-I release, samples were taken at 2, 4, 6, 8, and 10 minutes after ingestion. Participants were asked to rate their appetites using visual analogue scores for 120 minutes following ingestion, after which time they sat down to a meal and their food intake was noted.

Researchers found that there was no increase in appetite or energy intake after the 2-hour waiting period, however, what they found in the blood samples, is quite fascinating. The plasma insulin and GLP-I showed no significant change in the first 10 minutes and GLP-I and PYY concentration were similar in all groups. The stimulation of TIR receptors did not occur in the case of sucralose ingestion. As a result GLP-I and PYY were not secreted and appetite suppression did not occur. Perhaps the most interesting part is that in vitro sucralose did stimulate the receptors and, as a result, the L-cell secretions of GLP-I and PYY occurred. The reason for this disparity is still unknown at this point in time.

Though artificial sweeteners don't stimulate these receptors on their own, a study done on rat intestinal tracts was very informative as to the mechanism that is used. In this study on rat intestinal tracts, it was demonstrated that, when combined with a small amount of glucose, AS stimulate the GLUT2 response in a similar way to that of large amounts of glucose (Mace et al, 2007). The rapid absorption of glucose through this pathway is only first observed at a threshold value of 30 mM of glucose, even then it is a minimal response. However, when 20 mM of glucose were ingested in conjunction with just 1 mM of sucralose the rate of glucose absorption doubled (as compared to just 20 mM of glucose). This effect was equivalent to the effect of 75 mM of glucose ingestion. The rapid absorption may lead to a feeling of satiety, but blood glucose levels sky rocket as a result as well. High glucose levels will lead to fat production as a means of conserving all the extra energy in the body. Therefore, trying to save calories "part of the time" can actually have worse repercussions for weight gain and obesity than natural sugars can.

In another study examining a connected response, Graaf et al, studied the functional magnetic resonance images (fMRIs) of subjects who had recently ingested glucose, water, maltodextrin, or aspartame (Graaf et al, 2005). The objective of the study was to examine the separate effects of energy content and sweet taste on the hypothalamic responses, such as cephalic phase insulin response, and ghrelin (the hunger hormone) response suppression, which contribute to a sensation of satiety.

Five participants were scanned for 37 minutes at a time on 4 separate days. The participants were healthy normal weight males. A questionnaire was used to assess the general level of health in their daily lifestyle. Solutions were randomly assigned to participants by picking lots the day before each visit. The aspartame and maltodextrin solutions were matched for sweetness to that of the glucose solution. The subjects didn't know which solution they were receiving. One blood sample was taken before entering the fMRI machine, others were taken once the subjects were inside. The first was taken -5 minutes and -3 minutes before ingestion and then 1, 3, 5, 7, 10, 20, and 29 minutes after ingestion of the substance. Each subject's hypothalamus was segmented into four regions. The regions of interest (ROI) were the upper anterior hypothalamus (UAH) and upper posterior hypothalamus (UPH) because these are the regions known to respond to glucose (Smeets et al, 2005). At each time slot the mean gray matter value of the hypothalamus was calculated and compared to the 7-minute reference period of each participant.

Results of the study show that glucose was the only one of the four substances that resulted in a prolonged decrease in the hypothalamic hunger signal (ghrelin response). Neither the sweet taste of aspartame alone, or the caloric intake of maltodextrin alone elicited this same response. The results blood samples showed that both glucose and maltodextrin ingestion resulted in a cephalic phase insulin response and increased blood glucose levels. However, the glucose response was much stronger. Increased glucose levels result in leptin release, which is itself associated with a decrease in ghrelin signals, ultimately giving the person a feeling of satiety. Aspartame and water had no such effects. In a similar study, saccharin was tested in place of aspartame, the saccharin did not result in a CPIR either (Teff et al, 1995).

What these studies suggest is that artificial sweeteners do not send the same signals to our brain as real sugars. As a result one doesn't feel satisfied or rewarded after eating. In the absence of these biological reactions there is typically an increase in fat and protein calorie intake (Benton, 2005, Beaton et al, 1992). It has also been noted that the reward system for food shares the behavioral paradigm with all different forms of addiction (Avena

et al, 2008). And like other addictions a period of abstinence can lead to a period of over indulgence. Avena et al. noted that after a period in which rats were denied sucrose, an increase in sucrose self-administration occurred (Avena et al, 2005), quite similar to binge eating in humans. Applying this concept to artificial sweetener use, one can assume that replacing sugar with non-caloric sweeteners can actually result in an increase in caloric intake.

### **Gut Microbial Adaptation to Artificial Sweeteners:**

In the early 1980's it was suggested that there might be a link between the commensal flora of the gut and obesity. This suggestion came about when a noted change occurred in the gut microbiota composition after weight loss (Bjornekleit et al, 1981). In 2005 a well known study stated that obesity can result from a higher Firmicutes : Bacteroidetes ratio (Ley et al, 2005), further studies found that there is definitely an altered biome in the GI tract of obese people (Payne, et al., 2012). The debate on this topic is a cause or consequence question. Is it that individuals who have altered gut microbes become obese, or does the micro-biome only change once the person is already obese? Payne suggests that the cycle begins by not eating properly, thereby destroying the natural gut environment. The new ecosystem reacts differently to the substances that enter the system; this behavior can contribute to obesity.

Payne says that our non-diverse "fructose-and sugar substitute-laden, plant polysaccharide- poor Western diets" force the microbiota to adapt to the new and unknown substrates such as artificial sweeteners while being bombarded by familiar substances like fructose. These conditions force the environment to adapt, changing structure, enzyme production and patterns of energy absorption. This survival mechanism, called adaptive metabolism, was demonstrated in rat and pig models for D-tagatose fermentation (Laerke et al, 2000). At the same time that this diet creates new adaptive forms of bacteria, the normal diversity that exists begins to diminish. The link between obesity and a lack of diversity of gut microbiota is widely accepted (Turnbaugh et al, 2008; Ley et al, 2005; Turnbaugh et al, 2006). Turnbaugh et al's. study suggests that the typical western diet promotes growth of Firmicutes while it depletes Bacteroidetes contributing to the unhealthy ratio. Bacteroidetes are the ones most well equipped for the digestion of starch and sucrose.

This newly formed ecosystem evolved in order to promote efficient energy extraction. While the body can only absorb as much energy as was ingested, increased exposure to unknown substrates can put the body into panic mode. As a result of over exposure to unfamiliar substances the bacteria react by acquiring supplementary metabolic energy sources. For example

short chain fatty acids (SCFAs) taken up by the intestine can be converted to energy via the Krebs cycle (Leng et al, 1963). The idea of efficient energy extractions has been observed in obese individuals (Turnbaugh et al, 2006). The extra absorption creates more energy; energy that is unnecessary. The extra energy then has to be stored as adipose tissue, over time this can lead to a build-up and cause someone to become overweight and possibly obese.

### **Resting Metabolic Rate Adaptation to Artificial Sweeteners:**

The resting metabolic rate (RMR) of a person's body has a large effect on total energy expenditure (Ravussin et al, 1982) and low RMR (calculated by using fat-free mass as a reference point) puts them at a greater risk of obesity (Ravussin et al, 1988). In a study done by Kiortsis et al, obese children were put on a calorie restricting diet for six weeks (Kiortsis et al, 1998). After the six week period, weight loss occurred and lower BMI and FFM were calculated. RMR at this time averaged around 10.1% lower than the starting metabolic rate. As RMR went down so did the Serum tri-iodothyronine (Serum T3) levels. A correlation is not well understood but this may be an adaptive response attempting to conserve energy during a period of caloric deprivation.

The data gathered in this study can be applied to this discussion. Artificial sweetener use is a form of calorie reduction. When depriving the body of proper energy sources the RMR decreases. When a person goes back to eating the way they did before the calorie withdrawal period, their new, lower RMR will not be able monitor proper energy expenditure. The low metabolic rate also greatly increases an individual's risk of obesity, so the short term weight loss may not be all that successful.

### **“The Sweetening of the World's Diet” (Popkin, Neilsen 2003)**

The Sweeteners that have been approved by the FDA are intensely sweet. So much so that very little has to be used to achieve the sweetness of sucrose. Sweeteners, from aspartame, which is 180 times sweeter than sucrose, to neotame, which can be 7,000 to 13,000 times sweeter, have desensitized the present day palate. We are so used to products with this uber sweetness that companies that use real sugars are forced to manipulate their products so our trained palates recognize them as sweet. This extreme use of sugar in such large quantities is not healthy for anyone and, of course, contributes to the obesity epidemic.

### **“Low- Fat” Syndrome:**

As the prevalence of obesity rises and people become more and more aware of the dangers of being overweight a new culture has been born. Nearly every product known from chocolate to pasta to alcohol can now be found in a low fat, sugar free,

or low carb form. Studies show that these labels can distort a person's perception of serving size, and calories per serving (Wansink, Chandon, 2006). These assumptions then mold his or her anticipated pleasure, from the taste of the food, and/or guilt, from the calorie intake, that they will feel for consuming this product. The guilt experienced by consumers is a product of the conflict of interest that goes on in their heads. On the one hand they want the pleasure for the taste of the food, on the other they know the long-term health risks of eating unhealthy foods. These factors combined then determine how much the person will actually eat. When the guilt is decreased or completely erased from the equation, consumers make decisions that are extremely detrimental to their health.

A study was performed to see if this theoretical phenomenon proved to be real. It took place at a university open house to allow for diversity, 361 participants were included in the study. Upon arrival participants were brought to one of two bowls of regular M&M's. The first bowl was labeled “Regular M&M's” while the second was labeled “Low-Fat M&M's”. The participants were told to serve themselves what they thought was an average serving size, and their bowls were weighed. They were then asked to estimate how many calories they believed were in their serving size. After eating their M&M's the participants were asked how guilty they felt for eating them.

The results of the study show that low-fat labels can be extremely hazardous. Participants ate 28.4% more M&M's when they were labeled “low-fat”, their perceived serving size was 25.1% greater and their calorie estimates were nearly 300 calories lower as compared to regular M&M's. All participants felt guiltier for eating the regular M&M's than for eating the low-fat ones, however, overweight individuals felt less guilty about it than the normal weight individuals. The overweight individuals actually said they felt no guilt at all for eating the low-fat M&M's.

The larger problem that this presents is that low-fat does not necessarily mean low calorie. In a survey done on 17 brands that sold a regular and low fat version of the same product, it was determined that though low-fat products had, on average, 59% less fat than the regular products, they only had 15% less calories. Applying these statistics to the previous study outcomes would mean that though consumers had 48% less fat (based on the average lower fat percentage of low fat products) they would have had 9% more calories.

### **Conclusion**

This review was written as an attempt to understand the correlation between artificial sweetener use and weight gain. Multiple scientific and sociological/ psychological hypotheses were studied. Each one can explain this surprising phenomenon.

However, they don't have to stand alone. Combined the multiple hypothesis can tell the life story of an obese individual. It is a vicious cycle that has no real beginning and it can start at any point. But each leads to the next. If you begin at "The sweetening of the worlds diet" you can see an individual enjoying himself with all his overly sugary snacks, because that is what his palate has become accustomed to. Soon he notices his jeans have gotten a little snug so he begins eating "low-fat" products to reduce the guilt he feels for what he's doing to himself. The low-fat products, which contain artificial sweeteners, increase his appetite because they do not stimulate his taste receptors to provide a reward response in his brain. But, maybe this works for him for a while and he drops a few pounds. By then resting metabolic rate will have lowered putting him at a higher risk for obesity. When he can't deprive himself of sugar any longer he'll binge eat those calories that he's been missing. The lower RMR that was created can no longer handle these massive amounts of sugar and cause fat storage to occur. All the while he's been destroying his gut microbe environment. Now, whatever he ingests his body searches for additional energy sources because it fears the lack of sucrose will deplete its energy storage. Combining this glucose intake with AS use also leads to stimulation of the GLUT2 pathway for rapid unnecessary absorption. And so, more and more adipose tissue accumulates. Slowly, day after day, year after year this cycle occurs. Soon he finds himself obese, with metabolic syndrome, diabetes, and chronic heart disease. Though further research is necessary to understand how this affects different age groups, ethnicities, and genders, this can occur. And it's all a result of an attempt to create a non-caloric, healthier sweetener.

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