

Polyphenols and Glucose Homeostasis in Humans

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THE GLOBAL PANDEMIC OF TYPE 2 DIABETES mellitus places an incalculable burden on health care systems. In the United States alone, it is estimated that 52% of the population will have diabetes or prediabetes by 2020, conditions that already cost that country \$194 billion a year in health care spending.¹ Amelioration of type 2 diabetes mellitus risk usually targets lifestyle and diet, primarily with the aim of reducing obesity—the foremost risk factor in the development of insulin resistance and ultimately type 2 diabetes mellitus. However, particular dietary components, such as polyphenols, may assist in type 2 diabetes mellitus prevention in ways other than weight control.

Dietary polyphenols are chemicals of plant origin that are abundant in fruit, vegetables, chocolate, and nuts, as well as in beverages such as tea, coffee, wine, and soy milk.^{2,3} In tea leaves for example, polyphenols can account for up to 30% of their dry weight.⁴ As such, polyphenols are the most abundant antioxidants in the diet of human beings.⁵ Dietary polyphenol consumption is of interest because it is associated with lower rates of diabetes and cardiovascular disease.⁶⁻⁹ There are thousands of natural polyphenols in the plant kingdom (and in derived foods), all of which share the basic structure of an aromatic ring with attached hydroxyl groups. Variations in this structure led to individual classifications of polyphenols, with at least 10 separate classes identified,¹⁰ four of which are important in the diet of human beings: phenolic acids, flavonoids, stilbenes, and lignans.¹¹

Historically, it has been difficult to determine polyphenol concentrations in food items, or to identify foods that contain specific polyphenols. However, a collaborative project between food and nutrition practitioners, food scientists, epidemiologists, and bioinformaticians has recently produced a database encompassing 500 different polyphenols known to be present in more than 400 food items.¹² The amount and type of polyphenols consumed is largely dependent on the dietary patterns of individuals and populations. Nonetheless, it previously has been estimated that total polyphenol intake is approximately 1 g/day,¹³ which is likely to be a conservative

figure.¹⁴ Using the aforementioned database, the historical 1 g/day figure has been shown to underestimate intake by approximately 20%.¹⁵

In wealthier nations, such as the United States where the prevalence of type 2 diabetes mellitus is an ever-growing issue,¹ there is an enormous market for polyphenol formulations. The global nutraceutical market was estimated to be worth \$117.3 billion in 2007.¹⁶ Currently, there is a major imbalance between the published clinical studies on the benefits of polyphenols to human health and the marketing of these products. There is mounting evidence that polyphenols can reduce insulin resistance in *in vitro* and animal studies (which have been reviewed elsewhere¹⁷), but data from studies in human beings remains limited.

Thus, we address three primary questions regarding polyphenol action in human beings that remain unclear: Do polyphenols improve glucose homeostasis in human beings? What limits the effectiveness of dietary polyphenols? and, What role does the nutraceutical industry have in research related to the health benefits of polyphenols?

DO POLYPHENOLS IMPROVE GLUCOSE HOMEOSTASIS IN HUMANS?

In the attempt to answer this question, we focused on specific food sources, rich in dietary polyphenols, that highlight important issues in the literature:

- tea—arguably the most studied and single largest source of human polyphenol consumption; these studies are of heterogeneous design and have yielded conflicting results;
- chocolate—the variability of results from studies of which illustrate the importance of adopting appropriate methods to assess insulin sensitivity;
- red wine—a well-studied beverage with a polyphenol content that provides a new potential mechanism to improve health but also has potential adverse side effects; and
- soy—studies of which demonstrate that cardioprotection can occur independently from improvement in glucose homeostasis.

The literature on tea epitomizes the challenges in interpreting the data from studies on polyphenols due to conflicting results and heterogeneous design. Tea is rich in catechin (particularly epigallocatechin gallate) from the flavonoid class of polyphenols. Globally, tea is second only to water as a consumed beverage, so that it represents a significant source of polyphenol for a vast proportion of the world's population.⁴ Epidemiologic studies are contradictory with four studies showing no effect of tea intake on type 2 diabetes mellitus incidence,¹⁸⁻²¹ two showing some type 2 diabetes mellitus

protection in high consumption groups,^{22,23} and one demonstrating type 2 diabetes mellitus protection only in those individuals aged <60 years.²⁴ One study showed a cup per day of black tea was protective, whereas green tea consumption was not,²⁵ in contrast to another study showing that only green tea was protective.²⁶ A meta-analysis of these studies concluded that intake of approximately 4 c tea/day may prevent the development of type 2 diabetes mellitus.²⁷

Subsequent intervention studies (summarized in the Table) compound the difficulty in interpreting findings due to major variations in study design (including assessment of insulin sensitivity), study populations, adopted dosage of tea polyphenols, and conflicting results.²⁸⁻³⁸ Focusing on the study populations alone, all studies differed according to sample size, age ranges studied, sex distribution, health status of participants (from healthy to those with type 2 diabetes mellitus), and ethnicity. This heterogeneity in populations may account for some of these conflicting results, possibly due to background dietary differences and/or variable enzymatic activity and gut flora (which alter polyphenol metabolism) in human beings.³⁹ Of the 11 intervention studies, five were negative,^{28,30,33,35,36} and the three positive studies only yielded minor findings of questionable clinical significance.^{32,34,37} Hosoda and colleagues³⁸ showed clinically significant improvements in fasting glucose and fructosamine concentrations but with a required intake of 6 c oolong tea/day; this raises questions regarding the routine application of naturally occurring polyphenols to improve glucose homeostasis. The study by Venables and colleagues³¹ showed that with acute consumption of tea glucose homeostasis improved using oral glucose tolerance tests, but the number of participants was small. Only Nagao and colleagues²⁹ had a robust study design (double-blind randomized trial with 12-week follow-up) showing a clinically important result, as those on insulinotropic medications had higher insulin production and lower glycosylated hemoglobin after green tea supplementation. Overall, whereas tea polyphenols may potentially improve glucose homeostasis and prevent the development of type 2 diabetes mellitus, the evidence is inconsistent.

Dark chocolate is another food item particularly rich in polyphenols, including flavonols. The associated literature demonstrates the importance of which method is chosen to assess insulin sensitivity. Population studies have shown dark chocolate to be cardioprotective,⁴⁰ and the majority of clinical trials showed favorable effects on glucose homeostasis⁴¹⁻⁴⁵ when a proxy measure of insulin sensitivity was used; that is, homeostasis model assessment of insulin resistance. However, when the accepted gold standard method to measure insulin sensitivity (the hyperinsulinemic euglycemic clamp technique) was adopted, Muniyappa and colleagues⁴⁶ showed no improvement in insulin sensitivity after 14 days on flavanol-rich cocoa supplement, raising concerns on the reliability of proxy measures of insulin sensitivity. Further investigation is warranted, including more participants, long-term follow-up, and gold standard techniques to measure insulin sensitivity.

The polyphenol content in red wine may explain the so-called French paradox, where there is a low incidence of cardiovascular disease in France despite a relatively high intake of saturated fat.⁴⁷ Since Renaud and de Lorgeril's original article,⁴⁷ the subsequent literature has focused on the antioxi-

dant effect and lipid-lowering properties of red wine polyphenols, whereas some trials have investigated the effect of grape and wine products on glucose homeostasis.⁴⁸⁻⁵² Yet these studies have yielded contradictory results: two studies showed no improvement,^{49,51} one showed lowered fructosamine but no change in insulin sensitivity,⁴⁸ another demonstrated acute amelioration of glucose excursion when wine was taken with a meal,⁵² but only Banini and colleagues⁵⁰ found a clinically significant reduction in glycosylated hemoglobin (7.4% to 6.8%) in type 2 diabetes mellitus patients after 28 days of wine supplementation. The focus on red wine polyphenols has since shifted to resveratrol, a potent antioxidant found in red grapes and their products. Resveratrol has been shown to modulate the ageing gene Sirt1,⁵³ and Brasnyó and colleagues⁵⁴ demonstrated recently that it can improve insulin sensitivity in type 2 diabetes mellitus patients.

The focus of soy research has been its weak estrogenic influence on the cardiovascular system in postmenopausal women.⁵⁵⁻⁵⁹ Cardioprotective effects have been shown in epidemiologic studies,^{60,61} but they seem to be independent of improved glucose homeostasis. Two studies failed to show an improvement in glucose homeostasis,^{55,56} whereas two others yielded minimal changes of questionable clinical significance.^{58,59} A study by Ho and colleagues⁵⁷ only found improvement in fasting glucose concentrations in those individuals with the highest baseline results, and did not investigate insulin sensitivity. All the studies were performed exclusively on postmenopausal women, putting into question the broader applicability of the findings. The balance of clinical results suggests that the cardioprotective effects seen in epidemiologic studies are not mediated through improvement in glucose metabolism.

Another consideration is whether total dietary polyphenol intake is more important in regulating glucose homeostasis, in comparison to the intake of a single polyphenol in large quantities. A systematic review of 35 clinical trials confirmed improvement in insulin sensitivity on the Mediterranean diet,⁶² but an attempt to narrow improved insulin sensitivity down to olive oil polyphenols yielded a null result.⁶³ Although it is an enticing prospect to identify a single polyphenol that can improve glucose homeostasis, population data examining total dietary polyphenol load more consistently showed positive associations.^{9,22,23,27,64,65} However, a common problem with intervention trials using whole foods is the lack of specific information regarding which polyphenols are present and in what quantities.

In vitro and animal data covering a wide range of polyphenols have comprehensively shown favorable results in most physiologic processes involved in glucose homeostasis.¹⁷ Unfortunately, there is no conclusive evidence that individual polyphenols can favorably influence glucose homeostasis in human beings. Reproducing promising nonhuman data in clinical studies is challenging.

WHAT LIMITS THE EFFECTIVENESS OF DIETARY POLYPHENOLS?

The metabolism of polyphenols is likely to be an important factor determining whether a normal diet can deliver effective concentrations of polyphenols to target tissues. The bioavailability of differing polyphenols is highly variable, involving complex and diverse physiologic processes. There are also

Table. Summary of intervention trials examining the effects of tea consumption on glucose metabolism

| Author(s), year, reference | Study design | Intervention | Participants | Follow-up | Measurements | Results | Adverse events |
|--|---|--|--|---|---|--|------------------------------|
| Josic and colleagues, 2010 ²⁸ | Randomized, crossover, nonblind | 300 mL green tea, total catechin dose 202 mg, given with test meal | n=14 (50% men) Age 27±3 y BMI ^a 22.3±3.4 Healthy patients Ethnicity not reported | 2 h | Glucose Insulin Area under the curve | No difference in area under the curve Higher BGC ^b at 2 h ($P=0.019$) (absolute difference <1 mmol/L) | Not reported |
| Brown and colleagues, 2009 ³⁰ | Randomized, placebo controlled, double blind | EGCG ^c 800 mg daily, over 8 wk | n=88 (100% men) Healthy men 40-65 y BMI placebo 31.0±2.5 BMI intervention 31.2±2.8 Ethnicity not reported | 8 wk | HOMA(IR) ^d | No difference | Not reported |
| Venables and colleagues, 2008 ³¹ | Counter-balanced, crossover, placebo controlled, nonblind | Green tea extract with 136 mg EGCG, total polyphenol 340 mg | n=12 (100% men) Healthy men 23±2 y BMI 24.1±1.1 | 2 h | Matsuda index (insulin sensitivity index) | 13%±4% greater (more sensitive) ($P<0.05$) | Not reported |
| Nagao and colleagues, 2008 ²⁹ | Randomized, double blind | Green tea with either 583 mg catechins (intervention) or 96 mg catechins (control) for 12 wk | n=50 (38% men) Type 2 diabetes not taking insulin Intervention age 65±2 y Control age 63±2 y BMI intervention 25.6±1.8 BMI control 24.0±0.9 Japanese | 12 wk Sustained effect checked at 16 wk | Fasting glucose Fasting insulin Glycosylated hemoglobin | Only patients taking insulinotropic medications increased insulin production and significantly decreased their glycosylated hemoglobin | None observed |
| Fukino and colleagues, 2007 ³² | Randomized, crossover, nonblind | Green tea extract, daily dose 456 mg catechins and 102 mg caffeine | n=60 (85% men) 32-73 y Fasting glucose >6.1 or nonfasting >7.8 mmol/L (borderline diabetes) Japanese | 2 mo | Fasting glucose Fasting insulin Glycosylated hemoglobin HOMA(IR) | Small improvement in glycosylated hemoglobin ($P=0.03$) No difference in other parameters | Not reported |
| MacKenzie and colleagues, 2007 ³³ | Randomized, placebo controlled, blind | Teaflavin extract daily Arm 1: 150 mg green tea catechins, 75 mg black tea theaflavins, 150 mg other tea polyphenols Arm 2: 300 mg green tea catechins, 150 mg black tea theaflavins, 300 mg other tea polyphenols | n=49 (53% men) Type 2 diabetes >6 mo, not taking insulin Age 65 (49-86) y BMI (self reported) 30.7-34.8 over the three arms 47/49 white | 3 mo | Glycosylated hemoglobin | No difference | 1 profuse sweating 1 rash |

(continued on next page)

Table. Summary of intervention trials examining the effects of tea consumption on glucose metabolism (*continued*)

| Author(s), year, reference | Study design | Intervention | Participants | Follow-up | Measurements | Results | Adverse events |
|--|---------------------------------------|--|---|-----------|---|--|----------------|
| Bryans and colleagues, 2007 ³⁴ | Four-way randomized, crossover | Black tea extract 1 g arm: 350 mg polyphenols (39 mg flavan-3-ols, 21 mg theaflavins) 3 g arm: 1,050 mg polyphenols (127 mg flavan-3-ols, 63 mg theaflavins) | n=16 (25% men) 36±2 y BMI 23.8±0.7 Healthy Ethnicity not recorded | 2.5 h | Oral glucose tolerance test | Glucose significantly lower at 2 h in tea vs control Insulin levels increased at 90 min in tea vs control | Not reported |
| Ryu and colleagues, 2006 ³⁵ | Randomized, crossover, nonblind | 9 g green tea, dose of catechin not stated | n=55 (56% men) Type 2 diabetes 53±8 y BMI 25.0±2.2 Korean | 4 wk | HOMA(IR) | No difference | Not reported |
| Fukino and colleagues, 2005 ³⁶ | Randomized, non-blind | Green tea extract with 456 mg catechins, total 544 mg polyphenols | n=66 (80% men) 32-73 y with impaired glucose tolerance or diabetes Japanese | 2 mo | Fasting glucose Fasting insulin Glycosylated hemoglobin HOMA(IR) | No improvement compared to control | Not reported |
| Tsuneki and colleagues, 2004 ³⁷ | Nonrandomized, intervention, nonblind | Green tea powder 1.5 g. Dose of catechins not stated | 22 healthy volunteers No demographic data Presumably Japanese | 2 h | Oral glucose tolerance test | Lower glucose at 30 and 120 min ($P<0.05$) | Not reported |
| Hosoda and colleagues, 2003 ³⁸ | Randomized, crossover, nonblind | 1.5 L oolong tea daily for 30 d, containing 242 mg EGCG, 1,490 mg total polyphenols | n=20 (50% men) 61±8 y Type 2 diabetes not taking insulin BMI 22.6±1.1 | 30 d | Fasting glucose Fructosamine | Fasting glucose decreased 30% ($P<0.001$) Fructosamine improved 21% ($P<0.01$) | None observed |

^aBMI = body mass index.^bBCG = blood glucose concentration.^cEGCG = epigallocatechin gallate.^dHOMA(IR) = homeostasis model assessment (insulin resistance).

between-subject variations, which are partially explained by heterogeneity in enzymatic activity and gut flora in human beings.³⁹

In addition, the physiologic activity of polyphenol metabolites is yet to be fully understood. In investigations of polyphenol metabolite concentrations in humans after normal dietary exposure rarely rise above 1 $\mu\text{mol/L}$, with most polyphenols achieving concentrations significantly below this mark.² In vitro studies use media usually in excess of 1 $\mu\text{mol/L}$ for sustained periods of time.¹⁷ Blood concentrations may provide information on polyphenol absorption, but they do not necessarily correspond to target tissue levels. Thus, measuring polyphenol concentrations in plasma may not accurately assess exposure.² Indeed, in vitro and animal studies showed that polyphenols affect glucose homeostasis in many tissues beyond the blood stream, including carbohydrate digestion and glucose absorption in the intestine, stimulation of pancreatic β -cell insulin secretion, liver glucose metabolism, activation of insulin receptors, and glucose uptake in insulin-sensitive tissues.¹⁷

There are variations in the way ingested polyphenols are metabolized and absorbed,¹⁴ which may explain differences in their bioavailability. Initially, polyphenols are likely to be metabolized via gut enzymes, but if this does not occur, they are variably processed by gut microflora into metabolites that may be absorbed. For example, the metabolism of many polyphenols requires hydrolysis via lactase.⁶⁶ As a result, there is wide variation in this process among different ethnic groups, as 95% of adults of Asian descent, 70% of African, and 10% of European descent are lactase deficient.⁶⁷ In contrast, gut microflora are required for the metabolism of polyphenols that are esterified or glycosylated with rhamnose.⁶⁸ Because gut microflora vary considerably among individuals,⁶⁹ this will also affect polyphenol bioavailability. As an exception, flavonols do not require hydrolysis before absorption.¹⁴

Once absorbed, polyphenols undergo rapid reconjugation and excretion through similar pathways as pharmaceutical drugs.¹⁴ However, whereas pharmaceutical drugs manage to saturate these pathways, polyphenols in normal dietary concentrations do not.¹⁴ The rate of reconjugation of polyphenols is also associated with genetic polymorphism (eg, catechol-O-methyltransferase) and environmental factors (eg, smoking).⁷⁰⁻⁷⁶ In addition, the half-life and activity of metabolites remain poorly understood, and they may have more potent properties than polyphenols in their core state.^{12,77}

Nevertheless, the net effect of diverse bioavailability, failure to saturate metabolic pathways, and rapid clearance explains why plasma concentrations of polyphenols in most studies in human beings do not reach the required levels as per in vitro and animal studies. Although intestinal absorption can be high, measurement of the parent polyphenol in blood rarely exceeds 1% of the raw product.¹⁴ The half-life values for antioxidant, anti-inflammatory, and anticancer polyphenol properties obtained in vitro are 5 to 100 $\mu\text{mol/L}$,⁷⁸ a target rarely achieved in studies of human beings. For example, eating five apples led to no detectable antioxidant effects, even though just 1% polyphenol bioavailability would likely be necessary to yield the observed in vitro effects.⁷⁹ Catechin given in large supplemented doses leads to detectable blood concentrations, which would only be achieved by drinking many liters of wine.^{80,81} Flavanones (found only in citrus fruit

and soy) are an exception, and have been shown to reach serum concentrations of 5 $\mu\text{mol/L}$.²

To overcome the limitations associated with variable bioavailability and rapid metabolism, several studies of the effects of polyphenols on glucose homeostasis have used large doses with some success. For example, 20 g/day decaffeinated coffee solids (equivalent to 10 c coffee) lowered fasting glycemia in healthy volunteers after 2 weeks.⁸² Similarly, supplementation with 6 c green tea per day decreased fasting glucose concentrations by 30%.³⁸

Thus, to mimic an in vitro environment, several intakes a day of polyphenol-rich food would be required to ingest the amount and mix of polyphenols necessary to exert the observed beneficial effects on glucose homeostasis. Although this may not be feasible in practice in many cases, it is possible that subtle long-term dietary intake of polyphenols may yield health benefits.

WHAT ROLE DOES THE NUTRACEUTICAL INDUSTRY HAVE IN RESEARCH RELATED TO THE HEALTH BENEFITS OF POLYPHENOLS?

The size of the nutraceutical market indicates that consumers are willing to take polyphenol products despite the paucity of robust scientific data on health benefits, as previously discussed in relation to glucose homeostasis. If concentrated polyphenol formulations were shown to improve glucose homeostasis, the health benefits would be enormous, because the global incidence of type 2 diabetes mellitus is estimated to reach 360 million by the year 2030.⁸³ However, robust data from clinical trials using polyphenols are still lacking, and positive health outcomes following their application in individuals with type 2 diabetes mellitus are elusive.

Most clinical trials have attempted to deliver large quantities of individual polyphenols to overcome issues of rapid clearance, in the hope of achieving measurable health effects (see the Table). Typically, nutraceuticals contain polyphenol doses 100 to 1,000 times greater than those obtained from normal dietary intake. For example, a 150-mL glass of red wine contains on average 0.5 mg resveratrol,⁸⁴ but commercial formulations use up to 500 mg.⁸⁵ However, even though trials of human beings have used these commercially available products, these results have been inconsistent.

Nutraceuticals are not subject to the same level of regulation as pharmaceuticals, but there is some governance over their health claims and most countries have an associated regulatory framework. Although regulation is important for quality assurance, prohibition of claims on health benefits or disease prevention associated with food items limits consumers' ability to make healthy food choices.⁸⁶ Nutraceutical companies are regulated against making health claims until there is robust scientific evidence. This is not unreasonable due to safety concerns associated with the intake of high concentrations of individual polyphenols, which are powerful antioxidants. Several polyphenols have been shown to promote oxidative damage to DNA, lipids, and deoxyribose under certain conditions in vitro.⁸⁷⁻⁹¹ Safety is rarely reported in clinical studies. As long-term effects of supraphysiologic doses of polyphenols are unknown, detailed safety profiles should be reported in future clinical trials in human beings.

Nonetheless, supraphysiologic doses of polyphenols appear to be the only method adopted to achieve measurable concen-

trations approaching those seen in vitro and in animal studies. It is possible that nutraceuticals containing concentrated polyphenols could potentially exert effects on glucose homeostasis in human beings. Pharmaceutical companies have altered chemical structures to improve metabolism, and this may be a valid pathway for the nutraceutical industry. Whether or not nutraceuticals should deliver a single polyphenol or multiple polyphenols is yet to be determined, but it is still unknown whether nutraceuticals can actually deliver greater protective benefit against type 2 diabetes mellitus than a normal dietary intake of polyphenol-rich foods.

To clarify the role of polyphenols in glucose homeostasis, it is important that robust experimental designs are employed. Thus, future clinical trials should be consistent in design and outcome measurements to help reproducibility. Therefore, we suggest the following framework:

- Pilot studies should precede clinical trials, and assess bioavailability and metabolism of the polyphenol being investigated to establish dose response and plasma concentrations.
- Robust trial design, such as double-blind randomized placebo-controlled trial with crossover and washout periods.
- Accurate or gold standard methods to assess insulin sensitivity should be used; for example, hyperinsulinemic euglycemic clamp, minimal model, and Matsuda method.
- When assessing the effects of polyphenols on glucose homeostasis, both the acute (eg, mixed meal response) and chronic responses should be examined.
- When assessing the effects of polyphenols on glucose homeostasis, consider measuring a range of peptides involved in glucose regulation beyond just insulin, such as interleukin-6, adipocytokines, and incretins.

CONCLUSIONS

Despite promising data from in vitro and animal studies, the effects of polyphenols on glucose homeostasis in human beings have not been consistently shown. Further research in human beings should adopt robust randomized placebo-controlled study designs. Gold standard techniques to assess insulin sensitivity should be used where possible. Researchers should investigate molecular pathways involved in glucose homeostasis that may translate into long-term health benefits, which are not observed in short-term studies. However, a limitation in clinical studies is the heterogeneous bioavailability and rapid metabolism of polyphenols. In an attempt to overcome this issue, nutraceutical products are produced with high concentrations of polyphenols well above the normal dietary intake, which could lead to adverse effects. Despite the paucity of robust data showing beneficial health outcomes associated with polyphenols in human beings, these compounds already have a large commercial value. Further research in this area is urgently needed because prescribable polyphenols to treat (and preferably offset) the diabetes pandemic are an exciting prospect.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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