

# Effect of Nutritional Regulation on Adipokines in Obesity: A Review

Mansi Chopra<sup>1,\*</sup>, Anupa Siddhu<sup>1</sup>, Nikhil Tandon<sup>2</sup>

<sup>1</sup>Department of Food and Nutrition, Lady Irwin College, Sikandra Road, New Delhi, University of Delhi, India

<sup>2</sup>Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

\*Corresponding author: chopra.mansi2@gmail.com

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**Abstract** Childhood obesity has become a major public health problem worldwide and it increases the risk of developing severe obesity, coronary heart disease, type 2 diabetes and respiratory disease in adulthood. Low grade inflammation has been identified as a key factor in development of obesity. In obesity, the expanding adipose tissue makes a substantial contribution to the development of obesity-linked inflammation via dysregulated secretion of pro-inflammatory cytokines, chemokines and adipokines and the reduction of anti-inflammatory adipokines, such as adiponectin. The macronutrient composition of the diet regulates the overall body weight and metabolism and caloric intake is one of the major contributors to obesity, where certain kinds of diet (pro-inflammatory) can promote obesity, and other kinds (anti-inflammatory) can reduce it. Lifestyle interventions like caloric restriction and increases in physical activity can lead to weight control which induce attenuation of obesity-induced inflammatory responses, which is a risk factor for obesity related chronic diseases, along with a decrease in fat mass in obesity.

**Keywords:** nutritional regulation, obesity, adipokines, macronutrients, inflammation

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## 1. Introduction

Childhood obesity has become a major public health problem worldwide [1,2,3] and it increases the risk of developing severe obesity, coronary heart disease, type 2 diabetes, and respiratory disease in adulthood [4,5,6,7]. Obesity is characterized by excessive accumulation of fat in the white adipose tissue (WAT) due to a chronic imbalance between energy intake and expenditure. In fact, it is the surplus of energy derived from the metabolism of dietary carbohydrates, fats and proteins that end up being stored as triglycerides (TGs) in adipocytes causing expansion of the WAT over time [8]. Excess adipose tissue, particularly in the visceral compartment, is associated with systemic oxidative stress in humans and mice, and increased oxidative stress in accumulated fat appears to be an important contributor to the pathogenesis of obesity-associated metabolic syndrome. Visceral adiposity is characterized by low-grade systemic inflammation, and obese subjects exhibit elevated production of inflammatory markers [9].

## 2. Nutrient Balance

Total energy expenditure and total energy intake are not the only factors that regulate body fat, [10,11,12] but carbohydrate and protein balance seems to be strictly

controlled to adjust intake to oxidation (and vice versa) to reach an equilibrium state [13]. The macronutrient composition of the diet is a very important factor in the regulation of overall body weight and metabolism. Fats and carbohydrates are primarily considered to be sources of energy stores in either adipose tissue or liver, whereas proteins are considered to supply body-building elements. All three of these macronutrients can modulate feeding behavior in a manner that is mainly dependent upon their physical form, type, and quantity in the ingested diet [14,15]. Long-term ingestion of high fat/high-carbohydrate diets often leads to the development of overweight, and also of adiposity and metabolic abnormalities [16]. On the other hand, ingestion of high-protein diets leads to weight loss in combination with decreased energy intake [15]. This is mainly due to the high satiating effects of proteins when compared with fats and carbohydrates [17].

Although caloric intake is one of the major contributors to obesity, people have known for centuries the role that diet plays in obesity. Certain kinds of diet (pro-inflammatory) can promote obesity, whereas other kinds (anti-inflammatory) can reduce it [18,19,20,21,22]. A high-calorie, high-fat, and low-fiber diet usually promotes obesity; caloric restriction, exercise, and wholesome foods have been shown to reverse it [23,24,25]. It is generally believed that highly processed, packaged, and refined foods loaded with sugar and hydrogenated oils are likely to promote obesity [26].

### 3. Nutrient Regulation of Adipose Tissue-derived Adipokines known to Cause Inflammation

**3.1. Leptin:** is an adipocyte-derived hormone that acts to reduce food intake and increase energy expenditure. Although in the fed state circulating concentrations of leptin reflect the amount of energy stored in fat and correlate positively with indices of adiposity, individuals with similar degrees of adiposity exhibit great variations in serum leptin concentrations [27]. However, adipose tissue mass is not the only determinant of circulating leptin concentrations. Recent energy intake also has a major influence on plasma leptin levels. Plasma leptin decreases acutely during fasting [28] or energy restriction [29], whereas re-feeding (30) and overfeeding acutely increase leptin. Circulating leptin rises by 40% after acute overfeeding and more than 3-fold after chronic overfeeding [31]. These changes are disproportionate to the relatively small changes in body fat induced by these short-term interventions.

**3.1.1. Effect of Carbohydrate intake on Leptin levels:** Food consumption stimulates leptin secretion after the meal and high carbohydrate meals result in greater leptin responses as compared to high fat meals [32]. Diets rich in sucrose have been shown to increase postprandial leptin; however these higher postprandial leptin levels are not related to postprandial satiety or food intake. High-sugar, low fiber meals may therefore play a dual role in the current obesity epidemic: one, by increasing energy intake and affecting Leptin's ability to serve as an effective satiety signal, and two, through the possible negative effects of sugar consumption on prolonged physical activity levels [32].

A study conducted by Spruijt-Metz et al. (2009) involved participants receiving a High Sucrose (HS) cereal meal at one visit and a Low Sucrose (LS) cereal meal at the other visit (in random order). There was a negligible post-prandial decline in plasma leptin following the HS meal, whereas the LS meal was accompanied by a significant decrease in leptin. There was also a significant difference in leptin levels at 90 mins (LS vs. HS, mean 46.7 vs. 49.31 ng/ml,  $P = .017$ ) [32]. Although habitual carbohydrate intake and a high glycemic index diet have been reported to decrease leptin concentrations, glucose infusion or iso-energetic or ad-libitum overfeeding of carbohydrates or sucrose has been shown to result in a significant increase of leptin concentrations and/or to prevent a fasting-induced fall in leptin. More specifically, a Western dietary pattern and high-fat diet have been positively associated with plasma leptin concentrations in women [33] and men [34].

**3.1.2. Effect on BCAAs intake on Leptin levels:** Increase in circulating branched-chain amino acids (BCAAs) are likely to contribute to meal-induced increases in leptin. Administration of BCAAs, particularly leucine, elicits a rise in leptin after 3 hours, as shown by Lynch et al. [35]. Another study reported that, free leptin, as expressed by the ratio leptin/sOB-R (leptin receptor), was weakly, but significantly and negatively associated with the energy intake provided by carbohydrates (expressed either as absolute caloric intake or as a percentage of total energy intake), and weakly positively

associated with fat intake. These results indicate that in free-living, healthy young subjects, the macronutrient composition of the diet may have a significant influence on the serum concentrations of free leptin, the presumed biologically important form of leptin [27].

**3.1.3. Effect of Fat intake on Leptin levels:** Leptin action occurs through receptors expressed centrally and peripherally; one of its main functions is to be an afferent signal to the central nervous system; on a negative feedback basis, this helps regulate the quantity of adipose tissue, body weight and appetite [13]. These functions suggest that leptin promotes lipid oxidation and reduces the ectopic accumulation of fat, thus enhancing insulin sensitivity. This effect would be mediated by adenosine mono phosphate kinase (AMPK) activation through both a direct effect on skeletal muscle and an indirect effect on the hypothalamic axis in the central nervous system. Leptin, also through AMPK activation, seems to promote triacylglycerol (TAG) depletion and to stimulate lipolysis in skeletal muscle and white adipose tissue [13].

Regulation of leptin secretion by dietary factors and in particular by dietary fat has been investigated [36,37,38,39,40]. Those studies suggested that the mechanism of regulation include pre- and posttranscriptional modulation of leptin by the direct action of fatty acids as well as their indirect action on certain hormones or cytokines [41].

In the case of a reduction in leptin secretion or an enhanced resistance to its action, an increase in food intake would be due to impairment in satiety mechanisms, leading to increases in adiposity. The effect of a lipid-rich diet on leptin levels seems to be dependent on the type of dietary fat, on adipose tissue, and on timed consumption of hyperlipidic chow. Few studies show plasma leptin level reduction as a consequence of a lipid-rich diet in rats or humans. Hyperlipidic diets may lead to hyperphagia, or that they may cause metabolic effects, such as a leptin secretion reduction or a limitation in its action [13]. Another study by Townsend et al. [42] showed that both high-fat and low-fat diets predominant in saturated fat were utilized, and it was verified that animals submitted to the high-fat diet, despite having a reduced energy intake compared with the low fat group, featured higher weight gain, even with increased leptin levels [13]. The 24-hour diurnal leptin concentrations are reduced on a day when three high-fat meals are consumed when compared with high-carbohydrate/low-fat meals, which induce larger postprandial glucose excursions and greater insulin secretion.

**3.1.4. Effect of n-3 PUFA on Leptin levels:** Several studies have demonstrated the ability of dietary n-3 poly unsaturated fatty acids (PUFA) to modulate leptin secretion [43,44]. Eicosapentaenoic acid (EPA) increases glucose utilization, decreases anaerobic metabolism of glucose to lactate and increases glucose oxidation. Moreover, the ability of EPA to increase leptin production was found to be highly correlated with its effects to decrease anaerobic glucose metabolism to lactate [44].

Several in vivo studies in rats and mice have reported that prolonged intake of diets high in n-3 PUFA resulted in significant decreases in plasma leptin, which are likely to be secondary to decreases observed in WAT mass. However, it was also observed that the administration of highly purified EPA (1 g/kg) during 35 days significantly decreased the leptin circulating levels in lean rats fed on a

standard diet, while a significant increase of the adipokine was observed in overweight rats treated with fatty acid. This is in agreement with the study of Peyron-Caso et al. [45], which also described an increase in leptin concentrations in rats fed an n-3 PUFA-enriched diet. In addition, Rossi et al. [46] observed that dietary fish oil positively regulates the plasma leptin levels in sucrose-fed, insulin-resistant rats. Taken together, these data suggest that n-3 PUFA actions on leptin seem to be dependent on diet composition and the physiological and metabolic status of animals, which could be important to take into account when considering supplementation with n-3-enriched products [44].

**3.2. Adiponectin:** is a product of adipocytes and its levels in humans decrease in obese subjects [47,48]. Adipocytes secrete high levels of adiponectin that exert anti-inflammatory effects, most notably in atherosclerotic plaques. These effects occur due to the suppression of tumor necrosis factor-alpha (TNF-alpha) and pro-inflammatory cytokines such as interleukin-6 (IL-6) and interferon- $\gamma$ , along with the induction of other anti-inflammatory factors such as the interleukin-1 (IL-1) receptor antagonist. In contrast, adiponectin levels have been shown to be low in several different forms of insulin resistance. In vivo, adiponectin enhances energy consumption and fatty acid oxidation in the liver and muscle, which leads to a reduction of the tissue triglyceride content, thereby further enhancing insulin sensitivity [49].

**3.2.1. Effect of Carbohydrate intake on Adiponectin levels:** There is a growing body of evidence that adiponectin is involved in the regulation of both lipid and carbohydrate metabolism [50]. Decreased adiponectin levels have been associated with high levels of small dense low density lipoprotein (LDL), apolipoprotein B and triglyceride levels [51]. Adiponectin administration enhances insulin action in animals and low levels of adiponectin have been proposed to contribute to insulin resistance associated with obesity. Administration of adiponectin lowers circulating glucose levels without stimulating insulin secretion in both normal mice and in mouse models of diabetes. Adiponectin may act directly on the liver because adiponectin lowers hepatic glucose production in mice [50].

In one study, adiponectin treatment was reported to induce weight loss without decreasing food intake in mice consuming a high-fat high-sucrose diet—an effect associated with increased muscle fat oxidation and lowered circulating fatty acid concentrations [52]. There is evidence that the insulin-sensitizing effects of adiponectin in muscle, like those of leptin, also involve activation of the AMPK. Therefore, it appears that adiponectin can increase insulin action via direct effects on hepatic glucose production and by reducing ectopic fat deposition in liver and muscle via increases of fat oxidation. Accordingly, low adiponectin concentrations in obese adolescent subjects are associated with increased intramyocellular lipid deposition and impaired insulin action [50].

**3.2.2. Effect of n-3 PUFA on Adiponectin levels:** During the last few years, several studies suggested that the insulin-sensitizing properties of dietary fish oils could be related to the increase in circulating levels of adiponectin both in rodents and human subjects. The study of Flachs et al. [53] observed that feeding mice with a

high-fat diet enriched with EPA/ docosahexaenoic acid (DHA) concentrate (6% EPA, 51% DHA) for 5 weeks leads to elevated systemic concentrations of adiponectin and suggested that this increase could explain, to some extent, the anti-diabetic properties of these n-3 PUFA. Rossi et al. [46] also found that dietary fish oil positively regulates the plasma adiponectin levels in sucrose-fed, insulin-resistant rats. A recent study by Gonzalez-Periz et al. [54] reported increased adipose adiponectin mRNA levels in ob/ob mice receiving a diet enriched with n-3 PUFA for 5 weeks. Moreover, another study demonstrated that the ability of adipocytes to produce adiponectin was significantly increased by the administration of highly purified EPA ethyl ester in both lean and high-fat-induced overweight rats [44].

In another study, involving a 3-month treatment with EPA (1.8 g daily) in human obese subjects has been shown to increase adiponectin secretion. Regarding the mechanisms involved in the stimulatory action of n-3 PUFA on adiponectin, Neschen et al. [55] found that the up-regulation of adiponectin secretion by fish oil in vivo is mediated by a peroxisome proliferator-activated receptor gamma-dependent (PPAR) and PPAR alpha-independent manner in mice epididymal fat. Furthermore, the anti-diabetic efficacy of some insulin sensitizers, such as metformin and glitazones, involves the activation of AMPK. AMPK activation has been shown to stimulate the production of adiponectin by adipocytes. It has been suggested that AMPK activation could be involved in n-3 PUFA-induced improvements on insulin sensitivity. Moreover, two recent trials have described the ability of n-3 PUFA to activate AMPK in vivo. This has led to suggest that AMPK activation could be a potential mechanism underlying the stimulatory effects of n-3 PUFA on adiponectin levels [44].

**3.2.3. Effect of Calcium intakes on Adiponectin levels:** Calcium (Ca)-rich diets have been demonstrated to exert an anti obesity effect that appears to be mediated in part by suppressing circulating 1 $\alpha$ , 25-dihydroxycholecalciferol. Previous data demonstrate that 1 $\alpha$ , 25-dihydroxycholecalciferol favors fatty acid synthesis and inhibits lipolysis via modulation of calcium influx and suppresses uncoupling protein 2 expression via the nuclear vitamin D receptor and thereby decreases adipocyte apoptosis. In addition, 1 $\alpha$ , 25-dihydroxycholecalciferol regulates adipose tissue fat depot location and expansion by promoting glucocorticoid production and release, resulting in a selectively greater effect in visceral than in subcutaneous depots. Oxidative stress also appears to play a role in regulating inflammatory status in adipose tissue. The high-Ca diet has shown significant suppression of inflammatory cytokines and promotion of anti inflammatory cytokines in mice; increasing adiponectin under both eucaloric and hypocaloric conditions [56].

In another study, male transgenic mice were randomly divided into two groups. One group was fed suboptimal calcium diet (0.4% from calcium carbonate) and the other group was fed high calcium diet (1.2% from calcium carbonate). Feeding high-calcium ad libitum for 3 weeks significantly decreased weight and fat gain in mice. Adiponectin expression was similarly elevated in visceral fat of mice on the high-calcium diet vs. mice on the low-calcium diet ( $p < 0.025$ ) [9].

**3.3. Resistin:** Resistin, which is one of the most recently identified adipokines, has been proposed to be an inflammatory marker for atherosclerosis [49]. Resistin, a white adipose tissue-expressed polypeptide has also been linked to energy homeostasis, diet-induced obesity, and insulin resistance [27]. While it has been shown to induce increases in C-reactive protein (CRP) production by the macrophages, resistin appears to have contrasting roles when examined in mice versus humans. This may be due to the fact that resistin appears to be derived from different sources in humans as compared to rodents. This protein was initially shown to be released in large amounts from mouse adipocytes, with obese mice having elevated levels that were accompanied by insulin resistance. However, investigations in humans suggest that resistin is expressed in adipocytes with monocytes and macrophages. This lack of homology between the human and mouse resistin genes suggests a potential divergence in function. Since macrophages are known inflammatory modulators, resistin may be an inflammatory marker in humans [49].

In addition, there have been many recent reports that support a role for resistin in obese rodent models. Resistin has been found to modulate nutritional regulation and may possibly play a role in maintaining fasting blood glucose levels. Further rodent studies have also suggested that resistin mRNA levels are higher in abdominal fat depots, as compared to deposits in the thigh, and that these serum resistin levels are positively correlated with body mass index (BMI). Recent investigations in humans have shown that resistin levels are higher in obese subjects as compared to lean subjects. These higher levels are also positively correlated with changes in the BMI and the visceral fat area [49,57].

Resistin expression is markedly affected by nutritional and metabolic status, with food deprivation leading to a decrease in resistin mRNA expression, whereas circulating resistin is increased in obese insulin resistant rodents and humans [58].

## 4. Conclusion

Low-grade inflammation has been identified as a key factor in the development of metabolic syndrome features affecting obese subjects, leading to type 2 diabetes and cardiovascular disease. In obesity, the expanding adipose tissue makes a substantial contribution to the development of obesity-linked inflammation via dysregulated secretion of pro-inflammatory cytokines, chemokines and adipokines and the reduction of anti-inflammatory adipokines, such as adiponectin. Lifestyle interventions like caloric restriction and increases in physical activity can lead to weight control which induce attenuation of obesity-induced inflammatory responses, that is a risk factor for obesity related chronic diseases, along with decreased fat mass in obesity.

## Conflict of Interest

Authors have no conflict of interest.

## List of Abbreviations

AMPK- adenosine mono phosphate kinase

BCAA- branched chain amino acid  
 BMI- basal metabolic rate  
 CRP- C-reactive protein  
 DHA- docosahexaenoic acid  
 EPA- ecosapentaenoic acid  
 HS- high sucrose  
 IL1- interleukin-1  
 IL-6- interleukin-6  
 LDL- low density lipoprotein  
 LS- low sucrose  
 Ob-R- Leptin receptor  
 PPAR- peroxisome proliferator activated receptor  
 PUFA- polyunsaturated fatty acid  
 TAG- triacylglycerol  
 TG- triglyceride  
 TNF- tumour necrosis factor  
 WAT- white adipose tissue.

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