Refractory and Resistant obesity: Dynamic Concepts, Contemporary Definitions

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Abstract

Obesity is a chronic disease requiring a multi-disciplinary approach for its management. Despite multiple evolving and potent therapeutic options like GLP-1RA's and bariatric surgery, some patients do not achieve significant weight loss or expected metabolic outcomes. This manuscript highlights the concept of resistant and refractory obesity and provides an operational framework to assess adequacy of therapy, to rule out non-adherence, and to screen for non-adiposity related and iatrogenic causes of weight gain. This would help clinicians to assess clinical outcomes and plan management protocols in their clinical practice. Furthermore, a clear understanding of these concepts would streamline research in this area and facilitate policy making.

Keywords: Refractory obesity, resistant obesity, person centered obesity care, obesity management.

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Introduction

The dictionary uses the term 'resistant' and 'refractory' in similar ways. Refractory is an adjective which implies intractability or difficulty in management, and resistance to a particular process or stimulus.[1] The adjective resistant suggests opposition to change[2], and may be taken as a relatively less severe or extreme state of refractoriness.

Current Definitions

These adjectives have been used in metabolic medicine, and in endocrinology, to describe difficult-to treat, or unmanageable disorders.

Resistant hypertension, for example, is defined as uncontrolled blood pressure despite the use of ≥ 3 antihypertensive agents of different classes, at maximal or maximally tolerated doses. Hypertension is termed refractory if it is not controlled in spite of using ≥5 antihypertensive agents of different classes, at maximal or maximally tolerated doses.[3] A similar threshold of therapeutic intensity is used to define refractory congestive heart failure (CHF). Refractory CHF refers to persistence of symptoms of CHF at rest, or repeated exacerbation of CHF, despite "optimal" triple- drug therapy.[4]

The phrase 'refractory diabetes' has been used to describe a distinct subgroup of patients who are unable to achieve[5] glycaemic targets despite best possible intensive therapy. One of the earliest uses of 'refractory' and 'diabetes' in a title of a medical article dates to 1927, when Glassberg et al shared a case report of a person not responding to insulin.[6] Recently, a pharmacotherapy-oriented definition of refractoriness has been proposed in diabetes. The concept of oral antidiabetic (OAD) failure refers to a clinical situation where glycated haemoglobin remains above goal, despite concurrent use of three glucose lowering drugs of different classes.[7]

In all the disease states discussed above, viz, hypertension, heart failure and diabetes, the classes of drugs are specified clearly. In disease states such as hypothyroidism, where there is a single therapeutic agent, refractoriness is defined as biochemical, construct, with inability to achieve normal TSH levels despite increasing dosages of oral thyroxine beyond 2.5µg/kg/day.[8,9]

Refractory Obesity: Conventional Understanding

Obesity is a chronic metabolic condition, which is accepted as a disease in itself.[10] In spite of various non-pharmacological, drug-based, invasive and surgical methods of treatment, obesity still remains a clinical challenge.[11] It makes sense, therefore, to conceptualize and define resistant and refractory obesity, based upon contemporary understanding of the syndrome and its therapy.

A PubMed search reveals only 35 articles with the term 'refractory obesity' embedded in the title. Duncan et al (1960) were the first authors to use this term, in their controlled double-blind trial of phenmetrazine and methylcellulose in persons whose "obesity had proved refractory to routine dietetic advice".[12] Refractoriness was defined as failure to lose weight in the preceding three

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Figure: Algorithmic approach for assessing resistant and refractory obesity

months, despite being on a 1100-1600 calorie diet. While the caloric intake/kg body weight was not mentioned, the mean weight of their subjects (three group) was 184.3±16.0, 187.1±19.7 and 185.9±17.4 lbs.

The next few years witnessed publication of original articles and a few letters to the editor in response to these articles, using the title 'refractory obesity'. No effort was made to redefine the term, despite availability (and later withdrawal) of various pharmacotherapeutic options. In recent years, the term 'refractory obesity' has been used to define inclusion criteria for surgical means of management, or to characterized persons with 'severe' obesity due to comorbid conditions such as attention deficit hyperactivity disorder (ADHD).

Dynamic Concepts

The success of obesity management is conventionally measured by the percentage of weight reduction. Three thresholds: ≥5%, ≥10%, and >15% reduction of body weight, maintained over a particular period of time, are used to define treatment efficacy. A definition of resistant

or refractory obesity, therefore, should use inability to achieve the lowest threshold (5% weight loss) as a sign of therapeutic inadequacy.

At times, weight loss in an obese person may be due to unwanted metabolic, endocrine, medical or surgical disease. Examples include uncontrolled hyperthyroidism, diabetes mellitus, renal impairment, malignancy or gastrointestinal disease. Such a situation should be excluded from the definition of response to treatment. At the same time, conditions such as oedema and ascites may occur due to congestive heart failure, liver disease, renal disease, or uncontrolled hypothyroidism. These should be ruled out prior to labeling obesity as resistant or refractory.

It is well known that obesity is a multifactorial syndrome, which requires multifaceted interventions. Hence, obesity resistance or refractoriness must take into account the use of multiple treatment options.

Even within classes of treatment, newer options are emerging. Medical nutrition therapy, for example, can be administered in different ways, and newer glucagon-like peptide 1 receptor agonists are (GLP1RA) being developed. Dual agonists, too, are being studied for their use in obesity. Therefore, resistance or refractoriness to a particular drug preparation may not necessarily mean non-response to the entire class of drugs.

GLP1-RA as primary therapeutic options

The choice of GLP1RA as a primary pharmacotherapy (alluded to in the proposed definitions that follow) is based on the efficacy and cardiovascular benefits of this class of drugs. GLP1RA compare favourably with other classes of weight-reducing drugs (appetite suppressants and fat absorption inhibitors) in terms of efficacy, safety and tolerability. Liraglutide is approved in a daily dose of 3.0 mg for obesity management, but is also used, in lower doses, for diabetes. It has also been shown to confer cardiovascular benefits in persons with type 2 diabetes. Data points to its utility in associated metabolic conditions such as nonalcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). Semaglutide is another GLP1RA that is approved for use in type 2 diabetes, and is being studied, in higher doses, for obesity management. While daily oral doses of 7mg and 14mg, as well as weekly subcutaneous doses of up to 1mg are indicated in type 2 diabetes, a weekly subcutaneous dose of 2-4 mg is being evaluated in obesity.

Coformulations including GLP1RA are being developed as anti-obesity agents. These include a novel combination of GLP1RA and amylin agonist. Another dual agonist is tirzepatide, which is a GLP1 and glucose-dependent insulinotropic polypeptide (GLP) agonist.

Contemporary Definitions

Keeping the afore mentioned points in mind, we suggest the following definitions: Resistant obesity is defined as inability to achieve and maintain ≥ 5% weight loss in a person with obesity over 3 months, despite the use of ≥ 3 treatment modalities, at maximal or maximally tolerated intensity, while ensuring that treatable comorbid conditions, and concomitant drug treatments, contributing to weight gain have been excluded. The three treatment modalities must include intensive behavioural therapy (IBT), medical nutrition therapy (MNT), and the most effective GLP1RA that is available in the health care setup. In case a GLP1RA is not available or accessible in a particular country, the label of resistant obesity can be used if IBT, MNT and at least one pharmacological anti-obesity drug (orlistat, phentermine-topiramate, naltrexone-bupropion) have proved inadequate in lowering body weight by ≥ 5% over a period of 6 months. Pseudo-resistance must be ruled out prior to diagnosing resistant obesity. Inadequate adherence to suggested diet, physical activity and drug therapy, improper timing and technique of drug administration (e.g., injection technique of liraglutide/ semaglutide, or meal-medication gap with orlistat), and fluid retention due to diseases such as congestive heart failure, renal impairment, hepatic impairment or hypothyroidism, should be ruled out. Inappropriate use of drugs known to increase weight, such as glucocorticoids pioglitazone and high dose insulin therapy, should also be excluded.

Refractory obesity is defined as inability to achieve and maintain ≥ 5% weight loss in a person with obesity, over a period of 6 months despite the use of ≥ 5 treatment modalities, at maximal or maximally tolerated intensity, ensuring that treatable comorbid conditions and concomitant drug treatments contributing to weight gain have been excluded. The five treatment modalities must include IBT, MNT, and GLP1RA, as well as a trial of very low-calorie diet (VLCD) or low-calorie diet (LCD), and one more pharmacotherapeutic agent (orlistat, phentermine-topiramate, naltrexone- bupropion). In health care settings where multiple anti-obesity drugs are not available, the following operational definition can be used: Refractory diabetes is defined as inability to achieve and maintain ≥ 5% weight loss in a person with obesity despite the use of all available behavioral, lifestyle and pharmacological therapies, at maximal or maximally tolerated intensity, ensuring that treatable comorbid

conditions and concomitant drug treatments contributing to weight gain have been excluded.

The definitions of resistant and refractory obesity provide an operational framework to assess adequacy of therapy, to rule out non-adherence, and to screen for non-adiposity related and iatrogenic causes of weight gain. Hence, they help improve clinical bariatric practice. The definitions facilitate adults and analysis of outcomes, and can serve as benchmarks for health economics, health systems management, and clinical research. They bring into perspective a novel way of screening persons with obesity for intensification of therapy, and add objectivity to a rapidly growing (and challenging) field of medicine

Summary

Therapy of obesity is a dynamic area, with newer pharmacological interventions being developed and assessed. The operational definitions suggested, for resistant and refractory obesity, should be able to help plan management protocols and streamline research and policy making. These definitions incorporate expected developments in the field of obesity pharmacotherapeutics and should be able to stand the test time.

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