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REVIEW ARTICLE

Leptin Dysfunction in Sthaulya: An Integrative Pathogenesis

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ABSTRACT
Sthaulya (obesity), classified under Santarpanottha Vyadhi in Ayurveda, is characterized by Medadhatu vriddhi (excessive accumulation of Meda Dhatu), Agnidaurbalya (impaired metabolic fire), and Srotorodha (obstruction of physiological channels). In modern medicine, obesity is closely associated with leptin dysfunction—resulting from resistance at the hypothalamic receptor level despite elevated circulating leptin levels. To examine the integrative pathogenesis of Sthaulya with special reference to leptin resistance, thermogenesis failure, and genetic polymorphisms affecting leptin signalling. A qualitative review was performed using Ayurvedic classical texts and modern scientific literature including studies from endocrinology, molecular signaling, neurobiology, and genomics. Sources include peer-reviewed articles on leptin function, resistance mechanisms, and obesity. Ayurvedic descriptions of Sthaulya reflect pathophysiological patterns consistent with modern observations in obesity, especially leptin signaling failure. Classical Samprapti involving Meda Avarana, Agni Dushti, and Dhatu Kshaya maps well to impaired hypothalamic feedback, mitochondrial dysfunction, and systemic inflammatory burden observed in obese individuals. Additionally, gene polymorphisms such as LEP G2548A and LEPR Q223R contribute to congenital predisposition analogous to Beejadushti. Integrative interpretation of Sthaulya and leptin dysfunction provides a robust, bidirectional model of obesity. It highlights the need for personalized, multidimensional interventions rooted in both Ayurvedic diagnostics and molecular endocrinology.
Keywords: *Sthaulya, Meda Dhatu, Avarana Samprapti, Dhatu Kshaya, Obesity Pathogenesis, Leptin Resistance.*

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INTRODUCTION

Obesity is a global epidemic with multifactorial roots. According to the World Health Organization (WHO), over 650 million adults were obese as of 2016, and the number continues to rise [1]. Obesity is no longer defined solely by caloric surplus but as a complex neuroendocrine disorder involving dysregulated appetite, metabolic inertia, genetic susceptibility, and hormonal resistance—particularly of leptin [2].

Leptin, a 16 kDa peptide hormone primarily secreted by white adipose tissue, is integral to energy homeostasis, appetite regulation, and thermogenesis [3]. In obesity, paradoxically elevated leptin levels are observed—a hallmark of central leptin resistance. The impaired action of leptin on hypothalamic neurons, especially those expressing pro-opiomelanocortin (POMC) and neuropeptide Y (NPY), leads to hyperphagia, decreased energy expenditure, and progressive adiposity [4–6].

Ayurveda refers to obesity as *Sthaulya*, considered a *Santarpanottha Vyadhi* arising from over-nourishment and improper digestion. The pathogenesis involves vitiation of *Kapha*, excessive *Medavriddhi*, and blockade of *Vata* pathways due to *Srotorodha*. Acharya Charaka includes *Sthaulya* under *Ashta Nindita Purusha*, indicating its effect on vitality, longevity, and systemic health [7].

In recent years, attempts to align classical Ayurvedic descriptions with molecular findings such as leptin resistance and thermogenic failure have gained momentum. This paper presents an integrative understanding of *Sthaulya* in the light of leptin biology and associated signaling defects.

AYURVEDIC PATHOGENESIS OF STHAULYA AND ITS MODERN CORRELATION WITH LEPTIN DYSFUNCTION

1. Nidana (Etiological Factors) of Sthaulya [8]

The classical Ayurvedic texts, particularly *Charaka Samhita*, describe *Sthaulya* as a Kapha-dominant condition arising from excessive nourishment (*Atisampūrṇa*), leading to the pathological increase of *Meda* and *Māṃsa* Dhatus. The causative factors (*Nidanas*) include:

Ayurvedic Nidanas:

- *Atisampurana* – Overeating or excessive nourishment
- *Guru, Madhura, Śita, Snigdha Ahara* – Heavy, sweet, cold, unctuous food
- *Avyayama* – Lack of physical exercise
- *Divasvapna* – Daytime sleeping
- *Avyavaya* – Sexual inactivity
- *Harsa, Achintana* – Overindulgence in emotional ease
- *Beeja Svabhava* – Genetic predisposition

These causative factors contribute to *Kapha* and *Meda* aggravation and obstruct *Vata* in its physiological role, initiating *Avarana Samprapti* and *Dhatvagnimandya*, ultimately impairing tissue metabolism and promoting adiposity.

Table 1: Nidana Correlated with Modern Mechanisms

Ayurvedic Nidana	Modern Correlate	Reference
Atisampurna Ahara (Over-nourishment)	Chronic energy surplus, hyperleptinemia	[2,4]
Guru, Madhura, Snigdha Ahara	High-fat, high-sugar diets impair leptin signaling	[5]
Avyayama (Lack of exercise)	Reduced energy expenditure increases fat mass	[6]
Divaswapna (Day sleep)	Circadian disruption affects metabolic rate and leptin secretion	[4]
Achintana, Harsha	Emotional eating, hedonic dysregulation of hypothalamus	[9]
Beejadushti	LEP and LEPR polymorphisms linked to obesity risk	[10–12]

SAMPRAPTI OF STHAULYA (OBESITY) [13]

The progression of Sthaulya in Ayurveda is deeply rooted in the interplay of Meda Dhatu accumulation, Avarana (obstruction) of Vata, and Agni stimulation, forming a vicious metabolic cycle that accelerates degeneration and disease.

1. Srotorodha (Obstruction of Channels by Meda)

- As Meda Dhatu increases, it obstructs Srotas (body channels), particularly those that facilitate the movement of Vata.
- This Avarana leads to the confinement of Vata, especially Samana Vayu, within the Koshtha (abdominal cavity and gastrointestinal tract).

2. Agni Sandhukshana (Overstimulation of Digestive Fire)

- The confined Vata over-stimulates the Jatharagni (digestive fire), leading to:
    - Accelerated digestion
    - Hyper-absorption of nutrients
    - Early return of hunger, even after adequate meals

This causes the person to become a voracious eater, constantly craving food due to excessive Agni and disturbed satiety signaling.

3. Erratic Food Intake and Metabolic Derangement

- The individual consumes meals irregularly and often beyond physiological needs, violating Ahara Vidhi Vidhan (dietary discipline).
- This constant intake further increases Meda, perpetuating the obstruction-agni-hunger cycle.

4. Vata-Agni Aggravation: The Destructive Duo

- In this pathological state, Vata and Agni, which are normally regulatory, become destructive:
    - Agni continues burning improperly, leading to Dhatu Pachana (degradation of body tissues).
    - Vata, when unbalanced, disperses these improperly formed nutrients erratically.

5. Abnormal Meda and Mamsa Accumulation

- With time, Meda and Mamsa Dhatus begin to accumulate excessively, especially in:
  - Stana (breasts)
  - Sphik (buttocks)
  - Udara (abdomen)
- These areas become pendulous, with loss of tone and sluggish metabolism.

These regions reflect Shaithilya (flabbiness), indicating deficient Dhatu metabolism and Kapha dominance.

6. Vitiated Doshas Lead to Rapid Health Deterioration

- As Kapha, Meda, and Vata continue to disturb the internal environment:
  - The individual becomes more prone to grave systemic disorders.
  - The span and quality of life deteriorate rapidly.

LEPTIN AND THE MODERN PATHOGENESIS OF OBESITY

- **Leptin: Definition and Biological Role [14]**

Leptin is a peptide hormone primarily secreted by white adipose tissue and plays a pivotal role in the regulation of energy balance by inhibiting hunger and stimulating energy expenditure. It acts on specific receptors in the hypothalamus, especially the arcuate nucleus, to signal the status of fat stores and maintain body weight homeostasis. The hormone was first identified through the ob (obese) gene, and its discovery was instrumental in shifting the understanding of adipose tissue from a passive fat store to an active endocrine organ.

- **Obesity and Energy Dysregulation:**

Energy Imbalance:

Obesity results from a chronic imbalance between caloric intake and energy expenditure, resulting in progressive fat accumulation within adipocytes [15].

Adipocyte Hypertrophy and Hyperplasia:

Persistent overnutrition causes both hypertrophy (increase in size) and hyperplasia (increase in number) of adipocytes. This leads to adipose tissue stress, local hypoxia, and low-grade chronic inflammation [16].

Leptin Secretion by Adipose Tissue:

As adipose mass increases, leptin secretion proportionally rises. Leptin serves as a peripheral satiety signal to the hypothalamus, suppressing appetite and enhancing energy expenditure under normal conditions [14].

Leptin Resistance: Core Pathophysiological Event in Obesity:

Despite elevated leptin levels in obese individuals, the hypothalamus fails to respond, a condition known as leptin resistance [17]. This leads to unchecked appetite and reduced energy expenditure. Contributing mechanisms include:

- Impaired transport of leptin across the blood-brain barrier
- Downregulation or mutation of leptin receptors (Ob-Rb)
- Post-receptor signaling defects in the JAK2-STAT3 pathway
- Increased expression of SOCS3 and ER stress, which attenuate receptor signaling [18,19]

Hypothalamic Dysregulation of Appetite:

Leptin resistance alters hypothalamic neural circuits by:

- Upregulating orexigenic (appetite-stimulating) neurons: NPY, AgRP
- Downregulating anorexigenic (appetite-suppressing) neurons: POMC, CART

This imbalance leads to hyperphagia (excessive eating) and reduced satiety [3].

Impaired Thermogenesis and Reduced Energy Expenditure:

Leptin also stimulates the sympathetic nervous system (SNS) and brown adipose tissue (BAT) to promote thermogenesis. In leptin resistance, this process is impaired, resulting in decreased caloric burn and fat oxidation [20].

Adipose Tissue Inflammation:

Hypertrophic adipocytes secrete pro-inflammatory cytokines (e.g., TNF-α, IL-6, MCP-1), attracting macrophages and initiating adipose tissue inflammation. These cytokines further disrupt leptin signaling and promote insulin resistance [21].

Insulin Resistance and Metabolic Syndrome

Leptin dysfunction is strongly associated with the development of insulin resistance, type 2 diabetes mellitus, dyslipidemia, and hypertension, forming the clinical entity of metabolic syndrome [22].

Genetic and Epigenetic Factors

Mutations in the LEP (leptin gene) and LEPR (leptin receptor gene) can lead to congenital leptin deficiency, resulting in early-onset severe obesity [23]. Additionally, epigenetic modifications due to diet and environmental exposures can alter leptin expression and receptor sensitivity [24].

Vicious Cycle of Obesity Progression

As adiposity increases, leptin levels rise further, but resistance persists. The resulting feedback failure leads to:

- Increased food intake
- Decreased physical activity
- Further fat accumulation

Thus, a self-perpetuating cycle of obesity is established [25].

Table 2: Ayurvedic vs. Modern Pathogenesis of Obesity

Aspect	Ayurvedic View	Modern Correlation	Reference(s)
Initiation	Meda Vriddhi → Srotorodha → Vata Avarana	Energy imbalance → Adipocyte expansion	[13],[15]
Appetite	Vata stimulates Agni → Hyperdigestion, frequent hunger	Leptin resistance → Satiety failure, hyperphagia	[13],[17]
Metabolism	Ama formation, ↓ Dhatvagni → Dhatu Poshana Vaighunya	↓ Thermogenesis, ↓ fat oxidation	[14],[20]
Dhatu Kshaya	Asthi, Majja, Shukra undernourished due to Meda Avarana	Osteopenia, neuroinflammation, infertility	[3],[18],[25]
Structural Signs	Flabbiness in Sphik, Stana, Udara	Visceral obesity, sarcopenia	[13],[16]
Progression	Vitiated Doshas → systemic deterioration	Inflammation, insulin resistance, metabolic syndrome	[13][22]
Genetics	Beeja Dosha (congenital tendency)	LEP/LEPR mutations, epigenetic leptin signaling impairment	[23],[24]
Cycle	Meda↑ → Agni↑ → Ahara↑ → More Meda	Leptin↑ → Resistance↑ → Appetite↑ → Fat gain↑	[13], [25]

Dhatu Kshaya in Obesity Due to Meda Vriddhi: An Integrative Perspective

In the Ayurvedic framework, Meda Dhatu is one of the seven fundamental tissues, responsible for lubrication, strength, and energy storage. In Sthaulya (obesity), there is Meda Vriddhi—a pathological increase in adipose tissue—often accompanied by impaired Dhatvagni (tissue metabolism) and Srotorodha (channel obstruction). This disrupts the proper flow of nutrition to successive Dhatus, resulting in Dhatu Poshana Vaighunya and eventual Dhatu Kshaya (tissue depletion) [8].

Table 3: Dhatu Kshaya in Obesity – Ayurvedic and Modern Correlation

Dhatu	Affected Organ/System	Mechanism in Obesity	Clinical Manifestation	Reference
Asthi	Bone	Leptin resistance reduces osteoblast activity and increases inflammatory cytokines, impairing bone remodeling	Osteopenia, joint pain, weak bones	[26]
Majja	Bone marrow, CNS	Marrow adiposity, neuroinflammation, impaired leptin-mediated neurogenesis and hematopoiesis in obesity	Fatigue, reduced cognition, anemia	[18]
Shukra	Reproductive system	Disruption of the hypothalamic-pituitary-gonadal axis due to leptin resistance impairs reproductive hormone regulation	Infertility, menstrual dysfunction	[25]

DISCUSSION

The present review highlights a profound overlap between the Ayurvedic understanding of Sthaulya (obesity) and modern pathophysiological concepts surrounding leptin dysfunction. In Ayurveda, Sthaulya

is described as a Santarpanottha Vyadhi, predominantly involving Kapha Dosha, Meda Dhatu Vriddhi, and Avarana of Vata, culminating in Agni Dushti, Srotorodha, and eventual Dhatu Kshaya [13].

From a modern lens, obesity is increasingly recognized as a neuroendocrine disorder driven by leptin resistance, chronic inflammation, and metabolic inertia rather than mere overnutrition [2,4]. Despite elevated leptin levels in obese individuals, impaired hypothalamic leptin signaling—particularly in the arcuate nucleus—leads to persistent hunger (hyperphagia), decreased sympathetic activation, and thermogenesis failure [14,17,20]. This aligns with Ayurvedic descriptions where Samana Vayu, obstructed by Meda, overstimulates Jatharagni, resulting in increased appetite and erratic eating behavior [13].

Leptin resistance further initiates a vicious metabolic cycle, resembling the Ayurvedic Sthaulya Samprapti: Meda obstructs channels (Srotorodha), disrupts Vata (Avarana), impairs tissue metabolism (Dhatvagni Mandya), and causes Dhatu Kshaya of Asthi, Majja, and Shukra [8,13,18]. Modern studies support that obesity is associated with osteopenia, marrow adiposity, and hypogonadism, resulting from disrupted leptin-mediated signaling in osteoblasts, neuronal circuits, and the hypothalamic-pituitary-gonadal axis [18,25,26].

Moreover, genetic polymorphisms such as LEP G2548A and LEPR Q223R are linked with congenital leptin resistance and early-onset obesity [10,11,23]. These mirror the Ayurvedic concept of Beejadushti (genetic predisposition), one of the key Nidanas for Medoroga [8].

Environmental and lifestyle factors such as Divaswapna, Avyayama, and Ahara Atipravrtti also find clear parallels with circadian rhythm disruption, sedentary behavior, and high-fat diets shown to impair leptin signaling and promote weight gain [4,5,6].

Collectively, the classical model of Sthaulya offers a multi-dimensional pathogenic map that encompasses digestive dysfunction, metabolic blockage, and tissue-level degeneration—well mirrored in leptin dysfunction, adipocyte biology, and endocrine disruption observed in modern obesity.

CONCLUSION

The integration of Ayurvedic and modern paradigms uncovers strong pathophysiological convergence in the understanding of Sthaulya and leptin dysfunction. Ayurvedic concepts such as Avarana, Agnidushti, and Dhatu Kshaya map onto critical modern mechanisms including leptin resistance, hypothalamic deregulation, and genetic susceptibility [13,14,25].

Understanding obesity as a multi-systemic, chronic metabolic disease rather than a simplistic result of overfeeding is vital. Ayurveda's emphasis on personalized dietary practices, Agni preservation, and Dosha balance, complemented by modern insights into adipokine signaling and gene-environment interactions, enables a truly integrative model for prevention and treatment.

Future research should explore clinical interventions combining Ayurvedic diagnostics (e.g., Prakriti analysis, Doshic profiling) with biomarker-based assessments (e.g., leptin levels, LEPR genotyping) to develop personalized obesity therapeutics. This cross-disciplinary approach holds potential for evidence-based integrative care targeting both the root (Moola) and manifestations (Vyadhi Lakshana) of obesity.

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