The Islet De-stress Hypothesis: A potential explanation for the gluco metabolic effects of ketogenic diet

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Abstract
Ketogenic diet (KD) is an established therapy with indications which span multiple disciplines. Initial skepticism about the role of KD in diabetes and obesity has been replaced by interest in its mechanism of action. We propose that KD works by de-stressing the islet of Langerhans, and reducing its workload. This de-stress occurs at both beta and alpha cell, and suggests that the islet should be considered a single anatomic-functional unit. The Islet De-stress Hypothesis, as we term it, is based upon the Law of Endocrine Parsimony. Simply put, this states that minimal burden should be placed on any gland, including the islet of Langerhans, while managing endocrine disease.

Keywords: Glucagon, high protein diet, insulin, ketogenic diet, low carbohydrate diet, obesity, type 2 diabetes.

Introduction
Ketogenic diet (KD) has been in existence for over a century, and is gradually being accepted as a rational therapeutic option for various diseases.1 Though most scientific publications focus on its use in neurology and oncology, lay literature highlights its efficacy as a weight reducing and diabetes ameliorating treatment. The enthusiasm shown by unqualified KD evangelists is not shared by puritan medicine practitioners. Experts, till recently, have denounced it as a fad.2

Recent understanding of the physiology and biochemistry of glucose and weight homeostasis has forced a rethink of this issue, however. Results of randomized controlled trials, showing improvement in metabolic and anthropometric parameters, have added the strength of evidence to the rationality of reason.3,4 These trials provide a holistic overview of the utility of KD, as they have been conducted in participants with a large variety of metabolic phenotypes, over a wide spectrum of duration, using a range of protein-rich strategies and tools.

Reason and Rationale
Various explanations have been put forward to understand how KD helps in normalizing glycaemic levels.5-7 Broadly speaking KD increases satiety, reduces appetite, and increases energy expenditure during both fasting and postprandial states. Through these mechanisms, KD improves various parameters including weight, waist circumference, lipids and glucose. KD is a unique intervention in that it is able to reduce appetite and increase energy expenditure at the same time. With calorie restricted diets, appetite control is always a challenge, and resting energy expenditure usually falls.

The current theories however, are deemed inadequate to explain the entire gamut of KD effects related to weight and glucose modulation. This may be one of the reasons why KD is taking time to become as popular with endocrinologists8-10 as it is with neurologists. The lack of endocrine rationale for KD may also explain the discordance between patient expectations and physician beliefs regarding this mode of therapy. This disconnect may be severe enough to preclude meaningful dialogue between patient and physician, Such a gap is unfortunate, as it runs contrary to the basic philosophy of patient-centred care and shared decision making.11

The Law of Endocrine Parsimony
We propose the law of endocrine parsimony to create a mechanism of action of KD in obesity and type 2 diabetes. The law of endocrine parsimony states that minimal load should be placed upon an endogenous endocrine axis while treating any endocrine dysfunction. At the same time, optimal use of endogenously available resources such as fuels should be ensured. In the context of diabetes, for example, minimal load should be placed upon the beta cell to achieve glycaemic control. In complications such as nephropathy, vasculometabolic load on the glomerulus should be reduced. This law is followed in diseases such as hypopituitarism, hypothyroidism and hypoadrenalism: modern endocrine practice does not use hypothalamic or pituitary hormones or their agonists to flog failing glands to try and achieve euhormonal status in these conditions.
Endocrine Extravagance in Diabetes Management

In contrast, however, the law of endocrine parsimony is not followed faithfully in diabetes and obesity management. Many therapeutic modalities, such as exogenous insulin, secretagogues, and incretin-based therapies act by replacing or stimulating beta cell function, leading to a rise in circulating insulin. Yet others, such as SGLT2i, may increase glucagon levels and enhance endogenous glucose production. In fact, there are reports of post prandial hyper-glucagonaemia with chronic GLP1 receptor agonist use as well.

Ketogenic Diet and Endocrine Parsimony

With KD, endogenously available fuel (fat) is utilized for generation of energy (ATP), rather than the conventional source which needs to be imported (dietary carbohydrate). This is another dimension of the Law of Endocrine Parsimony, which enjoins us to use available endocrine resources, including fuel, optimally. An analogy can be drawn with a self-reliant economy that encourages consumption of domestic goods and services rather than depending on costly imports from abroad.

The Islet: Unitary Function

The islet of Langerhans may be viewed as a composite anatomically-functional unit. Its various components, especially the beta cells and alpha cell, are connected not only by anatomical contiguity, but also by paracrine relationships. The human islets of Langerhans show interspersal of both alpha and beta cells, though this is not the case in other mammalian species. It is postulated that a local intra-islet GLP1 system exists within human pancreatic islets: alpha cells contain both GLP-1 and the enzyme prohormone convertase 1/3, which is active in both glucagon and insulin biosynthesis. DPP4 is expressed only in alpha cells, and its activation may have a paracrine effect on neighbouring beta cells: human islets treated with the DPP4i vildagliptin secrete higher levels of both GLP1 and insulin.

The Insulin: Glucagon Fulcrum

It has earlier been suggested that insulin and glucagon form two ends of a metabolic fulcrum, which may be skewed in diabetes. Some persons, with a biochemical and anthropometric phenotype characterized by maladaptive anabolism, will have a high insulin: glucagon ratio. At the other end of the spectrum, persons in an extreme catabolic state will have a low insulin: glucagon ratio. In both cases, normalization of insulin: glucagon ratio is required. This awareness may serve as a basic tool to help decide choice of glucose-lowering therapy.

The bipolar metabolic fulcrum (anabolism/catabolism) or hormonal axis (insulin/ glucagon) model, however, does not take into account the absolute concentrations of these hormones. In states of insulin resistance, such as type 2 diabetes and obesity, both hyperinsulinaemia and hyperglucagonaemia may occur. Both beta cell and alpha cell are overworked, as they struggle to keep up with the requirements of a metabolically charged body. No glucose lowering therapy, with the exception of metformin and pramlintide, lowers both insulin and glucagon.

The Islet De-stress Hypothesis

We suggest that KD de-stresses the over fatigued bipolar insulin-glucagon axis by reducing both insulin and glucagon levels, bringing them down to near-normal and normal, while maintaining a healthy insulin-glucagon
ratio (Figure-1). These changes reduce the burden on the fatigued alpha and beta cells, allowing them rest, and a chance to rejuvenate themselves. While this is achieved, alpha and beta cell sensitivity (in response to hypoglycaemia and hyperglycaemia respectively) are restored. These changes kick start a virtuous cycle of eumetabolism, which allows maintenance of healthy behaviour, and outcomes, over prolonged periods of time. Lower levels of insulin lead to lesser appetite, which contributes to long term adherence to KD (Figure-2).

**Endocrine Rationale**
A state of ketosis is accompanied by low insulin levels, and various RCTs have demonstrated either reduction or no change in serum insulin levels with KD. We are not aware of any published study which shows hyperinsulinaemia with KD. Consumption of a ketone ester drink has been shown to reduce glycaemic response in an OGTT and improve insulin sensitivity, without increasing insulin secretion. Ketones are also known to be an inhibitory factor for glucagon secretion, and KD probably reduces glucagon levels in humans as well. In a study of elite athletes, glucagon and cortisol have been found to increase after keto adaptation. This may be a finding unique to ultra-endurance athletes, or may reflect heightened sensitivity of the alpha cell. Thus, available data supports the Islet de-stress hypothesis as an explanation for the beneficial effects of KD.

**Limitations and Potential**
One must be aware, however, of the (large) gaps in our understanding, and of conflicting evidence Ketone infusion have been found to have no effect on insulin and glucagon levels in both nonobese and obese subjects. At the same time, it should be understood that KD is characterized by high protein and fat intake in the absence of carbohydrates. This distinguishes it from experiments which use ketone or triglyceride loads in carbohydrate replete subjects. Free fatty acid elevation, caused by administration of triglyceride emulsion, is associated with significant decrease in glucagon, but stimulation of insulin levels, in canine models. This may contribute to the safety of nutritional ketosis, and prevent ketoacidosis from occurring. Other animal studies have shown a decrease in insulin secretion and glucose tolerance, and a reduction in alpha cell mass, and alpha to beta cell ratio, with ketogenic diet. As already mentioned, human islets of Langerhans differ from animal islets in their anatomy, and perhaps physiology. Thus clinically relevant inferences cannot be drawn from results of animal studies.

From a more holistic perspective, the islet distress hypothesis may be invoked to explain the benefits of other therapeutic measures such as calorie restriction and glucagon-like peptide 1 receptor agonist usage. Though
highly simplistic in its approach, this hypothesis does help clarify the role of KD, and similar therapies, to patients who wish to understand their mechanism in lay language.

Summary
We postulate that islet de-stress, and perhaps entero-endocrine sensitization, may be mechanisms by which KD improves glycaemic and metabolic parameters in diabetes and obesity. We base the hypothesis of islet distress on the law of endocrine parsimony, and on the concept that the islet of Langerhans is a single anatomico-functional unit, rather than a random collection of disparate cell types.

References