

The Insulin: Glucagon Ratio and Obesity

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Abstract

This communication discusses the physiology and pathology of the insulin glucagon ratio, with respect to obesity. Though high insulin levels are associated with obesity in this manuscript the authors specifically highlight its role in the causation and clinical management of obesity. It suggests that the term insulin glucagon ratio be used in preference to glucagon insulin ratio, and shares insights which may be helpful in informing future research.

Keywords: Diabetes, overweight, obesity, metabolic fulcrum, metabolic seesaw, ominous octet of obesity

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Introduction

The Ominous Octet of Obesity is a useful construct which highlights not only the various etio-patho-physiological but also clinical aspects of weight gain and obesity.¹ One of the drivers for obesity is insulin resistance, and the resultant hyperinsulinaemia. This finds expression in the syndrome of diabetes, which is characterized by the co-occurrence of both type 2 diabetes and obesity. Our appreciation of its significance is reflected in calls to overcome the Kg-A1c paradox², and aim for comprehensive glucobariatric, or baro glycaemic control while managing type 2 diabetes.³

Insulin and Glucagon: The Metabolic See-Saw

Most discussion on insulin sufficiency, and on insulin sensitivity or resistance, tends to be limited to a uni-hormonal or polar prism. Insulin is viewed as a hormone that works alone, and the beta cell, as an endocrine gland that exists in isolation. Earlier publications have pointed this out, and have called for a broader focus on the insulin glucagon ratio (IGR).⁴ Such as approach acknowledges

and appreciates the structural juxtaposition, as well as the functional interplay, between the alpha and beta cells, both of which are part of the islets of Langerhans.

Insulin and glucagon are two ends of a metabolic see-saw, and the IGR represents a metabolic fulcrum⁵ which decides the stability of metabolic homeostasis. Insulin is an anabolic hormone, which promotes formation of glycogen and triglycerides, thus promoting storage of energy in adipose tissue on the other hand, glycogen is a catabolic hormone which facilitates breakdown of glycogen to glucose, and of triglycerides to free fatty acids.

Insulin Glucagon Ratio and Diabetes

The IGR has been used as a tool to help characterize diabetes, and inform choice of glucose-lowering therapy.⁴ Varying clinical repercussions of the same IGR have also been conceptualized as part of the Islet cell distress hypothesis,⁶ which explains the mechanism of action of incretin-based therapy upon the islets of Langerhans.

Insulin Glucagon Ratio and Obesity

There is relatively less literature, however, on the relevance of IGR to the pathogenesis and management of obesity. It is noteworthy that recent authors use the term 'glucagon insulin ratio' (GIR)⁷. We suggest however, that IGR continue to be used, partly because insulin is an anabolic hormone (and was discovered first), and also because the acronym GIR may be confused with glucose infusion rate, as used in clamp studies.

Both animal and human studies have been done to explore the IGR in obesity, with and without dysglycaemia.^{8,9} A high IGR is associated with insulin resistance, and also with insulin sufficiency and beta cell function. Alpha cell resistance can occur in type 2 diabetes, and can prevent insulin-induced suppression of glucagon. Obesity has been shown to dysregulate fasting-induced changes in insulin glucagon ratio. While insulin levels fall equally in lean and obese mice, after fasting, glucagon levels rise only in lean mice. This means that obese alpha cells become unresponsive, or resistant, to cues of hypoglycaemia.

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Insulin Glucagon Ratio and Obesity Management

IGR, therefore, can be used as a tool to understand the pathophysiology of weight gain as well as dysglycaemia. It can also be used to classify glucose lowering and weight reducing drugs. Weight loss per se, irrespective of type of agent used, is able to “re-set” the insulin glucagon metabolic fulcrum to a lower levels. Some interventions, however, including carbohydrate- restricted diets, reduce insulin levels to normalize the IGR. Other drugs, such as sodium glucose cotransporter 2 inhibitors (SGLT2i), have been shown to increase glucagon secretion. Though this is probably a defensive mechanism against hypoglycaemia, that may be caused by excessive glycosuria, it serves to optimize the IGR.

The glucagon like peptide 1 receptors agonists (GLP1RAs), liraglutide and semaglutide, have been shown to increase glucagon secretion in certain situations. This may contribute to their anti-anabolic, or weight reducing effect. Newer dual agonists, including tirzepatide and CagriSema, too, may reduce the IGR, by a combination of reduction in insulin, and increase in glucagon, concentrations.

The Way Forward

We do not foresee that IGR will be used as a tool for characterization, risk stratification, or decision-making aid for choosing anti-obesity drugs in the near future. Its measurement is expensive, and there is no consensus whether it should be calculated in fasting or post-prandial

states, from peripheral or portal circulations. However, the IGR concept helps us approach obesity with a broad-based view, mindful of its multifactorial causation and clinical impact. We do feel that IGR will become an integral part of discussion and debate in barocrinology in the future.

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