

Effectiveness of carbohydrate diet restriction in type 2 diabetes mellitus on insulin and incretin-based therapies

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is the most common form of DM characterized by variable degrees of hyperglycemia, insulin resistance, and impaired insulin secretion. Insulin resistance and progressive failure of pancreatic β -cells reduce insulin secretion and consequently increase blood glucose and free fatty acid levels. The deterioration of pancreatic β -cell function in T2DM leads to therapeutic failure of oral agents over time. Hence, the most T2DM patients ultimately require insulin therapy, which may cause hypoglycemia. Regular carbohydrate intake with respect to time and amount reduces the risk for hypoglycemia in DM patients on fixed daily insulin doses. In T2DM, obesity aggravates the metabolic abnormalities such as hyperglycemia, dyslipidemia, and hypertension. Weight loss and exercise improve insulin resistance, glycemic control, and reduce risk factors in overweight and obese T2DM patients. Low caloric but healthful eating pattern promotes weight loss in overweight or obese T2DM adult patients. Incretins are released after ingestion of a meal augment the secretion of insulin and this account for the greater insulin response to oral glucose than to intravenous glucose. Incretin-based therapies along with reduced insulin doses sustain glycemic control without an increase in hypoglycemia or weight gain. The low-carbohydrate diets in T2DM patients on insulin and incretin-based therapies could increase the likelihood of hypoglycemia. Hence, as prevention of hypoglycemia is an essential part in the management of DM, the individualized dietary plan or eating pattern and adjustment of insulin and incretin doses should be considered for each patient based on his or her glycemic control.

Key words: Hypoglycemia, incretin-based therapies, insulin, low-carbohydrate diets, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century. Each year, more and more people are being affected with this condition, which can result in life-threatening complications. In addition to the estimated 415 million adults who currently have DM, there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing the disease in the future.^[1]

DM patients are more vulnerable to various chronic complications such as retinopathy, nephropathy, neuropathy, coronary heart disease, peripheral arterial disease, cerebrovascular disease, gastroparesis, infections, skin changes, and hearing loss.^[2] Involvements of peripheral and autonomic nervous systems are frequently encountered in DM.^[3] Some studies have reported the manifestations of central nervous system changes in DM patients at neurochemical, electrophysiological, structural, and neurobehavioral levels.^[3-6]

DM is classified based on the pathogenic process into two broad categories - type 1 and type 2. Type 1 DM (T1DM) most commonly develops due to an autoimmune beta cell destruction resulting to complete or near-total insulin deficiency. Type 2 DM

(T2DM), formerly known as non-insulin dependent DM, is the most common form of DM characterized by variable degrees of hyperglycemia, insulin resistance, and impaired insulin secretion.^[7]

T2DM occurs primarily due to a number of lifestyle factors and genetics.^[8] The lifestyle factors include physical inactivity, sedentary lifestyle, cigarette smoking, and abundant consumption of alcohol.^[9] A strong correlation has been observed between T2DM and obesity with 80–95% of T2DM patients being overweight or obese. The risk of developing DM increases in proportion to body mass index.^[10] In T2DM patients, obesity aggravates the metabolic abnormalities such as hyperglycemia, dyslipidemia, and hypertension^[11] and increases the risk of developing cardiovascular disease (CVD).^[12] Weight loss improves glycemic control and reduces risk factors in overweight and obese T2DM patients.^[13,14]

American Diabetes Association (ADA) used a term - medical nutrition therapy (MNT) to describe the optimal coordination of caloric intake with other modes of treatment in DM such as insulin therapy, exercise, and weight loss. The MNT for T2DM patients should focus attention to low-carbohydrate diet and increased physical activity. Increased consumption of soluble, dietary fiber

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may improve glycemic control in T2DM patients. Weight loss and exercise improve insulin resistance.^[15]

In T2DM patients, after 1 year a low-carbohydrate diet had similar effects on weight and glycated hemoglobin (HBA1C) as those seen with a low-fat diet.^[16] Recent studies suggest that although low-carbohydrate diets are effective for weight loss and improvements in glycemic control and CVD risk over the short term, they are not superior to other dietary approaches such as control diets with higher carbohydrate content over the longer term. Hence, low-carbohydrate diets cannot be recommended as the default dietary strategy for T2DM patients. Low-carbohydrates dietary restriction in T2DM patients remains an area of controversy.^[17] There is no standard meal plan or eating pattern, which works universally for all T2DM patients.^[18]

To be effective, nutrition therapy should be individualized for each patient based on his or her individual health goals, personal and cultural preferences, health literacy and numeracy, access to healthful choices, and readiness, willingness, and ability to change.^[19] The effect of carbohydrate dietary restriction in T2DM patients on insulin and incretin-based therapies is still not clear. Hence, in this review, we aimed to explore overview on the role of carbohydrate diet restriction in T2DM patients on insulin and incretin-based therapies.

INSULIN SECRETION AND ITS MECHANISM OF ACTION

Insulin is a dipeptide containing α - and β -chains linked by disulfide bridges, and containing 51 amino acids. It is secreted by the β -cells of the pancreatic islets of Langerhans.^[20] Both nutrient and non-nutrient factors stimulate synthesis and secretion of insulin. Nutrient factors such as glucose stimulate insulin secretion from the β cell by increasing intracellular ATP and closing K^+ -ATP channels. Glucose, fructose, mannose, or galactose does not require insulin for their entry into the β cells.^[21] Non-nutrient factors may act through peptide hormones and cationic amino acids or via neural pathways such as cholinergic and adrenergic.^[22]

Insulin secretion following intravenous glucose has a reproducible pattern whereas it is much more variable in response to oral glucose. Glucose ingestion is associated with gastrointestinal hormones and neural input, which modify the insulin response and insulin secretion and remains active sometime after glucose ingestion.^[23]

Insulin maintains normal blood glucose levels by facilitating metabolic effects through phosphatidylinositol 3-kinase (PI 3-kinase) pathway and promotes mitogenic effects such as cell division and growth through rat sarcoma (RAS) protein pathway. Insulin promotes intracellular glucose transport in resting skeletal muscle, cardiac muscle, and adipocytes by translocation of glucose transporter proteins (GLUT) 4 to the cell membrane through PI 3-kinase pathway.^[24] Insulin through PI 3-kinase mediates other metabolic effects of insulin such as glycogen, lipid and protein synthesis, and anti-lipolysis, and the control of hepatic gluconeogenesis. The RAS protein pathway, which activates mitogen-activated protein (MAP) kinase in nucleus, promotes other mitogenic effects of insulin such as cell division and growth.^[24-27]

INSULIN THERAPY IN T2DM AND HYPOGLYCEMIA

Insulin resistance and progressive failure of pancreatic β -cells occur in T2DM patients, which results in reduced insulin secretion and consequently increases blood glucose and free fatty acid levels. A vicious cycle initiated by the resulting glucotoxicity and lipotoxicity further compromises the insulin-secreting ability of β -cells in response to hyperglycemia or oral hypoglycemic agents. Furthermore, the inevitable deterioration of pancreatic β -cell function in T2DM leads to therapeutic failure of oral agents over time.^[28,29] Hence, the most T2DM patients ultimately require insulin therapy to achieve and maintain adequate glycemic control. Hypoglycemia may occur in T2DM patients treated with insulin or its secretagogues such as sulfonylurea or meglitinides.^[30]

Hypoglycemia relates to the recurrent morbidity and sometimes mortality. Hypoglycemia-associated autonomic failure, defective glucose homeostasis, and hypoglycemia unawareness create a vicious cycle of recurrent hypoglycemia.^[31] Regular carbohydrate intake with respect to time and amount improves glycemic control and reduces the risk for hypoglycemia in DM patients on fixed daily insulin doses. Low caloric but healthy eating pattern is recommended to promote weight loss in overweight or obese T2DM adult patients.^[32]

Prevention of recurrent hypoglycemia is an essential part of diabetes management, particularly in DM patients on insulin and its secretagogues. Therefore, educating them about proper use of the pharmacologic agents, especially insulin and its secretagogues, nutrition, and exercise is the key to prevent hypoglycemic episodes.^[33]

INSULIN RESISTANCE

Insulin resistance classically refers to impaired sensitivity to insulin-mediated glucose disposal.^[34] A normal or elevated insulin level produces an attenuated biological response in insulin resistance.^[35] It is believed that the insulin resistance in most cases manifests at the cellular level through defects in the post-receptor insulin signaling. The possible mechanisms of insulin resistance include downregulation, deficiencies, or genetic polymorphisms of tyrosine phosphorylation of the insulin receptor, IRS proteins, PIP-3 kinase, or may involve abnormal GLUT 4 function.^[36]

The factors associated with insulin resistance include chronic excess energy consumption,^[22] high-fat diets particularly saturated fat^[37] and trans-fatty acids,^[38] sleep deprivation,^[39] normal pregnancy,^[40] and obesity.^[41] Insulin resistance is a secondary phenomenon in acute illness, hepatic cirrhosis, renal failure, pregnancy, hyperthyroidism, Cushing's disease, Cushing's syndrome, acromegaly, and pheochromocytoma.^[42]

Insulin resistance syndrome describes the group of abnormalities that occur more frequently in insulin-resistant persons. The most common clinical syndromes associated with the insulin resistance are the metabolic syndrome and T2DM. Metabolic syndrome represents a group of risk factors that raises risk for heart disease and other health problems. Other conditions associated with the insulin resistance include hypertension, polycystic ovarian

syndrome, non-alcoholic fatty liver disease, certain forms of cancer, and obstructive sleep apnea.^[22,34]

Compensatory hyperinsulinemia occurs due to increased insulin secretion from the pancreatic β cells to maintain normal blood glucose levels when there is peripheral insulin resistance in muscle and tissue.^[22] The clinical manifestations of the insulin resistance exacerbated by high carbohydrate diets likely depend on the type of carbohydrate.^[43] Chronic excess energy consumption promotes hyperinsulinemia and insulin resistance through stimulation of insulin secretion, triglyceride synthesis, and fat accumulation with downregulation of insulin receptors and post-receptor signaling.^[23]

EFFECTS OF CARBOHYDRATE DIET ON INSULIN SECRETION AND SENSITIVITY

Glucose is the most potent stimulus for insulin secretion, though the amino acid arginine, non-esterified fatty acids, mixed meal, and incretin hormones may enhance insulin secretion.^[22] Glucose-stimulated insulin secretion occurs in two phases - an initial rapid phase followed by a less intense but more sustained release.^[44] Not all the carbohydrates have the same effect in insulin secretion. The amount, type, and rate of digestion of the carbohydrates consumed determine the postprandial glucose and insulin responses. The short-term improvement in insulin sensitivity has an association with high carbohydrate diets. High carbohydrate diets increase insulin's ability to promote glucose removal from plasma.^[45]

The rate of insulin secretion tends to be lower with the consumption of low glycemic index (GI) food. The food with low GI has a lower rate of digestion, absorption, and conversion to glucose.^[46] Fructose is converted slowly to the glucose in the liver, and less glucose enters into the circulation. Therefore, fructose tends to produce less glucose and insulin response.^[47] and large amounts of fructose consumption reproduce the features of metabolic syndrome.^[48,49] Hence, high fructose diet to reduce postprandial glucose and insulin in the management of the insulin resistance syndrome is not well-advised.^[46] The long-term consumption of high sucrose diet increases visceral adipose tissue deposition, which may have an association with the insulin resistance.^[50]

A low GI diet improves *in vitro* insulin responsiveness of adipocytes from women at risk for CVD and improves *in vivo* insulin sensitivity as measured by the rate of fall of plasma glucose after an intravenous insulin injection.^[22,51] The beneficial effects of the high-carbohydrate low GI diets on body weight,^[52-54] insulin sensitivity,^[55] β -cell function,^[56,57] serum cholesterol,^[58] and glycemic control in diabetes^[59] may probably decrease the risk of metabolic syndrome,^[60] T2DM,^[61] and CVD.^[62]

A recent systematic review and meta-analysis suggested that the greater improvements in glycemic control have been shown by low-carbohydrate, low GI, Mediterranean, and high protein diets than control diets.^[63] However, other literature supports that the low-carbohydrate diets do not necessarily have superior effect and different diets with varying amounts of carbohydrate improve glycemic control, reduce CVD risk, and increase weight loss.^[17]

High glycemic load diets cause weight gain by increasing postprandial hyperinsulinemia that favors fatty acid, uptake, inhibition of lipolysis, and energy storage.^[64] High glycemic load diets also cause other postprandial metabolic changes, including reduced glucose to the lowest-point and increased hormones responsible for increasing hunger and energy intake in the post-absorptive period, probably leading to weight gain over time.^[65] Himsworth, in 1935, found that the increased dietary carbohydrate improved the insulin's ability to lower blood glucose. A low-carbohydrate high-fat diet was associated with a decreased ability of insulin to lower plasma glucose concentration whereas a low-fat high-carbohydrate diet was associated with the increased ability of insulin to facilitate glucose disposal.^[66,67]

INCRETINS SECRETION AND THEIR ACTIONS

Incretins are hormones that are released after ingestion of a meal and augment the secretion of insulin.^[68] Nutrients in the gastrointestinal tract stimulate the secretion of incretins, which amplify glucose-induced insulin release. These account for the greater insulin response to oral glucose as opposed to intravenous glucose. The available literature suggests that there are probably many hormones with an effect on insulin secretion, which are released postprandial.^[69] However, the most important ones include glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).^[70] Ingestion of a mixed meal or a meal enriched with specific fats and complex carbohydrates stimulate endogenous release of GLP-1 and GIP in humans.^[71,72]

GLP-1 is synthesized and released by L-cells located predominantly in the ileum and colon although the GLP-1 producing enteroendocrine L-cells have also been identified more proximally in the duodenum and jejunum. GIP-secreting enteroendocrine K-cells are located mainly in the duodenum and proximal jejunum, which is an ideal location for sensing and responding to the ingested nutrients. GLP-1 is particularly effective to inhibit gastric emptying, glucagon secretion, and food intake. These actions of GLP-1 to lower the blood glucose level are preserved in T2DM patients. However, endogenously secreted GLP-1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV). Thus, complementary therapeutic approaches that inhibit DPP-IV-mediated incretin degradation and use of degradation-resistant, long-acting GLP-1 receptor agonists (GLP-1RA) have shown promising results in the treatment of T2DM.^[68,73,74]

EFFECTS OF INCRETINS ON INSULIN SECRETION

GIP when interacts with its receptor on the pancreatic β -cells, it increases intracellular cAMP levels, which results in increased intracellular calcium concentration and thereby enhances the exocytosis of insulin-containing vesicles.^[75] The rise in intracellular cAMP levels could also activate a number of other signaling pathways, including the MAP kinase and the PI 3-kinase/protein kinase B pathways.^[76-78]

The oral glucose elicits the increased concentrations of GIP, which can completely account for accompanying increased secretion of insulin from the pancreatic β -cells.^[79] GLP-1 is one of the most

potent substances to release insulin from the pancreatic β -cells and strongly insulinotropic.^[80] Animal experiments have revealed a significant role of GLP-1 in insulin response to oral glucose.^[81,82]

GLP-1 also has various other effects to potentiate glucose-induced insulin secretion. Some of those effects include facilitation of all steps of insulin biosynthesis, upregulation of insulin gene expression and expression of genes essential for beta cell function, mitosis of beta cells, and promotion of differentiation of duct progenitor cells to beta cells, which inhibits apoptosis of beta cells.^[83]

INCRETIN-BASED THERAPY IN T2DM

Incretins (GLP-1 and GIP) stimulate insulin secretion, inhibit glucagon secretion, delay gastric emptying, and decrease appetite.^[84] Two classes of incretin-based therapies are currently available: Injectable GLP-1 receptor agonists (GLP-1RAs) and oral DPP-IV inhibitors. Guidelines currently include incretin therapies at all stages of pharmacologically treated T2DM.^[85,86] They are recommended for initial therapy (usually in combination with metformin and as monotherapy in some patients), as add-on therapy to oral agents, and even in combination with insulin with or without additional therapies.^[85-87]

Incretin-based therapies target most of the dysfunctional organ systems in T2DM, potentially improve β -cell function,^[88-90] have minimal hypoglycemia risk, and are either weight neutral^[91] or induce weight loss.^[92-94] The greater weight loss seen with incretin-based therapies, particularly, GLP-1RAs were associated with more favorable cardiovascular risk profile.^[95] In combination therapy with insulin, GLP-1RAs lead to sustained glycemic control, along with reduced insulin doses without an increase in hypoglycemia or weight gain. As a whole, the incretin class of antidiabetes agents is very useful, and both DPP-4 inhibitors and GLP-1RAs have improved management of T2DM.^[96]

EFFECTS OF CARBOHYDRATE DIET ON INCRETIN RESPONSE IN T2DM PATIENTS

Incretin responses enhance in T2DM patients and lean and obese healthy subjects during a large meal test. The β -cell sensitivity to glucose tends to increase in obese healthy subjects, and possibly also in T2DM patients during the large meal, compared with a small meal. This increased insulin response during the large meal could be because of an increased secretion of incretin hormones. However, there could be the contribution of other factors such as differences between the amounts of additional, non-glucose constituents of the meal with a potential influence on insulin secretion.^[97] Modest but significant reductions in meal-stimulated circulating GLP-1 levels were observed in patients with diabetes or impaired glucose tolerance.^[98,99] However, normal or slightly increased circulating levels of GIP were found in T2DM subjects in the basal or postprandial states.^[99]

Improved insulin secretion by dietary carbohydrate modification, even in the absence of weight loss has been evidenced by previous studies.^[56,57] A high-carbohydrate, low GI diet improves insulin secretion compared with a high-carbohydrate, high GI diet in persons with impaired glucose tolerance (IGT).^[57] Rye bread has a lower GI than wheat bread does.^[100] Wolever and Mehling in

their study emphasized the rye bread and pasta as low GI diet and potato and wheat bread as the high GI diet.^[57]

Rye bread consists of phenylalanine derivatives^[101] similar to nateglinide, which is an oral hypoglycemic agent that improves early insulin secretion.^[102] Pasta consumption considerably reduces postprandial glucose and insulin responses compared with mashed or boiled potato consumption.^[100,103] Both rye bread and pasta consumption result in lower postprandial insulin and incretin responses than does wheat or oat bread consumption.^[104] Rye bread and pasta intake may improve acute insulin secretion in persons with metabolic syndrome by chronically lowering postprandial insulin responses and allowing β -cell function to recover.^[105]

EFFECTS OF CARBOHYDRATE DIET RESTRICTION IN T2DM PATIENTS ON INSULIN AND INCRETIN THERAPIES

Weight loss and decrease in the abdominal fat mass reverses insulin resistance. Hence, if safe and balanced lifestyle measures to lose weight can be sustained in the long term that will have the potential to improve insulin resistance and glycemic control. The long-term sustained weight loss is difficult to achieve, particularly in T2DM patients. The isoenergetic modification of the macronutrient composition and the quality of ingested foods may improve insulin sensitivity.^[106] A dietary pattern that includes carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged for good health. In diabetes management, it is important to match doses of insulin and insulin secretagogues to the carbohydrate content of meals. By testing pre- and post-prandial glucose, many individuals, use the experience to evaluate and achieve postprandial glucose goals with a variety of foods. To date, research has not demonstrated that one method of assessing the relationship between carbohydrate intake and blood glucose response is better than other methods.^[107] Both Diabetes UK and the ADA identify carbohydrate management as a key strategy and address both type and amount of carbohydrate, emphasizing unprocessed carbohydrate from whole grains, fruit, and vegetable sources.^[17] A recent recommendation from the ADA is that the diets should be individualized, as those that provide the same caloric restriction, but differ in protein, carbohydrate, and fat content is equally effective in achieving weight loss.^[108]

No standard meal plan or eating pattern benefits all the DM patients, although total energy intake is an important consideration, especially in overweight or obese DM patients.^[17] Malandrucco et al. have reported the evidence that short-term caloric restriction by itself improves glucose control and β -cell function in morbidly obese T2DM patients.^[109] However, the ADA in their current position statement have recommended to prescribe the diet, physical activity, and behavioral therapy designed to achieve >5% weight loss for overweight and obese T2DM patients who are ready to achieve weight loss.^[108]

Before recommending the popular weight loss diets, their potential effect needs to be carefully considered with the help of sound evidence.^[110] Hypoglycemia can occur due to the effect of

carbohydrate restriction on glycemic control in T2DM patients on glucose-lowering medication. Hence, it is recommended to reduce medications before initiating a low-carbohydrate diet.^[11]

CONCLUSION

Oral glucose is a potent stimulus for insulin secretion both through its direct action on the β -cells of the pancreas and indirect action by increasing incretin secretion. However, no carbohydrates have the same effect in insulin and incretin secretion. The postprandial blood glucose concentration and insulin responses depend on the amount, type, and rate of digestion of the carbohydrates. High GI diet increases the insulin secretion by increasing the blood glucose level, whereas a large-carbohydrate meal, even with low GI can increase the insulin secretion by increasing the secretion of incretins. The MNT in the management of T2DM focuses on increasing the insulin secretion and sensitivity. However, the nutrition therapy in the management of the T2DM patients on insulin and incretin-based therapies should focus attention to increase the insulin sensitivity, which can be achieved by the weight loss and reduction in abdominal fat mass. In such cases, reduced energy intake while maintaining a healthful eating pattern is recommended for overweight or obese T2DM patients to promote weight loss. It should be considered that low-carbohydrate diets in T2DM patients who are on insulin and incretin-based therapies could increase the likelihood of hypoglycemia. Hence, prevention of hypoglycemia in the management of T2DM is an essential part of the MNT. Based on the available literature, we conclude that the carbohydrate diet restriction in T2DM patients on insulin and incretin-based therapies becomes more effective if it is done with a focus on weight loss and prevention of the hypoglycemia. The individualized dietary plan or eating pattern and adjustment of insulin and incretin doses should be considered for each patient based on his or her glycemic control. However, more clinical data on effectiveness of various dietary patterns in T2DM patients on insulin and incretin-based therapies are sought in future studies.

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