Immune-Mediated Inflammation as a Driver of Obesity and Comorbid Conditions

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The prevalence of obesity is growing worldwide and has become a major global health challenge. Both overweight and obesity are characterized by the accumulation of excessive levels of body fat, and this creates an increased risk of cardiovascular diseases, some types of cancer, and overall mortality. In particular, abdominal fat, which is metabolically active, is associated with low-grade systemic inflammation and immune activation. Enlarged adipocytes and activated macrophages secrete proinflammatory cytokines, such as interferon-γ, and hormones, such as leptin, which have been shown to favor the cell-mediated Th-1-type immune response. Importantly, it is more the abdominal fat, and not the BMI, that leads to an accelerated production of Th1-type cytokines associated with the

![Figure 1](image.jpg)

**Figure 1** The induction of indoleamine-2, 3-dioxygenase-1 (IDO) by obesity. The process of obesity involves proinflammatory pathways, which include activation of the T-cell–macrophage axis in the framework of the cell-mediated (Th1-type) immune response. Thereby, interferon-gamma (IFN-γ) stimulates the conversion of essential amino acid tryptophan to kynurenine via the immunomodulatory enzyme IDO. The disturbed metabolism of tryptophan might affect the biosynthesis of serotonin and could increase susceptibility to mood disturbances, leading to increased caloric intake and obesity.

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metabolic syndrome (1). An upregulation of indoleamine 2,3-dioxo-
genase-1 activity catalyses the formation of kynurenine and limits
the availability of tryptophan, which has been related to inflamma-
tion and several pathophysiological conditions. 2,3-dioxogenase-1-
mediated tryptophan breakdown may reduce serotonin production
and subsequently cause impaired satiety and symptoms of depres-
ion. Such an emotional state leads many people to eating more,
ultimately contributing to increased caloric intake and obesity
(Figure 1).

Dietary restriction and exercise are useful methods for reducing
abdominal fat mass and concomitantly decreasing proinflammatory
adipokine secretion. Ramallal et al. (2) recently assessed the pro-
spective association of the inflammatory potential of a diet with
weight gain. The findings suggest that a proinflammatory diet (high
in saturated and total fat and low in fiber, vitamin, and flavonoid
values) can be an independent risk factor for developing new-onset
overweight or obesity. However, the role of inflammation induced
by diet on yearly weight change was small in terms of absolute val-
ues. There might be several reasons for this. Using BMI as anthro-
pometric adiposity measure may be limited by its dependence on
muscle mass, which has been linked to an anti-inflammatory state.
The metabolic endocrine system of young adults may be capable of
adapting better to the state of obesity because of the higher propor-
tion of lean mass. On the other hand, abdominal fat is associated
with risk factor levels in young to middle-aged adults, beyond that
of generalized adiposity (indicated by BMI) (3). Furthermore, recent
findings suggest that obesity itself may play an important role in
the pathway through which dietary patterns impact inflammation (4). In
the future, epidemiological studies should include additional
measures, which consider both adiposity (e.g., waist circumference)
and muscularity (e.g., grip strength) in order to elucidate the associ-
ations between diet, inflammation, and obesity.

Alternatively, moderate physical exercise has the power to reduce
systemic low-grade inflammation and thereby affect the metabolism
of serotonin, but it may also shift the hormone milieu toward a
reduction of hunger and thus reduced food intake (5). Assuming that
there is a reciprocal link in mood disorders and obesity, physical
activity could represent a proper strategy for losing or maintaining
weight via both an increase in energy expenditure with the potential
to generate an energy deficit and the induction of an anti-
inflammatory environment with a subsequent increased release of
serotonin. 

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