

Type 2 diabetes care and the law of endocrine parsimony

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Abstract

Diabetes care has become more and more complex and challenging. For the practicing physician, advances in pathophysiology and diagnostic/ monitoring tools are welcome, as they enhance understanding of the syndrome, its causation, and its natural history. The surfeit of drug classes and drugs available today however, create confusion and chaos as well. The almost infinite number of permutations and combinations that these can be used, poses a dilemma for the diabetes care professional. This communication proposes the Law of Endocrine Parsimony, and relates it to therapeutic targets as well as strategies in type 2 diabetes care. The Law of Endocrine Parsimony assists in decision making by positing: Hormones which are secreted in excess must be reduced, before trying to increase hormones which are relatively deficient, while managing diabetes.

Keywords: Insulin secretagogues, Insulin sensitizers, Insulin sparing drugs, Oral glucose lowering drugs, Type 2 diabetes.

Heterogeneity of Diabetes

Type 2 diabetes is a syndrome characterized by carbohydrate intolerance, which occurs due to a combination of relative insulin deficiency and insulin resistance. Concerted research has uncovered multiple pathophysiological mechanisms of diabetes, which have been termed as the Ominous Octet or the Dirty Dozen.^{1,2} This has led, however, to a meronymous approach to the study of diabetes, with experts debating the relative contribution of various etiopathologic abnormalities to the disease. Recent opinion, however, while expanding the pathophysiologic construct of diabetes, encourages a holonymous viewpoint by proposing a beta cell centric classification of diabetogenic pathogenetic mechanisms.³

Heterogeneity of Drugs

The surfeit of proposed etiologies and pathophysiological abnormalities in diabetes is matched by the vast spectrum of pharmaceutical agents developed to treat it.

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These drugs can be classified in various ways. A clinico-mechanistic taxonomic structure lists three class of drugs- insulin secretagogues, insulin sensitizers, and nutrient load reducers- and further classifies each category as directly and indirectly acting.⁴ An endocrine framework assesses glucose-lowering drugs based upon their effect on the insulin: glucagon ratio, while a biochemical approach uses the effect of these drugs on AMPK (adenosine monophosphate kinase) activity to distinguish between them.^{5,6} Both these processes are concordant with the metabolic fulcrum, which categories persons with diabetes as being 'eubolic', 'maladaptively anabolic', or 'predominantly catabolic'.

The Law of Endocrine Parsimony

In the current climate of multiple choices and options, it sometime becomes difficult for the diabetes care professional to choose the right drug, or combination of drugs, for an individual patient. We propose the Law of Endocrine Parsimony' to assist in this decision making. Simply put, this law states: "Hormones which are secreted in excess must be reduced, before trying to increase hormones which are relatively deficient, while managing diabetes" To paraphrase this further, we state: "Fix hyper secretion first".

Vicious Cycle of Endocrine Secretion

The islets of Langerhans, with their two main players, the alpha and beta cells, work around a metabolic fulcrum to maintain a state of eubolism. This is characterized by a balance between the catabolic effects of glucagon and the anabolic force of insulin. In most persons with prediabetes and diabetes, the first pathological abnormality is an increase in insulin resistance, which leads to hyper secretion of insulin, followed by a counterproductive, or maladaptive, increase in glucagon production.⁷ The increased release of these hormones, both counter regulatory to each other, creates a vicious cycle of one-upmanship, which serves to worsen, rather than mitigate, the disease process.

Drugs and Endocrine Parsimony

The law of endocrine parsimony becomes relevant in such a situation. As per this law, one should prefer glucose-lowering drugs, or combinations, which reduce insulin as

well as glucagon levels. This will help de-stress the beta cell, and facilitate breakage of the vicious cycle. Such a strategy can be planned using metformin with a GLP1RA, or with a GLP1RA+ SGLT2i combination. This is absolutely concordant with current consensus on hyperglycaemia management and cardiovascular risk reduction.⁸⁻¹¹

Limitations

The law of endocrine parsimony, however, does not apply to persons with a predominant insulin secretory defect. Such persons will require insulin, or insulin secretagogues, for management. These therapies are usually combined with metformin, to practice a 'preventative parsimony' of sorts, and reduce the dose requirement of insulin or its secretagogues.

Persons with disease such as acromegaly, Cushing's syndrome, and pheochromocytoma may develop secondary diabetes due to excessive release of counter regulatory hormones. The law of endocrine parsimony enjoins the treating clinician to focus on reducing levels of the offending hormone, whether by surgical, medical or radio therapeutic means, in order to mitigate hyperglycaemia. The use of mifepristone to manage hyperglycaemia associated with Cushing's syndrome is an example of a strategy aimed at achieving endocrine parsimony.

Therapeutic Parsimony

Thus, the Law of Endocrine Parsimony is applicable not only to targets of therapy, but also to choice of tools. From an endocrine-parsimonious perspective, rational therapy of diabetes should be based on minimally required doses of insulin, which are adequate to achieve glycaemic control. It must be noted here that endocrine parsimony or therapeutic parsimony¹² cannot be practiced without culinary or caloric or carbohydrate parsimony: adherence to appropriate diet plans should be the basis of diabetes management. At the same time, insulin sparing drugs should be utilized to reduce the requirement of exogenous insulin.

Critics may suggest that GLP1RA use, by introducing supraphysiological doses of a hormone analogue, defeats the concept of endocrine parsimony. This argument, however, is easily countered by evidence which shows that GLP1RA have an appetite suppressant effect, which facilitates caloric parsimony. GLP1RA and SGLT2i, along

with metformin, also have insulin sparing effects which allows them to respect the law of endocrine parsimony.

Summary

The law that we propose is not new. We do feel, though, that the basic philosophy of parsimony is losing ground to modern hedonistic forces. This is true of society and social behaviour in general, and of diabetes pharmacotherapy in particular. Modern guidelines encourage use of combinations of drugs, designed to meet multiple vasculometabolic targets, which seem never to stand still. The law of endocrine parsimony, as discussed in this report, may sensitize diabetes care professionals to the need for rational and pragmatic treatment of diabetes, designed to address the basic pathophysiology of disease.

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