Chocolate and Cardiovascular Health
The “Bitter” Evidence

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Overview of Talk

• History of chocolate
• Review of clinical research on health benefits of chocolate
• Our research on epicatechin
• Implications for you
CACAO in MesoAmerica

For over 3500 years, chocolate has been associated with luxury. The Olmeca, Aztec, and Mayan cultures were greatly influenced by Cacao.

The Maya culture transmitted knowledge of cacao by means of oral tradition, multicolored stone engravings, paintings, ceramics and codices where its medicinal uses were described.

A Divine God with a Cacao Pod
Cacao was used by the Aztecs and Mayans for its many health benefits

- Treating fatigue, faint heart and alleviating panting of breath
- Treating emaciated patients to gain weight
- Stimulate nervous systems of apathetic exhausted or feeble patients
- To improve digestion, stimulate kidneys and improve bowel function
The unusual powers of cacao

The Mayans & Aztecs believed that eating cacao would make them strong & invincible.
Cacao was used as currency & offered in religious ceremonies by the Aztecs.
Theobroma CACAO

One of the world's most magical and incredible trees is the cocoa tree. The botanical name is *Theobroma Cacao*, which, roughly translated, means “food for the gods” or more literally, “God food.” The name *Theobroma cacao* was first applied to the cocoa tree by Carolus Linnaeus.
Fast Forward to Modern Day:
The Kuna Indian Story
The Kuna Indians are living proof of the benefits of cacao consumption

Kuna islanders consume a high amount of a crude cocoa beverage containing high amounts of the compound epicatechin

Epicatechin is responsible for the “bitter” taste of dark chocolate
The consumption of cocoa high in epicatechin is thought to be responsible for the low incidence of cardiovascular disease in the Kuna Indians.
KUNA vs. US Death Rates

<table>
<thead>
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<th>DISEASE</th>
<th>MAINLAND</th>
<th>ISLAND</th>
<th>USA</th>
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<tr>
<td>CARDIOVASCULAR</td>
<td>83.4±0.7</td>
<td>9.2±3.1</td>
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<tr>
<td>CANCER</td>
<td>68.4±1.6</td>
<td>4.4±4.4</td>
<td>175</td>
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<tr>
<td>DIABETES</td>
<td>24.1±0.7</td>
<td>6.6±1.9</td>
<td>22</td>
</tr>
</tbody>
</table>

STATS PER 100,000

The processing of cacao

- To make 1 kg of chocolate, 300-600 beans are processed
- Beans are washed and roasted. Next they are de-hulled. The nibs are what is left and are ground into a thick creamy paste, known as chocolate liquor
- This "liquor" is separated into cocoa powder (50%) and cocoa fat (cocoa butter=50%). Cocoa powder has the flavanols which are very bitter in taste and acidic
- Cocoa butter is used in chocolate bar manufacturing, other confectionery, soaps, and cosmetics
- Adding an alkali produces Dutch process cocoa powder, which is less acidic, darker and more mellow in flavor, also lower in flavanol content
Epicatechin: A Pleiotropic Compound

- Decreases blood pressure
- Improved Insulin Sensitivity
- Decreases Platelet Adhesion
- Lowers incidence of MI and Stroke
- Prevents age related decline in kidney function
- Reduces LDL cholesterol
- No known toxicity

Adapted from Corti et al, Circulation 2009
Acute Consumption of Flavanol-Rich Cocoa and the Reversal of Endothelial Dysfunction in Smokers

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OBJECTIVES
This study was designed to assess the effect of flavanol-rich food on the circulating pool of bioactive nitric oxide (NO) and endothelial dysfunction in smokers.

BACKGROUND
Studies suggest that smoking-related vascular disease is caused by impaired NO synthesis and that diets rich in flavanols can increase bioactive NO in plasma.

METHODS
In smokers (n = 11), the effects of flavanol-rich cocoa on circulating NO species in plasma (RXNO) measured by reductive gas-phase chemiluminescence and endothelial function as assessed by flow-mediated dilation (FMD) were characterized in a dose-finding study orally administering cocoa containing 88 to 370 mg flavanols and in a randomized double-blind crossover study using 100 ml cocoa drink with high (176 to 185 mg) or low (<11 mg) flavanol content on two separate days. In addition to cocoa drink, ascorbic acid and NO-synthase inhibitor L-NMMA (n = 4) were applied.

RESULTS
There were significant increases in RXNO (21 ± 3 nmol/l to 29 ± 5 nmol/l) and FMD (4.5 ± 0.8% to 6.9 ± 0.9%, each p < 0.05) at 2 h after ingestion of 176 to 185 mg flavanols, a dose potentially exerting maximal effects. These changes correlated with increases in flavanol metabolites. Cocoa-associated increases in RXNO and FMD were reversed by L-NMMA. Ascorbic acid had no effect.

CONCLUSIONS
The circulating pool of bioactive NO and endothelium-dependent vasodilation is acutely increased in smokers following the oral ingestion of a flavanol-rich cocoa drink. The increase in circulating NO pool may contribute to beneficial vascular health effects of flavanol-rich food. (J Am Coll Cardiol 2005;46:1276–83) © 2005 by the American College of Cardiology Foundation
Coronary Heart Disease

Dark Chocolate Improves Coronary Vasomotion and Reduces Platelet Reactivity

Andreas J. Flammer, MD; Frank Hermann, MD; Isabella Sudano, MD, PhD; Lukas Spieker, MD; Matthias Hermann, MD; Karen A. Cooper, MSc, PhD; Mauro Serafini, PhD; Thomas F. Lüscher, MD; Frank Ruschitzka, MD; Georg Noll, MD; Roberto Corti, MD

Background—Dark chocolate has potent antioxidant properties. Coronary atherosclerosis is promoted by impaired endothelial function and increased platelet activation. Traditional risk factors, high oxidative stress, and reduced antioxidant defenses play a crucial role in the pathogenesis of atherosclerosis, particularly in transplanted hearts. Thus, flavonoid-rich dark chocolate holds the potential to have a beneficial impact on graft atherosclerosis.

Methods and Results—We assessed the effect of flavonoid-rich dark chocolate compared with cocoa-free control chocolate on coronary vascular and platelet function in 22 heart transplant recipients in a double-blind, randomized study. Coronary vasomotion was assessed with quantitative coronary angiography and cold pressor testing before and 2 hours after ingestion of 40 g of dark (70% cocoa) chocolate or control chocolate, respectively. Two hours after ingestion of flavonoid-rich dark chocolate, coronary artery diameter was increased significantly (from 2.36±0.51 to 2.51±0.59 mm, P<0.01), whereas it remained unchanged after control chocolate. Endothelium-dependent coronary vasomotion improved significantly after dark chocolate (4.5±11.4% versus −4.3±11.7% in the placebo group, P=0.01). Platelet adhesion decreased from 4.9±1.1% to 3.8±0.8% (P=0.04) in the dark chocolate group but remained unchanged in the control group.

Conclusions—Dark chocolate induces coronary vasodilation, improves coronary vascular function, and decreases platelet adhesion 2 hours after consumption. These immediate beneficial effects were paralleled by a significant reduction of serum oxidative stress and were positively correlated with changes in serum epicatechin concentration. (Circulation. 2007;116:2376-2382.)

Key Words: atherosclerosis ■ endothelium ■ nutrition ■ oxidative stress ■ platelets
Sustained Benefits in Vascular Function Through Flavanol-Containing Cocoa in Medicated Diabetic Patients

A Double-Masked, Randomized, Controlled Trial

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Aachen, Germany; Davis, California; and Rockville, Maryland

Objectives
Our goal was to test feasibility and efficacy of a dietary intervention based on daily intake of flavanol-containing cocoa for improving vascular function of medicated diabetic patients.

Background
Even in fully medicated diabetic patients, overall prognosis is unfavorable due to deteriorated cardiovascular function. Based on epidemiological data, diets rich in flavonols are associated with a reduced cardiovascular risk.

Methods
In a feasibility study with 10 diabetic patients, we assessed vascular function as flow-mediated dilation (FMD) of the brachial artery, plasma levels of flavonol metabolites, and tolerability after an acute, single-dose ingestion of cocoa, containing increasing concentrations of flavonols (75, 371, and 963 mg). In a subsequent efficacy study, changes in vascular function in 41 medicated diabetic patients were assessed after a 30-day, thrice-daily dietary intervention with either flavanol-rich cocoa (321 mg flavonols per dose) or a nutrient-matched control (25 mg flavonols per dose). Both studies were undertaken in a randomized, double-masked fashion. Primary and secondary outcome measures included changes in FMD and plasma flavonol metabolites, respectively.

Results
A single ingestion of flavanol-containing cocoa was dose-dependently associated with significant acute increases in circulating flavonols and FMD (at 2 h: from 3.7 ± 0.2% to 5.5 ± 0.4%, p < 0.001). A 30-day, thrice-daily consumption of flavanol-containing cocoa increased baseline FMD by 30% (p < 0.0001), while acute increases of FMD upon ingestion of flavanol-containing cocoa continued to be manifest throughout the study. Treatment was well tolerated without evidence of tachyphylaxia. Endothelium-independent responses, blood pressure, heart rate, and glycemic control were unaffected.

Conclusions
Diets rich in flavonols reverse vascular dysfunction in diabetes, highlighting therapeutic potentials in cardiovascular disease. (J Am Coll Cardiol 2008;51:2141–9) © 2008 by the American College of Cardiology Foundation
Epicatechin Reduces Infarct Size by 82%

Control: No treatment

Epicatechin 10 mg/kg

Infarcted area
Area at risk
Undamaged tissue

p=<0.001 n=6
Effects of (−)-Epicatechin on Myocardial Infarct Size and Left Ventricular Remodeling After Permanent Coronary Occlusion

Katrina Go Yamazaki, PhD,* Pam R. Taub, MD,* Maraliz Barraza-Hidalgo, BS,* Maria M. Rivas, BS,* Alexander C. Zambon, PhD,* Guillermo Ceballos, MD, PhD,† Francisco J. Villarreal, MD, PhD*

La Jolla, California; and Mexico City, Mexico

Objectives
We examined the effects of the flavanol (−)-epicatechin on short- and long-term infarct size and left ventricular (LV) structure and function after permanent coronary occlusion (PCO) and the potential involvement of the protective protein kinase B (AKT)/extracellular signal-related kinase (ERK) signaling pathways.

Background
(−)-epicatechin reduces blood pressure in hypertensive patients and limits infarct size in animal models of myocardial ischemia–reperfusion injury. However, nothing is known about its effects on infarction after PCO.

Methods
(−)-epicatechin (1 mg/kg daily) treatment was administered via oral gavage to 250 g male rats for 10 days before PCO and was continued afterward. The PCO controls received water. Sham animals underwent thoracotomy and treatment in the absence of PCO. Immunoblots assessed AKT/ERK involvement 2 h after PCO. The LV morphometric features and function were measured 48 h and 3 weeks after PCO.

Results
In the 48-h group, treatment reduced infarct size by 52%. There were no differences in hemodynamics among the different groups (heart rate and aortic and LV pressures). Western blots revealed no differences in AKT or ERK phosphorylation levels. At 3 weeks, PCO control animals demonstrated significant increases in LV end-diastolic pressure, heart and body weight, and LV chamber diameter versus sham. The PCO plus (−)-epicatechin group values were comparable with those of the sham plus (−)-epicatechin group. Treatment resulted in a 33% decrease in myocardial infarction size. The LV pressure-volume curves demonstrated a right shift in control PCO animals, whereas the (−)-epicatechin curves were comparable with those of the sham group. The LV scar area strains were significantly improved with (−)-epicatechin.

Conclusions
These results demonstrate the unique capacity of (−)-epicatechin to confer cardioprotection in the setting of a severe form of myocardial ischemic injury. Protection is sustained over time and preserves LV structure and function. The cardioprotective mechanism(s) of (−)-epicatechin seem to be unrelated to AKT or ERK activation. (−)-epicatechin warrants further investigation as a cardioprotectant. (J Am Coll Cardiol 2010;55:2869–76)

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Figure 2. IA as a Function of LV Area 3 Weeks After PCO in Rats Subjected to 10 Days of Vehicle or (−)-Epicatechin Pre-Treatment

(A) Representative LV equatorial ring sections of control and (−)-epicatechin-treated animals stained with triphenyltetrazolium chloride. (B) Dispersion plot of the IA in PCO (n = 12) and PCO plus (−)-epicatechin (n = 12) groups. Values are mean ± SE. *p < 0.02 versus PCO. Abbreviations as in Figure 1.
"I read an article about the health benefits of dark chocolate so I make sure all the donuts I eat are covered with dark chocolate."
Alterations in Skeletal Muscle Indicators of Mitochondrial Structure and Biogenesis in Patients with Type 2 Diabetes and Heart Failure: Effects of Epicatechin Rich Cocoa

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Abstract
(-)-Epicatechin (Epi), a flavanol in cacao stimulates mitochondrial volume and cristae density and protein markers of skeletal muscle (SkM) mitochondrial biogenesis in mice. Type 2 diabetes mellitus (DM2) and heart failure (HF) are diseases associated with defects in SkM mitochondrial structure/function. A study was implemented to assess perturbations and to determine the effects of Epi-rich cocoa in SkM mitochondrial structure and mediators of biogenesis. Five patients with DM2 and stage II/III HF consumed dark chocolate and a beverage containing approximately 100 mg of Epi per day for 3 months. We assessed changes in protein and/or activity levels of oxidative phosphorylation proteins, porin, mitofin, nNOS, nitric oxide, cGMP, SIRT1, PGC1α, Tfam, and mitochondria volume and cristae abundance by electron microscopy from SkM. Apparent major losses in normal mitochondria structure were observed before treatment. Epi-rich cocoa increased protein and/or activity of mediators of biogenesis and cristae abundance while not changing mitochondrial volume density. Epi-rich cocoa treatment improves SkM mitochondrial structure and in an orchestrated manner, increases molecular markers of mitochondrial biogenesis resulting in enhanced cristae density. Future controlled studies are warranted using Epi-rich cocoa (or pure Epi) to translate improved mitochondrial structure into enhanced cardiac and/or SkM muscle function. Clin Trans Sci 2012; Volume 5: 43–47
## Patient Summary

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<tr>
<th>Patient</th>
<th>Age</th>
<th>Heart Failure Characteristics</th>
<th>Other Medical Conditions</th>
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</table>
| 1       | 70  | Ischemic etiology with systolic and diastolic heart failure | 1. Multiple heart attacks with bypass surgery and implanted defibrillator  
                                                  2. Hypertension  
                                                  3. Hyperlipidemia |
| 2       | 71  | Ischemic etiology with systolic and diastolic heart failure | 1. Multiple heart attacks with bypass surgery and implanted defibrillator  
                                                  2. Hypertension  
                                                  3. Hyperlipidemia  
                                                  4. Peripheral Vascular Disease |
| 3       | 54  | Diastolic heart failure from hypertension                    | 1. Hypertension  
                                                  2. Hyperlipidemia |
| 4       | 62  | Ischemic etiology with systolic and diastolic heart failure | 1. Hypertension  
                                                  2. Hyperperlipidemia |
| 5       | 47  | Idiopathic dilated etiology                                 | 1. Hypertension  
                                                  2. Hyperlipidemia |
Increase in Serum Epicatechin levels after 3 months
Changes in Cristae After 3 months of Dark Chocolate Consumption
Representative changes observed in sarcomeric microstructure by EM (2 micron scale bar included) in two patients before (left panel A an B) and after treatment (right panel C and D) with ERC.
Changes in Sarcomere Morphology

Quadriceps Biopsy, Representative Patient

Before

After

EM scoring results (1-4 star rating)

<table>
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<tr>
<th>Evaluator</th>
<th>BEFORE</th>
<th>AFTER</th>
<th>t-test</th>
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<td>3 0.1</td>
<td>P &lt; 0.001</td>
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<tr>
<td>2</td>
<td>1.8 0.1</td>
<td>3.1 0.1</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

EM scoring was based on the analysis of 20 images/patient (10 before, 10 after) using naïve, blinded evaluators.
Recent Epidemiological Evidence


- Chocolate consumption is inversely associated with prevalent *coronary heart disease*: The National Heart, Lung, and Blood Institute Family Heart Study. Djoussé L et al., *Clin Nutr*, 2010

- Chocolate consumption is inversely associated with calcified *atherosclerotic plaque in the coronary arteries*: The NHLBI Family Heart Study. Djoussé L et al., *Clin Nutr*, 2010
Chocolate has shown favorable metabolic associations with blood pressure (BP),\textsuperscript{1-3} insulin sensitivity,\textsuperscript{1} and cholesterol level.\textsuperscript{3} Chocolate is rich in antioxidant phytonutrients like catechins that could contribute to favorable relationships of chocolate consumption to insulin sensitivity and BP. However, because chocolate is often consumed as a sweet and bears calories, there are concerns related to its intake.

Body mass index (BMI) is part of the metabolic syndrome (MetS) picture, and other MetS elements relate favorably to moderate chocolate consumption. Therefore, we hypothesized that the benefits of modest frequent chocolate intake might extend to reduced fat deposition, potentially offsetting the added calories. To evaluate this, we examined the cross-sectional relationship of chocolate consumption frequency to BMI.
Chocolate consumption and mortality following a first acute myocardial infarction: the Stockholm Heart Epidemiology Program

I. Janszky¹, K. J. Mukamal², R. Ljung¹,³, S. Ahnve¹, A. Ahlbom⁴ & J. Hallqvist¹,⁵

From the ¹Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden; ²Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³Centre for Epidemiology, The National Board of Health and Welfare, Stockholm; ⁴Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm; and ⁵Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
Epicatechin and Omega-3 Story
What you can do

• Consume **SMALL** amounts of dark chocolate (at least 60% dark) once a day.

• A small square = **30** CALORIES

• The more “bitter” the chocolate the better
Thank You