

The Ominous Octet of Obesity: A framework for obesity pathophysiology

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Abstract

The pathogenesis of obesity is complex and is beyond the simple equation of excess calorie intake and inadequate calorie expenditure. It involves the role of multiple organ systems and these complex interactions are often challenging to address in a busy clinical practice. We propose a simplified framework akin to the ominous octet of diabetes, to help understand the role of these different organ systems in relation to obesity. The Ominous Octet of obesity includes the hypothalamus, islet cells of Langerhans, gastrointestinal tract, adipose tissue, adrenal gland, gonads, thyroid gland and the muscle. This framework would also help to understand the use of different therapeutic targets in patients with obesity and improve the care of these patients.

Keywords: Appetite suppressants, barocrinology, GLP1RA, obesity, overweight, person centered medicine

Introduction

The Ominous Octet proposed by de Fronzo, has created a framework for diabetes pathophysiology which has stood the test of time.¹ This model has helped rationalize our understanding of etiopathogenesis, development of pharmaceutical interventions, use of surrogate markers for diagnosis and monitoring, and most importantly to guide the choice of glucose-lowering therapy. We propose a similar Ominous octet for obesity.

Spectrum of Obesity

Obesity is a complex syndrome with multiple etiopathologic mechanisms.² Conventionally, the condition has been studied from a bipolar perspective: genetics and environment.³ Contemporary opinion supports a wider prism of causative and promotive factors, which are included in the portmanteau term 'barocrinology'.⁴ Barocrinology is the study of hormonal and metabolic factors which influence obesity pathogenesis, clinical manifestations, natural history, and management.

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Ominous Octet of Obesity

The Ominous Octet of obesity is an organ-system based rubric, which helps in identification of various sites of dysfunction in a person living with obesity. These glands or organs can be impacted by genetic or environmental factors, or a combination of them. The Octet, however, makes it easy for the treating physician to assess the predominant contributors to a particular individual's barophenotype. This, in turn, facilitates appropriate choice of investigations, accurate counseling regarding realistic outcomes, adept use of available therapeutic options, and acceptance of the expected course or natural history of the syndrome.

The Ominous Octet of Obesity (Figure) lists the hypothalamus, islets of Langerhans, the gut and adipose tissue as four major contributors to weight dysregulation or obesity.⁴ Three more glands, the thyroid, adrenal and reproductive glands (ovaries and testes) are listed as they are associated with specific syndromes of obesity. The skeletal muscle is listed as the eighth angle of the octet, as muscle dysfunction is associated with obesity (sarcopenic obesity) and with poor response to anti-obesity interventions.

Limitations

We are mindful of the fact that there are many other organ-systems which have a rightful claim to joining the Ominous octet. The liver, for example, is a site of insulin resistance,

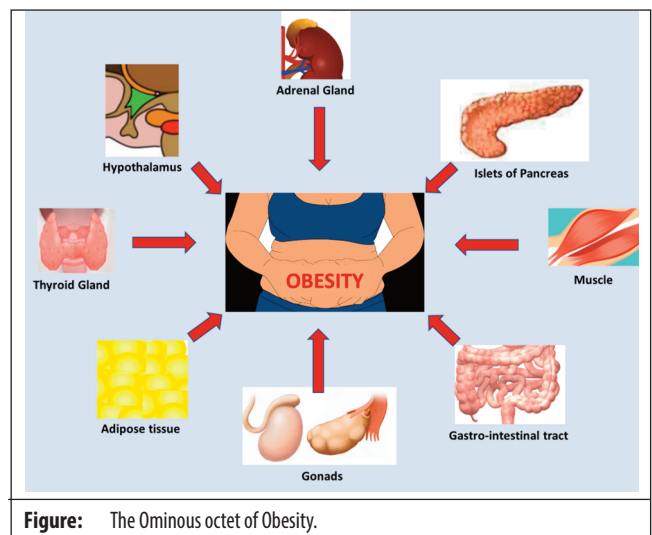


Figure: The Ominous octet of Obesity.

Table-1: The Ominous Octet of Obesity.

Site	Hormone	Examples	Preferred Intervention Along with Diet and Exercise
The Four Central Components			
Hypothalamus	Anorexic and orexic peptides	Syndromic obesity	Behavioural therapy; appetite suppressants. Setmelanotide (MC4R agonist)
Adipose tissue	Adipokines, including leptin	Leptin resistance	GLP1RA
Gut	GUT hormones Incretin hormones Hormones released by GUT Microbiota	Incretin deficiency/resistance	GLP1RA; orlistat
Islets of Langerhans	Insulin, and its impact on insulin receptors	Insulin resistance	Insulin sensitizers
The Four Peripheral Components			
Thyroid	Thyroid hormones	Hypothyroidism	Thyroid replacement
Adrenal	Cortisol	Cushing's syndrome	Etiology-specific management
Gonads	Testosterone excess in women; deficiency in men	Polycystic ovary syndrome; hypogonadism	Androgen optimization
Skeletal muscle	Myokines eg: Irisin	Sarcopenic obesity	Resistance exercise; Insulin sensitizers

and is actively involved in weight homeostasis. However, this has been included as part of the islets of Langerhans and adipose tissue in our model, as predominant link with obesity through ectopic fat deposition and consequent insulin resistance.⁵ The adipose tissue and skeletal muscle influence weight through multiple ways, of which insulin resistance/sensitivity is just one mechanism. Hence, their inclusion as separate "corners" of the octet is justified.

Clinical Utility of the Ominous Octet

Table lists the components of the Ominous Octet of obesity, along with common mechanisms of action and suggested interventions. This classification is a basic structure which can evolve further with time. Newer advances in pathophysiology, biochemistry and pharmacology will help further expand the Ominous Octet. Till then this rubric will certainly facilitate conversations between people living with obesity and their health care providers. The listing of organs and glands, done in a non-

judgmental or non-hierarchical manner, ensures that all aspects of potential pathology are given equal importance. It reinforces the fact that all eight corners must be optimized to create an Octet of Optimal Weight. While intensive behavioural therapy with diet and physical activity, will always remain the foundation of obesity management, our model explores ways of identifying person-centered choices of treatment.⁶

Conclusion

In conclusion, the 'Ominous octet' framework for obesity, provides a simple yet a comprehensive layout of understanding the pathogenesis of obesity. It emphasizes the role played by different organ systems in a person living with obesity. This will not only help the treating physicians in understanding and addressing the different players but would also help to provide a patient centric approach in the management of obesity. This framework would also help to understand the use of different therapeutic targets in patients with obesity and improve the care of these patients.

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