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# Use of Dark Chocolate for Diabetic Patients: A Review of the Literature and Current Evidence

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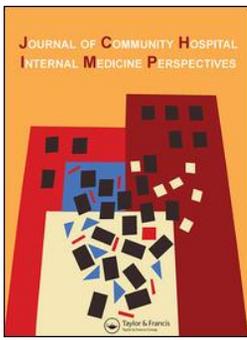
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## Use of dark chocolate for diabetic patients: a review of the literature and current evidence

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### ABSTRACT

Dietary changes are a major lifestyle factor that can influence the progression of chronic diseases such as diabetes. Recently, flavanols, a subgroup of plant-derived phytochemicals called flavonoids, have gained increasing attention, due to studies showing an inverse correlation between dietary intake of flavanols and incidence of diabetes. Flavanoids in the cocoa plant may ameliorate insulin resistance by improving endothelial function, altering glucose metabolism, and reducing oxidative stress. Oxidative stress has been proposed as the main culprit for insulin resistance. The well-established effects of cocoa on endothelial function also points to a possible effect on insulin sensitivity. The relationship between insulin resistance and endothelial function is a reciprocal one. Overall, the evidence from these studies suggests that cocoa may be useful in slowing the progression to type 2 diabetes and ameliorating insulin resistance in metabolic syndrome. Additionally, results from several small studies indicate that cocoa may also have therapeutic potential in preventing cardiovascular complications in diabetic patients. Studies highlighting the potential of cocoa-containing diets, in large-randomized controlled trials should be performed which might give us a better opportunity to analyze the potential health-care benefit for reducing the risk of complications in diabetic patients at molecular level.

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## 1. Introduction

Dietary changes are a major lifestyle factor that can influence the progression of chronic diseases such as diabetes [1]. Recently, flavanols, a subgroup of plant-derived phytochemicals called flavonoids, have gained increasing attention, due to studies showing an inverse correlation between dietary intake of flavanols and incidence of diabetes [2–4]. Foods rich in dietary flavonoids have therefore been targeted as potential dietary adjuncts in the management of diabetes [5].

Dark chocolate is one such food and, historically, chocolate was used for healing purposes [6]. Foods and beverages made from beans from the *Theobroma cacao* tree have been consumed by humans since at least around 500 AD [7]. However, chocolate consumption has been on the rise in recent years with wider availability of commercially-produced products. Worldwide, chocolate consumption ranges from 120 g per person per year in China to around 12 000 g per person per year in Ireland. The USA is in the middle of this range, with consumption of approximately 500 g per person per year [8]. The focus of research on dark chocolate to date has been primarily on its effect on cardiovascular risk, though

there are studies indicating the potential benefit of dark chocolate consumption on other organ systems and conditions [9]. This article reviews the effects of dark chocolate consumption on glucose metabolism with suggestions for future research.

## 2. Positive effects

### 2.1. Dark chocolate and pre-clinical studies

Flavanoids in the cocoa plant may ameliorate insulin resistance by improving endothelial function, altering glucose metabolism, and reducing oxidative stress [2–5]. Oxidative stress has been proposed as the main culprit for insulin resistance [10]. This hypothesis is supported by the observation that many anti-diabetic drugs demonstrate antioxidant effects. This effect may be direct – as in the case of calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and statins – or indirect – as in glinides and acarbose, which prevent oxidative stress caused by postprandial hyperglycemia [10]. If this hypothesis is proved correct, the demonstrated antioxidant activity of dark chocolate could theoretically also protect against insulin resistance [11]. However,

there is presently stronger evidence for an insulin-sensitizing effect mediated by altered glucose metabolism and changes in endothelial function [11].

Many polyphenols, including epicatechin and catechin, have been found to alter glucose metabolism in *in vitro* laboratory studies [12]. Similarly to acarbose, the epicatechin and catechin in dark chocolate inhibit alpha-glucosidase activity [13]. These compounds have also been shown to inhibit absorption of glucose from the intestine [13]. In *in vivo* studies, diabetic rat models confirmed the insulin-sensitizing effect of dark chocolate. In two such studies, epicatechin increased insulin secretion and regenerated pancreatic  $\beta$ -cells [13–15]. Similarly, supplementation of diabetic rats with cocoa extract for four weeks was dose-dependently associated with reduced serum glucose, post-prandial hyperglycemia, atherogenic lipid levels, insulin resistance, and 8-isoprostane, a biomarker of oxidative stress [14–17]. These studies established the efficacy of cocoa extract/dark chocolate in reducing insulin resistance in animals.

## 2.2. Dark chocolate and human studies

Similarly, positive effects of cocoa have also been found in human studies. The well-established effects of cocoa on endothelial function also points to a possible effect on insulin sensitivity in human studies. The relationship between insulin resistance and endothelial function is a reciprocal one. Decreased insulin sensitivity worsens endothelial function; conversely, a decline in endothelial function can decrease insulin sensitivity [18]. In healthy individuals, insulin increases blood flow to skeletal muscles and glucose uptake by muscle cells through vasodilation. In contrast, in insulin-resistant individuals, insulin-mediated vasodilation is impaired leading to impaired glucose disposal. Insulin resistance has been associated with reduced activity of endothelium-derived nitric oxide synthase (NOS) with subsequent increased plasma levels of asymmetric dimethylarginine (ADMA), which is an endogenous NOS inhibitor [19]. Elevated ADMA levels therefore lead to impaired endothelial function and promotion of atherosclerosis [19,20]. Thus, the availability of nitric oxide (NO) likely plays a role in initiating cellular response to insulin. The ability of cocoa extract to increase bioavailability of NO and the possible relationship between dark chocolate consumption and insulin resistance led to several investigations in human special populations, particularly the hunter-gatherer Kuna in Panama, whom have significantly lower cardiovascular disease and cancer death rates than the USA population and a higher consumption of cocoa-containing beverages when living on the Ailigandi Islands, but have increasingly migrated to urban areas and adopted a more Western diet with subsequent increases in cardiovascular disease, diabetes, and cancer [21].

In this population, ingestion of a more traditional amount of flavonoid-rich dark chocolate for 15 days was associated with improved endothelial function and improved insulin sensitivity in hypertensive, urbanized Kuna [22,23]. These results were replicated in healthy individuals as well as in hypertensive patients with impaired glucose tolerance [23]. In the former study, subjects received oral glucose tolerance tests (OGTT) after consuming either dark chocolate or white chocolate for 15 days. Compared with white chocolate, ingestion of dark chocolate was associated with lower quantitative insulin-sensitivity check index values and higher homeostasis model insulin resistance (HOMA-IR) values [22]. In the latter study, hypertensive, glucose-intolerant subjects also received OGTT after 15 days of daily consumption of either flavanol-rich dark chocolate or white chocolate [23]. Therefore, dark chocolate increased  $\beta$ -cell function, increased insulin sensitivity, and decreased HOMA-IR, compared to white chocolate.

Similarly, cocoa-rich foods showed significant effect insulin sensitivity in those patients with insulin resistance on the basis of weight indices. Insulin sensitivity improved significantly in non-diabetic overweight adults consuming high-flavanol cocoa (900 g flavanols) for 12 weeks compared to low-flavanol cocoa [24]. Cocoa's effects on insulin resistance may be dependent on its continual consumption over a longer period of time. Two studies have indicated improvements within two weeks of insulin-mediated vasodilation (through increased NOS levels) and fasting capillary whole blood glucose, but the two week trial period did not demonstrate improved measures of insulin resistance [20,25].

## 2.3. Dark chocolate and effect on gut microbe

Another important discussion is the effect of dark chocolate and flavanols on gut microbe. Most of the effects are individualized to the type of microorganisms. The bioavailability and effects of polyphenols greatly depend on their transformation by components of the gut microbiota. For example, gram-negative bacteria are more resistant to flavanols owing to their different wall composition, as compared to gram-positive bacteria [26]. Effects can also be modified by bacterial growth and metabolism of flavanols and dark chocolate. Studies suggest a dose-dependent activity of flavanols on bacteria, inhibiting their growth [27–29]. Some studies suggest that bacteria in the gut may also be affected by the production of hydrogen peroxide produced by substances in flavanols [29].

On the other hand, flavanols in dark chocolate inhibit toxins in bacteria like *H. Pylori*, including suppression of urease, hence, damaging bacterial membranes [30]. Few studies have also linked affects of flavanols on gut microbe as protective against various cancers. However, the exact mechanism of action are unknown [31].

It is clear that dietary polyphenols and their metabolites contribute to the maintenance of gut health by the modulation of the gut microbial balance through the stimulation of the growth of beneficial bacteria and the inhibition of pathogen bacteria, exerting prebiotic-like effects. However, data on the impact of polyphenols on the gut microbiota and their mechanisms of action in humans are scarce. In addition, a better understanding of the dietary phenolic and gut microbiota relationship by the combination of metagenomic and metabolomic studies provides more insight into the health effects of polyphenols.

#### 2.4. Dark chocolate and arterial stiffness

In a one-year intervention study of postmenopausal Type 2 diabetes patients, daily dark chocolate consumption had a positive effect on arterial stiffness in a subgroup analysis of 35 participants [32]. In a cross-over study where healthy participants were assigned to receive five treatments of daily intake of cocoa powder with different doses of flavanols for one week each, cocoa consumption improved arterial stiffness [32,33].

Overall, the evidence from these studies suggests that cocoa may be useful in slowing the progression to type 2 diabetes and ameliorating insulin resistance in metabolic syndrome. Additionally, results from several small studies indicate that cocoa may also have therapeutic potential in preventing cardiovascular complications in diabetic patients. In one such study, flavanol-rich cocoa consumption three times daily for 30 days increased flow-mediated dilatation by 30% in medicated diabetics [23].

Although large-scale studies in humans with diabetes are lacking, animal studies, small-scale human studies, and biological plausibility support potential beneficial effects of cocoa on glucose control, with possible reductions in cardiovascular risk in diabetics. Additional larger scale studies to confirm these effects in humans are therefore needed.

### 3. Negative effects

Dark chocolate is commonly regarded as an energy-dense food and excess consumption of any energy-dense food may have adverse metabolic effects, including weight gain [32]. While several short-term (i.e., 2–8 weeks) studies have examined changes in body weight following consumption of chocolate, only one study, performed in overweight and obese women, has compared the effects of chocolate against non-chocolate intake specifically on changes in body weight and composition during energy restriction [34,35]. In this feasibility study, inclusion of a dark chocolate or non-chocolate sweet snack as part of the diet resulted in losses in fat mass, body weight and body fat percentage,

with no significant differences between the two snack groups. However, the sample size of this pilot study was small, and outcomes were limited to body composition and without further exploration of biomarkers of metabolic health [34].

The majority of these studies lacked a true control arm and few studies on the effects of consumption on weight used dark chocolate. All of the studies either used white chocolate, cocoa butter, or chocolate bars without flavanols as a control, in order to create conditions with equal energy intake. For ethical reasons, deliberate attempts were made to avoid positive energy balance in participants with an increased risk for chronic diseases. Therefore, during both the intervention (chocolate) and control (no chocolate/placebo) periods, the energy intake in the habitual diet was reduced by ways of reducing the participant's daily snack consumption. However, it is not clear whether these control 'placebos' are neutral, since it cannot be excluded that the placebo itself might have included something which led to physiologic effects and detected changes. Therefore, while it is possible that there are deleterious effects of dark chocolate consumption on diabetics, appropriate studies to assess this have not yet been performed.

### 4. Summary

In summary, there are plausible mechanisms for the antioxidant effects of cocoa polyphenols to directly influence insulin resistance and, in turn, reduce risk for diabetes. Cocoa may induce pancreatic  $\beta$ -cell regeneration and stimulate insulin secretion, have a hypoglycemic effect, and improve glucose tolerance. The vasodilatory effects of cocoa can also improve insulin sensitivity mediated by endothelial function. Sustained consumption of cocoa over long periods may affect insulin resistance to a greater degree than single doses of cocoa products. Studies highlighting the potential of cocoa-containing diets, in large-randomized controlled trials should be performed which might give us a better opportunity to analyze the potential health care benefit for reducing the risk of complications in diabetic patients at molecular level.

### Disclosure statement

No potential conflict of interest was reported by the author.

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