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Glucagon-like Peptide 1 and Evidence Around Diabetes Specific Nutrition

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Abstract

There has been significant research and development in pharmaco-therapeutic molecules for management of type 2 diabetes mellitus (T2DM). Diabetes specific nutrition (DSN) intervention and newer hormonal therapies are gaining a lot of attention. (Particularly incretins, a group of metabolic hormones that stimulate a decrease in blood glucose levels.) Since incretins play an essential role in augmenting the post-prandial release of insulin, it is important to understand the science behind them and their modulation by DSN. The purpose of this article is to summarize the available science around one of the incretin hormones, glucagon-like peptide 1 (GLP-1). It is responsible for nearly half the insulin secreted after a meal. We focus on the role of nutrition, particularly diabetes-specific nutrition, in enhancing GLP-1 release, which has implications both for diabetes management and possibly for new methods of controlling obesity.

Literature published in PubMed, Google scholar and Embase were studied up to the end of August 2018. The key words of GLP-1, T2DM and Nutrients were used in different combinations.

It was found that some macronutrients, including complex carbohydrates, soluble fibre, proteins and high monounsaturated fatty acids augment GLP-1 secretion from intestinal L-cells. This may be attributed to insulin-trophic effects of DSN as well as its effects in causing deceleration in gastric emptying and reducing food intake. Hence, it was concluded that augmenting GLP-1 secretion in response to the intake of certain nutrients helps in modulating insulin secretion, achieving metabolic homeostasis, decelerating gastric emptying, and reducing food intake. DSN increases endogenous GLP-1 secretion which in turn improves insulin secretion and sensitivity. Thus, integrating DSN into mainstay diabetes management plans may result in better glycaemic and metabolic controls, particularly when GLP-1 based therapies are concurrently in use. Improved modulation of GLP-1 secretion by dietary means may provide better management and prevention of nutrition-related disorders like diabetes, obesity, liver disease and other metabolic diseases.

Key Words: Type 2 Diabetes Mellitus (T2DM), Incretin, Glucagon-like Peptide-1 (GLP-1), Diabetes Specific Nutrition (DSN), obesity

Key Messages: DSN containing complex carbohydrate, soluble fibre, proteins and high monounsaturated fatty acids (MUFAs) augments GLP-1 secretion which in turn improves insulin secretion and sensitivity.

Introduction

Diabetes requires a holistic management approach, including a focus on nutrition, exercise, life style and medications. Research regularly updates the medication management, but research is infrequent when it comes to nutrition intervention. Every diabetic patient worries about their diet and thus diabetes-specific nutrition (DSN) should receive more attention from public health nutritionists. Literature regarding the scientific benefits of such nutrition is evolving. In this paper, we focus mainly on understanding the benefits of DSN on GLP-1 and how augmenting GLP-1 secretion benefits type 2 diabetes mellitus (T2DM) patients. The term "formula" is used in this paper, not to refer to an infant feeding product, but to a scientifically formulated nutrition supplement commonly used in the management of diabetes. This review does not relate to any specific product.

Context

Enteroendocrine cells (EEC) in the small intestine secrete various hormones like cholecystokinin, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). They play major roles in the regulation of food intake, gastric emptying and gastro-intestinal motility (Coate et al, 2014).

L cell sub-types of EEC are present over a substantial portion of the GI tract, starting in the proximal small intestine, and progressively increasing in density towards distal colon. L-cells secrete GLP-1 in response to nutrient intake. GLP-1 uses endocrine and neuronal routes to act on the pancreas and the central nervous system (Holst, 2007). GLP-1 is responsible for nearly half of post prandial insulin secretion (Cancelas et al, 2006).

Impaired secretion of GLP-1 adversely affects insulin resistance related diseases. GLP-1 based therapies (glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-IV inhibitors) are now well accepted in the management of T2DM.

Nutrition intervention has also been found to positively augment GLP-1 secretion and improve glycaemic and metabolic controls in T2DM patients. Nutrition modification now constitutes an important part of the holistic management of T2DM, alongside the pharmacologic intervention.

Here, we review the physiology of GLP-1 and the modulation of GLP-1 secretion by various macronutrients in the context of DSN in T2DM management.

Physiology of GLP-1

GLP-1 exists in two biologically active forms: GLP-1 (7–37) and GLP-1 (7–36) amide, the former having a higher post- prandial concentration in blood (Drucker et al, 2006 and Bradford et al, 2008). The hormone peaks at 20 to 30 minutes after meals, depending on the size and nutritional composition of meals (Prigeon et al, 2003). The circulating levels decline rapidly due to enzymatic inactivation, mostly by the enzyme dipeptidyl-peptidase IV, neural endo-peptidase, and renal clearance (Drucker et al, 2006 and Plamboeck et al, 2005). Thus, GLP-1's half-life is very short – about 1-2 min (Cani et al, 2005 and Cani et al, 2006).

Only 10-15% of the newly secreted bioactive GLP-1 enters the systemic circulation (Deacon et al, 1996 and Hansen et al, 1999). Consequently, targeting GLP-1 receptors' (GLP-1 R) activation with GLP-1 analogues and increasing GLP-1 half-life in the bloodstream by GLP-1Rs agonists and DPP-IV inhibitors respectively, has become an area of interest for T2DM and obesity management (Drucker et al, 2006 and Prasad-Reddy et al, 2015).

Functions of GLP-1

GLP-1 regulates secretion and sensitivity of insulin while suppressing glucagon secretion (Holst 2004). It plays a role in metabolic homeostasis, including stimulation of glucose-dependent insulin release; deceleration of gastric emptying, acid secretion, and food intake; and attenuation of blood sugar, non-esterified fatty acids, and postprandial triglyceride concentrations (Paniagua et al, 2007 and Dao et al, 2011). It also inhibits hepatic glucose production while stimulating glucose uptake in an insulin-dependent manner in both adipose tissue and muscles. Activation of GLP-1 receptors reduces the death of the pancreatic beta-cells that secrete insulin. GLP-1 can decrease endogenous glucose production under fasting conditions. It also promotes satiety through central mechanisms, thereby reducing postprandial glucose levels, and making it of interest in the context of obesity control.

Regulation of GLP-1 secretion

A complex neuroendocrine loop (proximal-distal endocrine loop), involving the enteric nervous system, vagus nerve and the duodenal hormone glucose-dependent insulin-tropic peptide (GIP) regulate GLP-1 secretion (Rocca et al, 1999). Plasma levels of GLP-1 increase rapidly after meals, suggesting the existence of a proximal gut signal regulating GLP-1 release from the small intestinal L cells (Rocca et al, 1999). Various factors like nutrition, surgical procedures, drugs and eating habits also influence GLP-1 secretion.

Table 1: Site and Actions of GLP-1

Site of action	Description	Effects
Pancreatic	• Increase Insulin secretion • Increase Insulin gene transcription • Reduce Glucagon secretion	• Increase uptake of blood glucose • Suppression of hepatic glucose production • Reduction of post-prandial glucose levels

Extra-Pancreatic	• Incretin Effect • Increase somatostatin secretion • Reduce smooth muscle contractions in stomach and ileum	• Augment endogenous Insulin secretion • 'Ileal brake' phenomenon • Reduce gastric acid secretion
Central Nervous System	• Activation of anorexigenic POMC/CART* neurons • Activation of orexinergic NPY/ AgRP** neurons	• Increase satiety leading to reduction in food intake

* POMC/CART (Pro-opiomelanocortin/ Cocaine and Amphetamine-regulated transcript
** NPY/ AgRP (Neuropeptide Y/ Agouti-related peptide)

Methods--Evidence Acquisition

Various literature including original and review articles discussing the science of GLP-1 and influence of dietary macronutrients on the same were studied on popular scientific data bases like PubMed, Google Scholar and Embase published between 1965 up to end of August 2018. Literature was reviewed for contextual relevance. Randomised control trials (RCTs) evaluating role of DSN formula on endogenous GLP-1 secretion and consequent benefits were also reviewed.

Results

Nutrition and the regulation of GLP-1 secretion

Various nutrients cause GLP-1 and PYY release from ileum (Ripken et al, 2014). Delivery of 'non/pre-digested' macronutrients to the ileum activates satiety signals and decreases subsequent food intake in healthy volunteers (Van Avesaat et al, 2015). In humans, post-prandial blood concentrations of GLP-1 increase 2-4-fold in comparison to fasting levels. In the second hour after standard meals, GLP-1 concentrations start to decrease gradually until the next prandial episode. Neuroendocrine and nutritional factors influence the bi-phasic secretion of GLP-1. Phase 1, detectable 10-15 minutes after food ingestion, is mostly influenced by neuroendocrine factors and, to a lesser extent, by the interaction of nutrients with L-cells in the proximal small intestine. Conversely, phase 2 of GLP-1 secretion, occurring 30-60 minutes postprandially, is mostly influenced by the arrival of nutrients in the distal part of small intestine and colon (Nauk et al, 1996).

Meal components such as a carbohydrate (like complex, low Glycaemic Index GI), protein (casein), lipids (like MUFAs) and sucralose (a non-caloric sweetener) are found to be potent stimulants of endogenous GLP-1 secretion (Ripken et al, 2014). The direct exposure of L cells to luminal nutrients appears to be the primary route for GLP-1 stimulation (Singh, 2015, Alsalim et al, 2015 and Ahlkvist et al, 2012). Indirect pathways via "neural" or "upper gut"

signals stimulate GLP-1 secretion even before the luminal contents reach the proximities of L cells (Alsalim et al, 2015). Digested nutrients trigger GLP-1 exocytosis from L-cells' secretory granules. Modulation of GLP-1 secretion by digested nutrients may provide a novel nutritional alternative for better management and prevention of nutrition related disorders like diabetes, obesity, liver disease and other metabolic diseases (Zhou et al, 2008, Burcelin, 2005 and Brynes et al, 2000).

Role of carbohydrates

Parenteral vs Enteral Glucose

In normal subjects, insulin secretion is much higher after oral than IV glucose (Mcintyre et al, 1965 and Shapiro et al, 1987). The greater insulin response to oral glucose (the "incretin" effect) is due to release of gastrointestinal hormones that stimulate insulin secretion. Hermann et al found that basal GLP-1 levels remained unaltered after administration of 25 mg intra-venous glucose. However, the levels were raised after administration of 100 mg of oral glucose and showed a long-lasting plateau (300% above basal levels 90 minutes oral glucose consumption) (Herrmann et al, 1995).

Surgery results in a pathophysiological state similar to type 2 diabetes mellitus (T2DM) due to blunted stimulation of nonoxidative glucose disposal in the liver and skeletal muscles. Preoperative oral carbohydrate treatment is found to increase insulin-stimulated glucose uptake and significantly increase glucose oxidation, consequently attenuating the development of immediate postoperative insulin resistance (Soop et al, 2004).

Complex Carbohydrates

Glycaemic index (GI) and glycaemic load (GL) are recognised means to categorize foods based on glycaemia evoking potential of the carbohydrate composition. Studies have shown that metabolic parameters deteriorate more with higher GI and GL of a nutrition formula. Replacing high GI-carbohydrates with low-GI alternatives improves glycaemic control over long-term consumption (Devitt et al, 2012). Low GI DSN formula consumption resulted in higher endogenous GLP-1 secretion and better metabolic controls in comparison to conventional standard feeds.

Voss et al. (2008) found a lower area under the curve for glucose and insulin with DSN (low GI and GL) formula feeds in comparison with the standard formula feed. The adjusted GLP-1 concentration at 60 min was higher for the DSN formula compared with other diabetic formula and standard formula.

Soluble, fermentable fibre

Soluble (prebiotic) fibre is easily fermented into biomass, short-chain fatty acids (SCFA) and gases by the colonic microflora. Fermentable dietary fibre and their SCFA metabolites augment endogenous GLP-1. Compared to a standard diet, the consumption of a diet enriched in fermentable fibre for 50 days increased GLP-1 concentrations in the proximal colon cells (Cani et al, 2005). Another study found that consumption of a diet enriched with fermentable fibre for 4-6 weeks increased GLP-1 concentrations as well as proglucagon expression in the proximal colon (Cani et al, 2005 and Cani et al, 2006). Chambers et al (2015) recently showed that acute targeted delivery of propionate (a type of SCFA) in the colon stimulated GLP-1 secretion and reduced energy intake in overweight or obese adults at a buffet-style lunch. Along with the acute effects of GLP-1 on appetite and food intake, daily delivery of propionate in the

colon over a period of 6 months also reduced body weight, abdominal fat and hepatic fat accumulation.

Thus, evidence supports that low GI complex carbohydrates along with soluble/fermentable fibre have beneficial effects in diabetes and obesity.

Role of proteins

In individuals with T2DM, ingested protein appears to increase insulin response to dietary carbohydrates without increasing plasma glucose concentrations (Laymann et al, 2008). Dietary intake of protein effectively improves the glycaemic response due to its ability to increase GLP-1 secretion (Olivos et al, 2014 and Raben et al, 2003). Chen et al (2009) tested the comparative efficacy of branched-chain amino acids (BCAAs) and dairy proteins in regulating satiety in human intestinal cell line (NCI-H716). They found that skimmed milk, casein, isoleucine and 2% leucine stimulated GLP-1 secretion by 1.6, 2.5, 2.6, and 4.7 - fold respectively. Milk-based products may therefore induce GLP-1 secretion due to their high content of BCAAs. Proteins stimulate GLP-1 release more than carbohydrates (Deacon et al, 1996).

Role of Lipids

Unsaturated long-chain fatty acids, are potent stimulators of GLP-1 release (Edfalk et al, 2008 and Hauge et al, 2015). Paniagua et al. (2007) found that ingestion of a Mediterranean diet rich in olive oil (high MUFA content) for 28 days in obese and T2DM adults resulted in significantly higher postprandial GLP-1 blood concentrations. With similar energy contents, diets richer in MUFAs or omega-3 polyunsaturated fatty acids (PUFAs) than saturated fats could increase endogenous GLP-1 secretion. This results in increased insulin secretion, insulin sensitivity, β-cell proliferation, as well as improved glucose tolerance.

Role of artificial sweeteners

Non-nutritive sweeteners (acesulfame K, sucralose, neotame, saccharin, aspartame) affect the food intake and maintain diet palatability by delivering a sweet taste without adding calories or any glycaemic effect (Matte et al, 2009 and Pepino et al, 2011). Stimulation of enteroendocrine L cells in mice with high-potency sucralose induced GLP-1 secretion in a concentration-dependent manner (Margolskee et al, 2007). Jang et al, 2007 reported similar results when the effect of sucralose on human NCI-H716 enteroendocrine L cells was analysed. However, ingestion of aspartame or its constituent amino acids decreased GLP-1 secretion in human subjects (Hall et al, 2003). Recent findings from rat models showed diminished results in GLP-1 release during the oral glucose test in a saccharin-exposed group. Hence, sucralose has been found to favourably increase GLP 1 levels but the same is not the case with other artificial sweeteners like aspartame or saccharin.

GLP-1 challenges in T2DM

A low GLP-1 level has been identified as an important risk factor for T2DM (Lastya et al, 2014). Fasting and postprandial GLP-1 levels were found to be significantly lower in T2DM patients than those with normal glucose tolerance (Lastya et al, 2014). Reduced levels of GLP-1 in obesity and T2DM are likely due to reduced GLP-1 secretion (Baggio et al, 2007 and Vilsboll et al, 2003). Vollmer et al, 2008 suggested that GLP-1 secretion was unimpaired in diabetic patients with well controlled blood glucose, while it was diminished in patients with poor glycaemic control.

A disturbance has been seen in the normal diurnal GLP-1 level rhythm (maximum GLP-1 levels at 4:00 pm and minimums at 8:00 am and 8:00 pm) in overweight/obese subjects (Galindo Munoz et al, 2015). Obese adipose tissues are hypoxic and express hypoxia-inducible factor- (HIF-) 1α. Deletion of this factor in adipocytes may improve glucose tolerance by enhancing insulin secretion through the GLP-1 pathway.

Endogenous (Diet induced) GLP-1 secretion in T2DM and Obesity

As a potential strategy to enhance GLP-1 actions, the metabolic effects of intravenous administration of GLP-1 analogues have been widely investigated. Patients with T2DM and obesity exhibited similar metabolic and appetite responses compared to healthy counterparts, when GLP-1 analogue was administered (Toft-Nielsen et al, 1999) indicating that GLP-1 secretion is hampered but not sensitivity to GLP-1's action.

Consequently, targeting GLP-1's activation with GLP-1R analogues and increasing the GLP-1 half-life in the bloodstream with DPP-4 inhibitors has become an area of interest for management of obesity and T2DM. Another relevant strategy to increase GLP-1 action is to augment its endogenous secretion through nutritional approaches.

DSN and GLP-1

One objective of nutritional intervention in T2DM is to ensure adequate endogenous GLP-1 secretion. Hence, DSN should ideally be a good blend of macronutrients known to augment endogenous GLP-1 secretion. As described above, low GI complex carbohydrates, casein, pre-biotic soluble fibre and high MUFAs could be the primary components of a DSN diet or formula. Devitt et al found that T2DM patients consuming DSN formula at breakfast had significantly higher median adjusted plasma GLP-1 (188 pmol/L/min) curves over time in comparison to the GLP-1 response after a conventional oat meal breakfast (40 pmol/L/min) (Devitt et al, 2012).

DSN such as meal replacements have been included as an integral part of the recently published Transcultural Nutrition Algorithm that advocates lifestyle modification as an adjunct to pharmacotherapy. Low GI and GL DSN formulae have been shown to exert better glycaemic control than standard formulae when used as a meal or calorie replacement or as a dietary supplement as part of overall nutritional management of diabetes (Elia et al, 2005). Tatti et al found significant reductions in HbA1c levels and body weight, and improvement of metabolic parameters like the serum lipid profile and blood pressure in T2DM obese patients consuming low GI DSN supplements as meal replacements (Tatti et al, 2009).

Conclusions

Complex carbohydrates, proteins, MUFAs and pre-biotic fibre augment GLP-1 secretion. Thus, including them in the diet represents a promising lifestyle strategy for T2DM management and may have implications for obesity control. The therapeutic potential of GLP-1 has already been established and it is successfully being used for blood glucose management in individuals with T2DM.

In comparison with individual nutrients, mixed-nutrient meals or feeds such as DSN formulae theoretically constitute a more promising and practical option since various macronutrients target enteroendocrine and neural pathways simultaneously. DSN formulae containing complex carbohydrates, proteins, soluble/ fermentable fibre and high amount of MUFAs have been shown to augment endogenous GLP-1 secretion, thereby improving the glycaemic and

metabolic parameters in T2DM. Well-designed scientific trials (Devitt et al 2012 and Voss et al 2008) evaluating the impact of DSN formulae in promoting GLP-1 secretion and improving overall metabolic parameters have demonstrated favourable outcomes in T2DM patients.

The pharmacological action of various GLP-1 based therapies depend on the bioavailability of endogenous GLP-1 in the blood-stream. Combining the use of these drugs with a DSN diet or formula promoting endogenous GLP-1 secretion could augment action and efficacy of such therapies. Therefore, it would be worthwhile to investigate the relationship between DSN and the efficacy of GLP-1 based therapies in future studies.

Editor's note: *Anshu and his two co-authors all work for the Scientific and Medical Affairs Department of Abbott Nutrition. They stated when they declared when they submitted their paper that they had no conflicts of interest. I asked them fill in a detailed COI form and corresponded with them a few times on this issue. Their article uses the word "formula" but this does not refer to infant formula, but to those used in diabetes specific nutrition therapy. While Abbott produces such a formula, they say their paper does not relate to it and was not done to assist Abbott in improving it or designing any other product. When I wrote asking why Abbott would let them do such work unrelated to their commercial activities, they responded as follows: "We are free to take projects of academic interests, which help to propagate scientific concepts to broader community health care. Such projects are not necessarily meant for supporting Abbott Nutrition or any specific organisation. This is how Medical & Scientific Affairs department differ from the commercial counterparts in our organisation."*

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