The etiopathogenesis and management of obesity: The quintessential quincunx

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Abstract

This communication uses the quincunx, i.e, a quadruple surrounding a central point, to create a model that describes the etiopathogenesis, as well as informs the management strategy of obesity.

With the energy fulcrum (mismatch between energy intake and expenditure) at its centre, the model lists two external influencers-the physical environment and psychosocial environment, and two internal influencers-the hypothalamo-bariatric axis and the endocrine system, to explain the etiopathogenesis of obesity. Genetics factors are included with the hypothalamo-bariatric axis. The same model can be used to explain the five pillars of management: lifestyle and nutritional modification at the centre, along with environmental optimization, behavioural therapy, baro-thalamic modulation, and endocrine optimization

Keywords: Anti-obesity medication, bariatric medicine, bariatric surgery, barocrinology, obesity, person-centred care, semaglutide, tirzepatide.

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Introduction

Obesity is a complex disorder. Initially thought to be a mismatch between energy intake and energy expenditure, it is now understood that there are multiple facets of its etio-pathophysiology.[1] While the basic cause does remain energy imbalance, both genetic and acquired factors contribute to this.

Various authors have proposed models to understand the syndrome of obesity. Some models focus on diet alone: the caloric excess/model and carbohydrate insulin model propose that overconsumption of calories and carbohydrates, respectively, lead to obesity.[2] The classic energy intake-expenditure fulcrum balances food intake and absorption against resting energy expenditure, food-induced thermogenesis, non exercise activity thermogenesis and exercise.[3] The Ominous Octet of obesity lists and describes four central and four peripheral endocrine players in the development of obesity. These include the hypothalamus, gut, adipose tissue and islets of Langerhans (central), as well as thyroid, adrenals, gonads and muscle (peripheral).[4] Broader rubrics include the role of environmental triggers, such as urbanization, in the causation of obesity.[5]

The need for a comprehensive model

None of these models, however, are able to encapsulate the entire spectrum of obesogenic factors in an easily understandable, reader-friendly format. Not only this, the current models are not concordant with available therapeutic interventions.[6] We propose a quincunx to drive the quintessential debate regarding etiology of obesity towards a logical conclusion, and create synergy with the therapy of obesity as well. A similar model has been used to structure health care delivery in a person-centred manner.[7] Thus, a single format can be used to understand obesity as well as its treatment. We term our proposal a quincunx, because it looks like one (a quadrangle surrounding a central point), and quintessential, because we hope it will provide a comprehensive overview of obesity evaluation and management for the foreseeable future.

The quintessential quincunx

At the centre of the quincunx is the classical energy fulcrum. We enlist gut microbiota[8] as part of the factors influencing energy intake, along with calorie intake and absorption.(Figure 1)

The four angles of the quincunx are taken up by two external and two internal influencers. The four influencers impact the energy fulcrum independent of each other. At the same time, they are influenced by each other as well. These multidirectional influences are visible in the diagram.

The two external influencers include the physical and psycho-social environment, each of which has multiple

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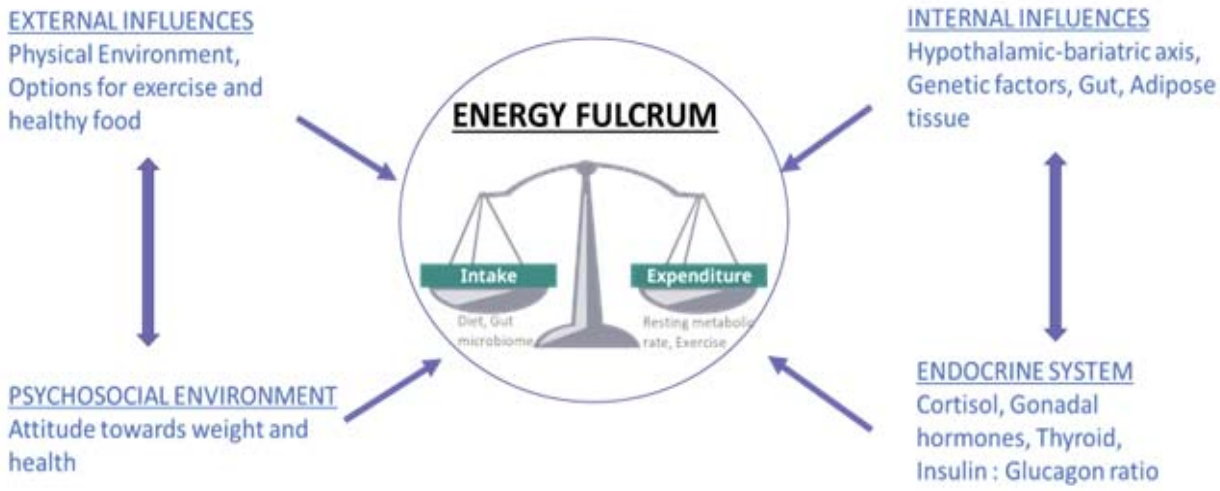

Figure-1: : 1-Aetiopathogenesis of obesity; the quintessential quincunx.

facets and aspects. These have been discussed at length elsewhere.

We choose to term the first internal influencer as the "baro-thalamic" or "hypothalamo-bariatric" axis, which incorporates not only the hypothalamus and adipose tissue, but the gut (including incretin system) as well. The last angle of the quincunx is occupied by endocrine factors, including cortisol, gonadal hormones, insulin, glucagon and thyroid hormones. The impact of these internal influences' is reviewed in the Ominous Octet of obesity. Genetic factors are listed as part of the hypothalamo-bariatric axis, because the maximum number of single nucleotide polymorphisms and monogenic syndromes associated with obesity are co-expressed in the nervous system.[9]

Concordance with management

The quintessential quincunx is a perfect rubric and aid in deciding choice of anti-obesity therapy.(Figure 2) While increased exercise or thermogenesis, and reduced dietary intake are of basic management of all obesity, the model

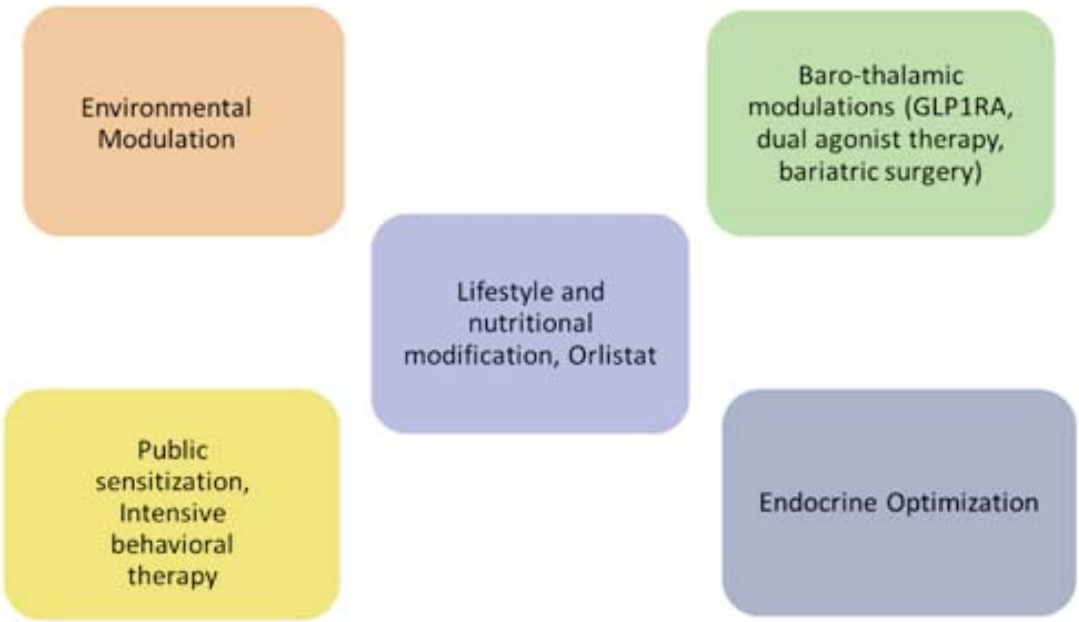

Figure-2: : The management of obesity; the quintessential quincunx

that we use helps prioritize other interventions. Environmental modulation and public sensitization to correct the external environment, and intensive behaviour therapy to combat psychological issues, are important, yet neglected aspects of treatment.

Management will neither be complete, nor effective, if baro-thalamic modulators (GLP1RA such as liraglutide, semaglutide, dual peptide agonists like tirzepatide are not prescribed. At the same time, endocrine optimization is necessary to ensure optimal results of weight management.

The way ahead

The strategic plan that emerges from our discussion is a comprehensive, yet simple, description of modern weight management. Life style and nutritional optimization remains the core, along with the equally important aspects of environmental modulation, behavioural therapy, baro-thalamic modulation, and endocrine optimization This tool is not only person-centric in its approach, but user-friendly as well. It allows the health care professionals to assess and evaluate the relative impact of each causative factor, and plan treatment in an appropriate manner. It also views anti-obesity medication such as orlistat, liraglutide, semaglutide and tirzepatide in a rational manner, reminding the prescriber that other aspects of management are equally important. The same holds true for bariatric surgery.

There may be criticism that the quincunx is over-simplified, and we accept this with humility. However, this model does contribute to the evolution of bariatric science and medicine. We hope that this rubric will prove beneficial for health care professionals managing obesity, and through them, for all persons living with obesity

References

1. Kalra S, Kapoor N, Bhattacharya S, Aydin H, Coetzee A. Barocrinology: The Endocrinology of Obesity from Bench to Bedside. Med Sci (Basel). 2020;8:51. doi: 10.3390/medsci8040051. PMID: 33371340; PMCID: PMC7768467.
2. Hall KD, Farooqi IS, Friedman JM, Klein S, Loos RJF, Mangelsdorf DJ, O'Rahilly S, Ravussin E, Redman LM, Ryan DH, Speakman JR, Tobias DK. The energy balance model of obesity: beyond calories in, calories out. Am J Clin Nutr. 2022;115:1243-1254. doi: 10.1093/ajcn/nqac031. PMID: 35134825; PMCID: PMC9071483.
3. Kalra S, Das S, Kota S, Anne B, Kumar A, Punyani H, Joshi A, Unnikrishnan AG, Bhattacharya S, Kapoor N. Barophenotypic Characterization - The key to Person Centric Management of Obesity. Indian J Endocrinol Metab. 2021;25:295-298. doi: 10.4103/ijem.ijem_285_21. Epub 2021 Dec 15. PMID: 35136735; PMCID: PMC8793949.
4. Kalra S, Arora S, Kapoor N. The Ominous Octet of Obesity: A framework for obesity pathophysiology. J Pak Med Assoc. 2021;71:2475-2476. PMID: 34974599.
5. Kalra S, Kapoor N. Environmental Endocrinology: An Expanding Horizon. 2021 Mar 14. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 33734659.
6. Kalra S, Arora S, Kapoor N. Person-centered choice of anti-obesity pharmacotherapy. J Pak Med Assoc. 2022;72:1449-1450. doi: 10.47391/JPMA.22-80. PMID: 36156581.
7. Kalra S, Kapoor N, Kota S, Das S. Person-centred Obesity Care - Techniques, Thresholds, Tools and Targets. Eur Endocrinol. 2020;16:11-13. doi: 10.17925/EE.2020.16.1.11. Epub 2020 Feb 4. PMID: 32595763; PMCID: PMC7308102.
8. Gomes AC, Hoffmann C, Mota JF. The human gut microbiota: Metabolism and perspective in obesity. Gut Microbes. 2018;9:308-325. doi: 10.1080/19490976.2018.1465157. Epub 2018 May 24. PMID: 29667480; PMCID: PMC6219651.
9. Kapoor N, Chapla A, Furler J, Paul TV, Harrap S, Oldenburg B, Thomas N. Genetics of obesity in consanguineous populations - A road map to provide novel insights in the molecular basis and management of obesity. EBioMedicine. 2019;40:33-34. doi: 10.1016/j.ebiom.2019.01.004. Epub 2019 Jan 10. PMID: 30638866; PMCID: PMC6412867.