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# Nutritional Deficiencies Associated with Obesity

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**Abstract**

Obesity is a serious problem in the United States and developing countries. Obesity leads not only to serious chronic health problems but is also associated with approximately 40% higher health care costs than normal weight individuals. Long standing theories of weight loss rested on the simplistic idea that one must expend more calories than one consumes. Although this is a mainstay of weight loss regimens, the underlying causes of obesity are more complex than previously considered. Research has noted nutritional deficiencies in subjects that are overweight, obese and morbidly obese. Is the cause of this contradictory deficiency due to low-cost, nutrient poor food or do findings suggest that there is an alteration in absorption, distribution, metabolism and/or excretion of these nutrients in overweight and obese individuals. Nutrient deficiencies in obese populations are very common with vitamin D deficiency being the most prevalent affecting approximately 57-94% of obese individuals. Interestingly, correction by protein-rich diet supplementation containing vitamins and minerals did not correct levels. In contrast, micronutrient levels remained low or became even lower. This discrepancy may be explained by gastrointestinal barrier dysfunction, intestinal microbiota or increased metabolic demand. There are also theories examining amino acid and neurotransmitter depletion that disrupts feedback mechanisms. There are several neurotransmitters that regulate weight, appetite and satiety. Findings suggest that a low level of neurotransmitters, amino acid precursors or receptors had a direct impact on a subject's weight. The review of research reveals that obesity is a complex problem with multiple contributing factors. Further understanding of the dietary deficiencies and the regulation of the metabolic pathway is fundamental towards effective treatment.

**Keywords:** Neurotransmitters; Amino acids; Dopamine receptors; Metabolic imbalance; Obesity; Nutritional deficiencies; Serotonin

## Introduction

Even though there is an abundance of food in the United States, nutritional deficiencies are paradoxically found in both normal weight and obese populations. Interestingly, the prevalence of nutrient deficiency is higher in overweight, obese, and morbidly obese individuals as compared to those who fall in a normal weight category. Accordingly, the cause of obesity may be addressed by the following theories:

Is low-cost, nutrient-poor food the root of the problem or,

Do findings suggest that even though obese patients consume an excess of dietary energy in the form of calories, there may be an alteration in the absorption, distribution, metabolism and/or excretion of these nutrients in overweight and obese individuals [1]. This paper seeks to summarize current research and shed light on that question.

The most common theory on obesity rests on the idea that you are consuming more calories than you are expending. A calorie-is-a-calorie theory dates back to 1878 when the German nutritionist Max Rubner established the isodynamic law. The isodynamic law is based on the idea that what you eat is irrelevant, different food may replace one another in accordance with their caloric values when burned in a calorimeter. The reasons behind obesity are not that simple and research has shown that the causes of obesity are more complex than previously considered.

## Nutrient Deficiency

Recent research has focused on the presence of nutrient deficiencies in obese populations. Examination of obese individuals demonstrates vitamin D deficiency as the most prevalent affecting approximately 57-94% of obese individuals. Calcium, magnesium, vitamin B6 as well as iron deficiency have also been described [2,3].

Researchers found that patients who were obese and also had low vitamin D levels were at a higher risk of insulin resistance than if they had either factor alone [4]. Although further studies are needed to better understand how nutritional management of obesity may improve the gastrointestinal barrier dysfunction, studies to date have shown that micronutrient deficiency present in obese individuals is not corrected by protein-rich formula diet supplementation containing vitamins and minerals. In contrast, micronutrient levels remained low or became even lower which may be explained by increased metabolic demand and/or an unbalanced distribution in the body [5,6].

It has also been hypothesized that toxic by-products of incomplete biochemical reactions resulting from excessive intake of calories and the chronic state of micronutrient deficiencies could lead to further weight gain or development of associated metabolic diseases [1]. Considering the epidemic proportions of obesity, it is reasonable to conclude that a significant part of the obese population, including those in developed countries, could be affected by micronutrient deficiency.

Researchers also evaluated Dietary Reference Intakes (DRI) to analyze if the DRI met the micronutrient requirements of obese

individuals. Dietary reference intakes for the daily supply of vitamins and minerals apply to healthy, normal weight individuals. Therefore, DRI may not necessarily meet the metabolic needs of obese individuals. A formula diet providing 100% of micronutrients according to DRI did not cover the demands of some micronutrients in obese subjects. The significant decrease in micronutrients observed in obese individuals suggests that the deficiency is not only caused by intakes that are below DRI but also appear to be the result of metabolic alteration. This may represent an oxidative stress in obese individuals therefore necessitating a higher demand of antioxidative vitamins compared to healthy, normal weight subjects [6].

McClung hypothesized that obesity also influences iron absorption by inflammatory mediated mechanisms. Proinflammatory cytokines promote hepcidin release in liver and fat tissue, which is involved in iron homeostasis, in turn inhibiting absorption in enterocytes. This hypothesis is supported by a significantly negative correlation of iron concentration with CRP levels observed in obese study subjects [7].

Further, obesity is also linked to a number of adverse health conditions including: hypertension, diabetes and hyperlipidemia. The risk of Type 2 diabetes is increased 4-fold in obese patients. Research has demonstrated the importance of certain micronutrients as co-factors in the glucose metabolic pathway suggesting that a deficiency in these micronutrients may play a role in the development of Type 2 diabetes.

## The Role of Amino Acids

Recent studies focusing on amino acids and their metabolites have consistently revealed disruption of normal amino acid metabolism in obese, insulin-resistant states and Type 2 diabetes [8].

It has also been observed that a change in blood concentrations of select essential amino acids and their derivatives, in particular branched chain amino acids, sulfur amino acids, tyrosine, and phenylalanine, are present with obesity and insulin resistance, often before the onset of clinically diagnosed Type 2 diabetes [9].

The research demonstrates that amino acids are important modulators of glucose metabolism, insulin secretion and insulin sensitivity. Although total amino acid levels are similar in patient with diabetes, impaired glucose tolerance and control subjects, the individual levels of several amino acids differ significantly between these groups. These variations contribute to the disruption in insulin secretion and may provide a rationale for amino acid supplementation to diabetic patients [10]. Further research is needed to fully understand the changes in essential amino acid metabolism in obese and insulin resistant patients.

## Intestinal Microbiota and Permeability

Another area of research has focused on the metabolic role of gut microbes in energy production, storage and expenditure related to obesity. Evidence suggests that the composition of the gut microbiota differs in lean and obese humans and animals. Research has demonstrated that the introduction of gut microbiota from conventionally raised mice into germ-free mice resulted in a 60% increase in body fat and insulin resistance within two weeks despite reduced caloric consumption and increased activity [11].

In humans, it has been suggested that the relative composition of the gut microbiota during early life predicts the subsequent development of weight gain and obesity. A study of pregnant, overweight women and pregnant, normal weight women found that the microbiota composition is different, with a proportionally higher number of *Bacteroides* and *Staphylococcus* in women who are overweight during pregnancy [12]. It is postulated that this is one underlying mechanism by which a propensity for obesity is conferred from the parent to the infant because the mother influences the original inoculums and subsequent development of the infant microbiota.

## Neurotransmitter Depletion

Neurotransmitters are intricately involved in the feedback mechanisms that regulate appetite and satiety and studies suggest a common underlying neural pathway that regulates body weight [13,14].

Observational studies further support the theory that several neurotransmitters regulate body weight. These neurotransmitters are important orexigenic/anorexigenic mediators that convey information to neurons and other regions of the brain that regulate energy balance [15]. Imbalance of these key neurotransmitters will impact weight regulation, appetite and satiety (Table 1).

| Neurotransmitter | Precursor | Effect on Energy Economy |
|---|---|---|
| Dopamine | Tyrosine | Decreases appetite |
| Epinephrine | Tyrosine | Stimulates fatty acid oxidation |
| Serotonin | 5-hydroxytryptophan | Decreases appetite and carbohydrate-craving |
| Histamine | Histidine | Increases CRF; inhibits NPY |
| D-serine | L-serine | Modulates availability of serotonin to the brain |
| Glutamate | Glutamate | Stimulates appetite by central mechanisms involving N-Methyl-D-Aspartate (NMDA) receptor activity |
| Acetylcholine | Choline | Regulates gastrointestinal peptide secretion in response to food |

**Table 1:** Neurotransmitter Depletion.

The hypothalamus establishes a threshold at which food intake will be initiated or terminated to maintain a proper energy balance. It is theorized that in obese individuals, the hypothalamic set point appears to be elevated suggesting that homeostasis has been reset to maintain fat reserves. The high set point allows an excess amount of food to be ingested before satiety cues are triggered.

The Paraventricular Nucleus of the Hypothalamus (PVH) is also involved in the control of body weight and is a major brain site of melanocortin action. Recent studies looked at the Melanocortin Receptor 4 (MC4R) as a well established mediator of body weight homeostasis. Restoring neuronal expression of the MC4R receptor dramatically reduced obesity in mice. However, the anti-obesity effect was reversed by selective disruption of glutamate release from the same neurons. Thus, this study established glutamate as the primary neurotransmitter that mediates body weight regulation [16].

Further studies also established that PVH contains a diverse group of neurons that use peptides, glutamate, GABA or dopamine as neurotransmitters [17,18]. Neurotransmitters, particularly serotonin, play a key role in appetite. Serotonin is synthesized by the precursor tryptophan and is unique in the fact that the amount of neurotransmitter released is controlled by food intake [19]. It has been observed that low serotonin levels trigger carbohydrate cravings and consumption which in turn affects the plasma tryptophan ratio increasing serotonin release. A study of the plasma concentrations of tryptophan in obese subjects produced surprising results. Plasma tryptophan concentrations and ratios of tryptophan to large neutral amino acids in the obese subjects were low at all times, even after weight reduction. Researchers postulate that the altered tryptophan metabolism and continued low level of tryptophan even after weight loss may be a reason for relapse and weight gain after diet induced weight loss [20].

As previously noted, a lack of serotonin leads to strong carbohydrate cravings, this in turn can lead to an overconsumption of calories. The inverse relationship between serotonin level and food intake is a current area of treatment focus. Treatment in the form of serotoninergic mechanisms reduces body weight by accelerating the onset of satiety [21] and increasing the metabolic rate [22].

There is also increasing evidence that dopamine plays a role in the development of obesity. It has been observed that low levels of the neurotransmitter dopamine leads to over eating. The observation of compensatory eating is due to hypofunctionality of the dopaminergic system. For example, nicotine excites dopamine containing cells, a rebound effect of eating behavior after dopaminergic overstimulation could account for the weight gain often associated with smoking cessation. Obese individuals were also noted to have fewer dopamine receptors than normal weight subjects and an inverse relationship exists between the number of dopamine receptors and the subject's body mass index.

Additionally, weight gain is often a side effect of many antidopaminergic medications. Antidopaminergic medications such as tricyclic antidepressants, lithium and some anticonvulsants commonly result in an increase in weight due to the down regulation of the dopaminergic system [23]. Continuing research focused on the neurotransmitters involved in body weight regulating pathways and the diverse group of neurons that use glutamate, GABA or dopamine as neurotransmitters will assist in developing effective therapy and further understanding of obesity [17,18].

The foregoing reveals that obesity is complex. Its effects both for the individual and society are difficult and far-reaching. Obesity itself exacts a tremendous price on individuals leading to serious chronic health conditions and disability. From an economic standpoint, obesity is associated with health care costs that are approximately 40% higher than those for normal weight individuals. Employers also report higher medical, disability and workers compensation claims from obese individuals. The overall cost to society is immense and growing.

This review of research related to the causes of obesity brings us back to the underlying question: Is diet the main contributing factor behind obesity or is it a metabolic imbalance? One must look at not only the increased availability of low-cost, high-calorie, nutrient-poor foods as a key component in the link to obesity but also specific micronutrient deficiencies and metabolic disorders that may also influence the increasing incidence of obesity in this county and throughout the world.

Both are likely contributing factors to the obesity epidemic. Further understanding of the dietary deficiencies and the regulation of the metabolic pathway is, however, fundamental towards effective treatment.

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