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Review

Protective effects of tea, red wine and cocoa in diabetes. Evidences from human studies

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ABSTRACT

Prevention of diabetes through the diet has recently received an increasing interest, and polyphenolic compounds, such as flavanols, have become important potential chemopreventive natural agents due to their proved benefits on health, with low toxicity and cost. Tea, red wine and cocoa are good sources of flavanols and these highly consumed foods might contribute to prevent diabetes. In this regard, there is increasing evidence for a protective effect of tea, red wine and cocoa consumption against this disorder. This review summarizes the available epidemiological and interventional human studies providing evidence for and against this effect. Overall observational data suggest a benefit, but results are still equivocal and likely confounded by lifestyle and background dietary factors. The weight of data indicate favourable effects on diabetes risk factors for tea, red wine and cocoa intake, and a number of plausible mechanisms have been elucidated in human studies. However, despite the growing evidence it remains uncertain whether tea, red wine and cocoa consumption should be recommended to the general population or to patients as a strategy to reduce the risk of diabetes.

Contents

Abbreviations: AGE, advanced glycation end products; Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; BW, body weight; Ch, total cholesterol; CRP, C-reactive protein; EC, epicatechin; ECG, epicatechin gallate; EGC, epigallocatechin; EGCG, epigallocatechin gallate; FFA, free fatty acid; GLP-1, glucagon-like peptide 1; Gluc, glucose; GSH, glutathione; GTE, green tea extract; GTP, green tea polyphenols; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IFN-γ, interferon-γ; Ins, Insulin; IL-6, interleukin-6; IR, insulin resistance; LDL, low-density lipoprotein; MDA, malondialdehyde; ROS, reactive oxygen species; TAC, total antioxidant activity; T2D, type 2 diabetes; TG, triglyceride; TNFα, tumour necrosis factor α; UACR, urinary albumin-creatinine ratio.

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1. Introduction

Diabetes mellitus is a complex metabolic syndrome, and constitutes a rising world health problem, being type 2 diabetes (T2D) the most common form of diabetes and one of the most common chronic diseases in almost all countries (Whiting et al., 2011). This disease is characterized by hyperglycaemia, which is very commonly followed by hyperlipidaemia (Poitout and Robertson, 2008). In fact, after the onset of the disease both alterations contribute to the deterioration of the pancreatic β-cell function and other tissues such as liver, muscles or adipose tissue, etc. Therefore, glutoxicity and lipotoxicity should be taken into account in T2D, as both hyperglycaemic and hyperlipidaemic abnormalities exert damaging or toxic effects in different tissues of the organism and are also responsible for the serious health complications associated to this disease (cardiovascular disease, kidney failure, blindness, neuropathy, etc.) (Chaturvedi, 2007).

Due to the relevance of T2D, many drugs have been developed trying to ameliorate or cure this disease, although the current medications are not sufficiently effective in maintaining long-term glycaemic control in a high percentage of patients. Indeed, at present it is considered that the most efficient approach to prevent or delay the onset of diabetes at the lowest cost is at nutritional level (Dembinska-Kiec et al., 2008). Then, the identification of dietary components as potential antidiabetic agents has become an essential subject in the current research. In this regard, polyphenols, which are present in fruits and vegetables, have attracted a great deal of interest because of their potential ability to act as highly effective chemopreventive agents (Dembinska-Kiec et al., 2008). Indeed, tea, red wine and cocoa are good sources of flavanols (a class of polyphenol), but it is not completely established whether these foodstuffs exert a beneficial effect against diabetes. Therefore, the present review is focused on describing the current evidence on the link between tea, red wine or cocoa consumption and diabetes, based on epidemiologic and interventional studies in humans.

2. Physiopathology of diabetes

Hyperglycaemia, which is the biochemical hallmark of T2D, results from a combination of genetic and acquired factors. The main pathophysiologic features driving T2D are peripheral insulin resistance (IR) and eventual destruction of insulin producing beta-cells in pancreas (Guillausseau et al., 2008). Although IR, which is characterized by high circulating levels of glucose and insulin, is the earliest detectable abnormality of T2D, it has been pointed that changes in insulin secretion determine both the onset of hyperglycaemia and the progression toward insulin therapy (Marchetti et al., 2012). Actually, during IR beta cells maintain normal glucose tolerance by increasing insulin output, but when beta cells cannot secrete adequate amounts of insulin to cope with IR chronic hyperglycaemia appears. At the early stages of the illness, hyperglycaemia increases gradually but patients do not notice any classic symptom; therefore, T2D usually remains undiagnosed for many years. Together with hyperglycaemia, elevations of plasma free fatty acid (FFA) levels that often accompany insulin resistance, also play a pathogenic role in the early stages of the disease (Poitout and Robertson, 2008). Once the primary pathogenesis of diabetes is established, hyperglycaemia and very commonly hyperlipidaemia exert additional damaging or toxic effects (glucotoxicity and lipotoxicity, respectively) in a variety of tissues including beta cells and those involved in insulin resistance leading to the progression of T2D (Poitout and Robertson, 2008).

The pathogenic effect of hyperglycaemia, in concert with FFA release, is mediated to a significant extent via increased generation of intracellular reactive oxygen species (ROS). Several pathways are identified in the literature as major contributors of ROS production in the organism: activation of polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased expression of AGEs receptor and its activating ligands, activation of protein kinase C and excessive activity of the hexosamine pathway (Robertson, 2004). ROS can directly inflict damage on macromolecules and can also indirectly lead to tissue damage by activating a number of cellular stress-sensitive pathways. Accordingly, beta cells are especially vulnerable to ROS because of its low intrinsic level of antioxidant enzymes (Robertson, 2010). Chronically excessive ROS levels cause decreased insulin gene expression, content and secretion and also accelerate rates of apoptosis contributing to the inexorable decrease of beta cell mass and functionality (Robertson, 2004). Similarly, oxidative stress is believed to modify a number of signalling pathways within the cell that can ultimately provoke insulin resistance. In particular, elevated ROS production inhibits insulin signalling in peripheral tissues leading to the inability of insulin to increase glucose disposal and to suppress glucose production. Altogether, these effects significantly accelerate the development of the disease (Bashan et al., 2009).

Oxidative stress has also been implicated in the progression of diabetic complications. Increase in ROS levels is associated with long-term dysfunction and failure of various organs, especially eyes, kidneys and nerves (Wei et al., 2009). Interestingly, the vascular endothelium has been identified as a most important component in diabetes-associated complications, which include many cardiovascular disorders such as atherosclerosis, hypertension and peripheral neuropathy. Increased ROS levels impair endothelial nitric oxide synthase activity resulting in diminished nitric oxide bioavailability and vascular endothelial dysfunction (Kolka and Bergman, 2013). Intrinsic properties of the injured endothelium result in vasoconstriction, smooth cell proliferation, coagulation disorders, leukocyte aggregation, thrombosis, and vascular inflammation predisposing to atherosclerosis (Versari et al., 2009). Therefore, biomarkers of endothelial dysfunction, such as vascular cell adhesion molecule-1, and markers of systemic inflammation including C-reactive protein (CRP) and tumour necrosis factor (TNF)-α are pathologically enhanced in diabetic subjects (Tousoulis et al., 2013).

Currently there are different classes of antidiabetic agents approved for the management of T2D. However, the usage of these drugs is often associated with serious undesirable side effects, including weight gain, hypoglycaemia and gastrointestinal disturbances (He, et al., 2015). Considering the importance of ROS and oxidative stress in the aetiology of diabetes and its complications, one of the main challenges of research in recent years has been to identify natural dietary compounds that can attenuate oxidative stress. Accordingly, several findings suggest the potential use of phenolic compounds, with demonstrated pharmacological properties, as a potential strategy to prevent the development and the progression of diabetes and its associated complications (Del Rio, et al., 2013). In this context, tea, red wine and cocoa have received much attention because they are particularly rich in flavanols, a main class of polyphenols with strong antioxidant properties.