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Review Article

Effect of Green Tea on Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) is currently one of the most significant public health challenges worldwide. Over the past three decades, the number of people with Type 2 DM (T2DM) has more than doubled globally; and this number is projected to rise further over the next few decades. Uncontrolled glycaemia in patients with DM is associated with various acute and chronic complications, with associated adverse impact on their overall quality of life. Amongst various aetiopathogenetic factors for diabetes-related chronic complications, glycated lipids play a significant role; more specifically, they are produced during the non-enzymatic reaction between amino acids and reducing sugar (glucose) and contribute to oxidative stress and angiogenesis in DM. Recently there is considerable interest in relationship between the Green Tea (GT) and its beneficial effects in DM and related chronic complications. Produced from the plant *Camellia sinensis*, the GT contains certain polyphenolic compounds – called as Catechins – which help promote good health and benefit diabetics too. Catechins are flavonoids and include such flavanols as epigallocatechin gallate, epigallocatechin, epicatechin gallate, and epicatechin. Studies have shown that GT extract (GTE) containing these biochemical compounds helps in beta cell up-regulation to increase insulin secretion and also augments glucagon-like peptide 1 to lower glucagon secretion, which control blood glucose levels and improve insulin resistance in patient with T2DM. Available literature suggests that GT lowers fasting blood glucose and fasting serum insulin levels and helps improve glycated haemoglobin (a marker of glycaemic control in diabetics). Studies have also demonstrated anti-hyperglycaemic and anti-oxidative properties of GTE, which may prevent or delay complications in patients with T2DM. Moreover, intake of GT and/or GTE in moderate amounts is considered harmless and has been reported to be well-tolerated. However, the results of human clinical trials investigating the effects of GT and GTE on glycaemic control and insulin sensitivity vary; and further research and larger, longitudinal epidemiological studies are required to fully understand mechanisms of the beneficial effects of GT on human health in general and in diabetes in particular.

Keywords: Diabetes Mellitus; Epicatechin; Epicatechin Gallate; Epigallocatechin; Epigallocatechin Gallate; Green Tea; Insulin Resistance

Abbreviations

AMPK: 5'-Adenosine Monophosphate-Activated Protein Kinase; BT: Black Tea; DM, Diabetes Mellitus; EC: Epicatechin; ECG: Epicatechin Gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin Gallate; GLUT 2: Glucose transporter 2; GLUT 4: Glucose Transporter 4; GT: Green Tea; GTE: Green Tea Extract; HbA1c: Glycated Haemoglobin; OT: Oolong Tea; ROS, Reactive Oxygen Species; SGLT 1: Sodium-Glucose Linked Transporter 1; T2DM: Type 2 Diabetes Mellitus.

Introduction

Diabetes mellitus (DM) is chronic metabolic disorder caused due to inherited and/or attained deficiency in production of insulin by beta cells of pancreas or inefficient uptake and/or effectiveness of insulin in target tissues, associated with elevated levels of blood glucose (hyperglycaemia). Long-standing hyperglycaemia, in turn, affects almost all body organs and organ-systems leading to various complications, particularly affecting eyes, heart, kidneys, blood vessels and nerves [1].

There are two principle forms of diabetes:

- Type 1 DM in which the insulin is not produced by the beta cells in the pancreatic islets of Langerhans. This form of DM commonly develops in children and adolescents.
- Type 2 DM (T2DM) in which either the pancreas is not able to produce enough insulin or the body's end-user cells are resistant to the insulin produced by the beta cells. T2DM is a serious public health issue worldwide as it is majorly associated with lifestyle factors (like improper diet, physical inactivity, nicotine consumption, obesity, alcohol consumption, etc.) and contributes to increased cardiovascular morbidity and mortality [1].

Various studies have shown that, under low insulin conditions in T2DM, the glycated lipids formed from the reactions between lipids and glucose lead to glycation of the cell membrane phospholipids, which in turn generates reactive oxygen species (ROS) causing oxidative damage to peripheral tissues and other problems in patients with T2DM [2-4].

Hyperglycaemia is coupled with irregular metabolism of carbohydrates, fats, and proteins consequential from endocrine defects in insulin actions, secretion, or both. An inhibition of alpha-amylase and alpha-glucosidase (carbohydrate hydrolyzing enzymes) can considerably diminish post-prandial hyperglycaemia, which is thus considered a vital therapeutic tactic in the management of blood glucose levels in T2DM. Such inhibition of these enzymes delays the breakdown of polysaccharides and glucose absorption, thereby decreasing the level of glucose in the blood [5,6].

Potential sites of action of dietary polyphenols present in tea on carbohydrate metabolism and glucose homeostasis

For individuals at risk of T2DM, a key dietary modification aimed to prevent or delay the onset of the disease involves consumption of food products from plant sources (such as grains, vegetables, fruits and berries). These foods items are known to have good quantities of dietary fibre along with variable amounts of polyphenolic compounds. As shown in Figure 1, the polyphenolic compounds tend to influence glucose metabolism through several processes such as inhibition of carbohydrate digestion, absorption of glucose from the intestine stimulating secretion of insulin from the pancreatic beta cells, modulation in the release of glucose from liver, activation of the insulin receptors thus allowing glucose uptake in the insulin-sensitive tissues, and modulation in the hepatic glucose output [7].

Dietary polyphenols may be present in different combinations of metabolites from different chemical classes. In T2DM, the most widely studied plants and metabolites include tea, mainly for its condensed tannins, in particular the epigallocatechin gallate (EGCG) [8].

An overview of effects of tea consumption on risk of T2DM and other diseases

Tea is the most common drink in the world. There are many types of tea such as black, sour, white, oolong, green tea, etc. Various types of tea are differentiated based on their manufacturing processes. The green tea (GT) is manufactured by aerating fresh tea plants. It contains certain characteristic polyphenolic compounds viz. epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC), which are usually called as catechins. A classic tea beverage is primed in a ratio of 1 g leaf to 100 ml water in a 3-min brew; generally contains 250–350 mg tea solids; and is made up of 30-42% catechins and 3-6% caffeine [11]. EGCG is abundantly present in tea and has attracted the most attention in the scientific research. On the other hand, in making of the black tea (BT), the tea leaves are trampled to allow the polyphenol oxidase to catalyze the oxidation, leading to polymerization of catechins. In brewed BT, the residual catechins account for 3-10% of the solids; the typical color and taste of BT is due to the theaflavins (consisting of theaflavin, theaflavin-3-gallate, theaflavin-39-gallate and theaflavin-3,39-digallate) which account for 2-6% of the solids in brewed BT [12]. The oolong tea (OT) is fashioned by partial fermentation. Of the tea formed worldwide, 78% is BT which is frequently consumed in the Western countries; 20% is GT which is generally consumed in Asian countries; and 2% is OT which is consumed mainly in Southern China [13].

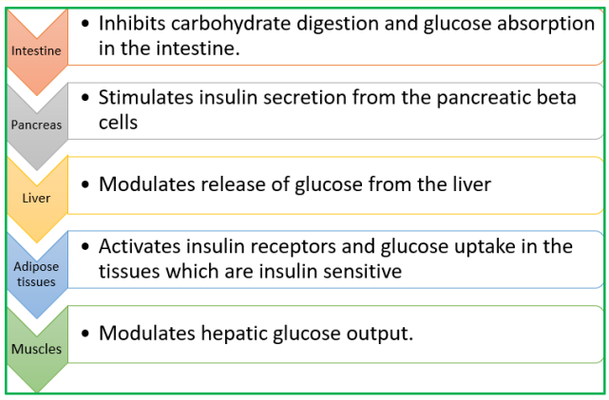

Figure 1: Potential sites of action of dietary polyphenols in carbohydrate metabolism and glucose homeostasis [7].

Several studies have shown an inverse relationship between the tea consumption and high blood glucose levels. Drinking tea has recently attracted scientific attention as a potential nutritional strategy to prevent a broad range of disorders including DM, cardiovascular disease, arthritis, neurological defects (such as Parkinson's disease) and cancer. Studies have shown that the polyphenols present in tea show antioxidant properties by attaching to metal ions, which eliminates ROS and may exert beneficial effects [9,10].

Beneficial effects of tea

Tea lowers the risk of T2DM

Tea improves insulin sensitivity and reduces blood glucose levels. Feasible mechanisms of action for tea on T2DM may involve one or more physiological pathways. For example, tea catechins have been shown to inhibit carbohydrate digestive enzymes, which indicates that glucose production may be decreased in the gastrointes-

tinal system resulting in lesser levels of glucose and insulin secretion. BT, GT, and OT have also shown to increase insulin sensitivity by raising insulin-stimulated glucose uptake in adipocytes. GT may avert damage to pancreatic beta cells. Some observational reports have also linked consumption of tea to significant falls in plasma glucose and glycated haemoglobin (HbA1c) levels suggestive of better glycaemic control in diabetics [14].

Tea contains bioactive compounds that improve health

Bioactive compounds have activities in the body that may promote good health. They decrease development of free radicals in the body, protect cells and molecules from damage, and are thus considered helpful in prevention of cancer, heart disease, and other diseases. Examples of key bioactive compounds include tannins, lycopene, resveratrol, lignan, and indoles. Teas are excellent sources of dietary phenolic compounds and tannins, and the content of these compounds in the infusion is higher with the longer infusion time. GT leaves have the highest phenolic content, followed by teas of decaffeinated GT bag, GT bag, BT bag, decaffeinated BT bag, BT leaves, and OT leaves [15].

Tea compounds improve brain functions

Teas contain L-theanine which stimulates the activity of the inhibitory neurotransmitter gamma-aminobutyric acid which in turn increases secretion of dopamine and exerts anti-anxiety effects. Evidence from human electroencephalograph studies have illustrated that L-theanine has a direct effect on the brain; and at higher doses (as found in BT), it appreciably increases activity in the alpha frequency band thereby relaxing the mind as well as improving attention [16].

Tea increases fat burning and improves physical performance

Tea elevates energy expenditure by 4% and increases fat oxidation by 17% signifying that it helps burn body fat. Tea contains such sympathomimetics as caffeine, ephedrine, and capsaicin, which have therapeutic applications in management of obesity. For instance, a combination of caffeine and ephedrine has been shown to be useful in long-term weight management, likely due to diverse synergistic mechanisms (though, undesirable effects of ephedrine tend to foil this approach in practice). Capsaicin has been found to be successful; however, this also requires a tough acceptance to a definite dosage clinically. GT may perform by constituting both tea catechins and caffeine [17].

Antioxidants in tea lower the risk of various cancers

Protective effects of antioxidants may abridge the possibility of breast, prostate, and colorectal cancers. The chief polyphenols in GT (viz. EGCG, EGC, ECG and EC) and BT (viz. theaflavins and thearubigins) have antioxidant activity. Tea polyphenols also show inhibiting properties towards tumor cell production and may induce apoptosis. Tea catechins have properties to inhibit angiogenesis and tumour cell invasiveness and may protect in opposition to damage produced by the harmful ultraviolet radiation. They have also been shown to have protective effect on the immune system functions [18].

Role of catechins on carbohydrate homeostasis measured *in vitro*

The intestinal absorption of glucose is facilitated by its active transport via the sodium-glucose linked transporter 1 (SGLT 1) and the glucose transporter 2 (GLUT 2) [7,14]. The tea catechins have been shown to restrain the glucose transport. Studies have shown that a tea polyphenol, theaflavin-3-O-gallate, lowers the postprandial glucose in response to maltose inhibition and not by inhibiting the intestinal sucrose activity or glucose transport. In addition, an inhibitory effect of EGCG was found in L6 skeletal muscle cells on insulin resistance prompted by dexamethasone (a glucocorticoid); and a 24-hr action with EGCG impaired the effect of dexamethasone on glucose uptake and ameliorated insulin-stimulated glucose uptake in a dose-dependent manner by enhancing the glucose transporter 4 (GLUT 4) translocation to plasma membrane. EGCG was able to raise the phosphorylation of 5'-adenosine monophosphate-activated protein kinase (AMPK), suggesting that AMPK signaling pathway is likely accountable for the EGCG stimulated GLUT 4 translocation [19].

Possible mechanisms to explain these observations in T2DM may involve dietary amplification of EGCG resulting in condensed endogenous liver glucose output and rise in glucose-induced insulin secretion; it may be related to an inhibition of genes intricate in gluconeogenesis (with reduced hepatic gluconeogenesis) and a stimulation of genes involved in glycogenesis [19]. Studies suggest that an exposure to EGCG or tea extract causes diminished glucose production by inhibiting the expression of key gluconeogenetic enzymes (viz. phosphoenolpyruvate carboxykinase and glucose-6-phosphatase) in a parallel manner to insulin. Additional experiments have revealed that EGCG activates AMPK (which is necessary for the inhibition of gluconeogenesis) through the calmodulin-de-

pendent protein kinase. Moreover, the EGCG induces ROS which is required for the activation of AMPK and inhibition of gluconeogenesis [7]. The theaflavins activate AMPK in HepG2 cells, which leads to restraint of hepatic gluconeogenesis and initiation of fatty acid beta oxidation that augments hepatic glucose utilization and insulin sensitivity [13].

The above series of events suggest that the enhanced result of tea on the increase of insulin resistance is an initial mechanism. The subsequent mechanism is in the course of an impact of tea consumption on hepatic gluconeogenesis (which is not only for GT but also for OT). The defensive action of tea on the pancreatic tissue is the third mechanism. Both GT and BT preserve the insulin secretory machinery and protect pancreatic beta cells. These points are in alignment of the observations that a daily consumption of more-than-three cups of tea is associated with a lower risk of T2DM [2].

Effect of GT on insulin resistance and sensitivity

Current *in vivo* and *in vitro* studies have revealed that the GT extract (GTE) can considerably reduce fasting plasma concentrations of glucose, HbA1c, and insulin. Experimental studies in rats have shown that GTE improves the capability of fat cells for glucose uptake and increases specific insulin bonding and GLUT 4 content in fat cells. These studies have also revealed that catechins ingestion can prevent the onset of streptozotocin-induced diabetes by protecting pancreatic islets. In other studies, GT significantly lowered fasting glucose concentrations and HbA1c, but did not notably affect fasting insulin. The advantageous effects of GT on fasting glucose concentrations could only be observed when the perplexing effect of caffeine was removed. In people consuming high dose of catechins, the GT appreciably lowered fasting glucose concentrations. Biochemical compounds in GTE help in beta cell up-regulation to increase insulin secretion and also augments glucagon-like peptide 1 to lower glucagon secretion, which control blood glucose levels and improve insulin resistance in patient with T2DM [11].

GTE remediate the diabetes-induced oxidative stress in diabetic rats and improves the capability of fat cells and skeletal muscle for glucose uptake by increasing the protein content and translocation of GLUT 4. A 16-week treatment with decaffeinated GTE resulted in decreasing body weight and body mass index but there was no significant change in other anthropometric data (like waist circumference and hip circumference). The glucose-lowering effects of GTE were shown better in patients with diabetes history of less than 5 years than those with a history of more than 5 years. Studies have indicated that a daily intake of 856mg of decaffeinated GTE for 16 weeks is safe and results in no adverse effects on health [7].

Anti-hyperglycaemic benefits of GT

Observational studies have shown that elevated frequency of GT consumption was associated with improved glycaemic control and reduced risk of T2DM. GT absorption was better in the fasted state than in the postprandial condition. GT has plentiful biological activities that can possibly provide anti-hyperglycaemic benefits which may include the following [5]:

- Inhibition of intestinal alpha-amylase, sucrose, and alpha-glucosidase leading to a fall in carbohydrate absorption from the intestine;
- Inhibition of hepatic gluconeogenesis during a decreased expression of gluconeogenic genes in liver;
- Improvement of insulin sensitivity and insulin-like activity; and
- Progression in oxidative stress.

The beneficial effect of GT with or without caffeine intake on fasting blood glucose was observed when the period of consumption was a little more than 12 weeks. Interventional studies with GTE in healthy rats and humans have confirmed improved insulin sensitivity subsequent to an oral glucose tolerance test based on lower insulin levels and unaffected glucose levels. Furthermore, EGCG was the catechin found to have the most insulin-enhancing activity in an animal *in vitro* study [7].

Effect of GT on AMPK

AMPK is an energy-sensing molecule which gets activated by EGCG in hepatocytes, adipocytes, cancer cells, and endothelial cells. It contributes to inhibition of gluconeogenesis, stimulation of lipolysis, apoptosis, and reduction of endothelin-1 expression. This activity may contribute to improvement of insulin sensitivity and vasodilation. EGCG is furthermore identified to hinder the activation of I-kappa kinase (a serine/threonine kinase drawn in the pathogenesis of insulin resistance). The GTE also includes pyrroloquinoline quinone, a recently revealed cofactor in GT. They have been shown to improve the basal and insulin-stimulated glucose uptake of rat adipocytes, to slow down intestinal glucose uptake by inhibiting the sodium-dependent glucose transporter of rabbit intestinal epithelial cells, and to reduce serum glucose level in alloxan-diabetic rats [20].

Conclusion

According to various observational studies, GT absorption is better in the fasted state than in the postprandial condition which improves the insulin sensitivity of the cells. EGCG present in GT inhibits cellular glucose uptake, indicating its beneficial effect in controlling glycaemia. Consumption of EGCG also activates AMPK which further inhibits gluconeogenesis. These process and mechanisms help control glycaemia and may prevent or delay complications in diabetics. However, the exact underlying mechanisms in this regard are yet not very clear. Future research needs to define the benefits of GT which would establish the safe range of consumption and its mechanism of action.

Conflict of Interest

None. There is no direct or indirect real or perceived financial interests or conflicts; and this work of the authors is without any prejudice to their professional association with HCL Healthcare India.

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