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I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

"Blueberries, grapes, and apples"

9-1 FRUIT CONSUMPTION AND RISK OF TYPE-2 DIABETES: Results from three prospective longitudinal cohort studies.

Fruits are rich in fiber, antioxidants, and phytochemicals that may have beneficial health effects. Increasing fruit consumption has been recommended for primary prevention of many chronic diseases, including type-2 diabetes (DM-2). Epidemiological studies have been mixed regarding the link with risk of DM-2. Studies suggest that individual fruits might not be equally associated with risk because they have variable contents of fiber, antioxidants, and phytochemicals that may jointly influence the risk of DM-2. The glycemic index may vary substantially for individual fruits.

This study examined the risk of DM-2 using data from 3 studies in US adults.

STUDY

1. Used data from the Nurses' Health Study I and II (n = 238 371; 1994-2008), Health Professionals Follow-up Study (n = 51 529; 1996-22008).
2. Every 2 years since baseline, follow-up questionnaires updated nformation on lifestyle practices and occurrence of chronic diseases. Follow-up rates were approximately 90%.
3. Exclusions at baseline: Subjects who reported type-1 and type-2 diabetes, cardiovascular disease, cancer, and those with incomplete data. This left 187 332 participants available for analysis. (36 123 men and 151 209 women). Ages at baseline ranged from late 30s to early 50s.
4. Assessment of fruit consumption: Periodic food-frequency questionnaires (118 items) asked participants how often, on average, they consumed each food in a standard portion size. Consistently asked about 10 individual fruits. Calculated total whole fruit consumption by summing up the consumption levels of all 10 fruits.
5. Follow-up questionnaires every 2 years updated information of anthropomorphic and lifestyle factors for chronic disease.
6. Updated information about incidence of type-2 diabetes. Determined incidence of deaths.
7. Estimated the hazard ratios and 95% confidence intervals of DM-2 for fruit and fruit juice consumption. Also examined whether associations of individual fruit consumption with risk of DM-2 depended on their glycemic index/glycemic load. Categorized individual fruits into 3 groups depending on their glycemic load per serving (high, moderate , and low).

RESULTS

1. Durant 3 464 641 person-years, 12 198 participants developed DM-2.

2. At baseline total fruit consumption:

	Number of participants
< 4 servings/week	34 955
1 serving /day	38 679
≥ 3 servings /day	37 467

3. Individual fruit consumption after adjustments for covariates:

For every 3 servings per week, the pooled hazard ratio (HR) of risk: for DM-2:

Blueberries	0.74	
Grapes and raisins	0.83	
Apples and pears	0.83	
Bananas	0.95	
Grapefruit	0.95	All statistically significant

Total whole fruit consumption was associated with a lower risk of DM-2. (HR = 0.98 for every 3 servings per week). Total whole fruit, HR of 1 serving per day = 0.84.

Cantaloupe was associated with an increased risk (in HR = 1.10).

Strawberries tended toward the null.

4. Associations between fruit consumption and risk of DM-2 by glycemic index and glycemic load: greater consumption of high glycemic load fruits was associated with lower risk of DM-2.

5. Fruit juice consumption was associated with an increased risk of DM-2.HR = 1.09.

6. Results of replacing each 3 servings/week of fruit juice with the same amount of total or individual whole fruits (after adjustment):

7% lower for total whole fruits

33% lower for blueberries

19% lower for grapes and raisins

14% lower for apples and pears

13% lower for bananas

12% lower for grapefruit

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DISCUSSION

1. Associations of risk of DM-2 differed significantly among individual fruits. Greater consumption of blueberries, grapes, apples, bananas and grapefruit was significantly associated with reduced risk of DM-2. Most of these associations were quite consistent among the 3 cohorts.
2. The glycemic index/glycemic load values did not seem to be the factor that determined the associations with DM-2.
3. Substitution of whole fruits for fruit juice was associated with lower risk, except for strawberries and cantaloupe.
4. Previous studies on the same associations have been conflicting.
5. Further research is needed to confirm these findings of this study on specific fruits in relation to DM-2 and to elucidated underlying mechanisms.

CONCLUSION

These findings suggest that there is significant heterogeneity in the associations between individual fruits and risk of DM-2.

Greater consumption of specific whole fruits, particularly blueberries, grapes, and apples, was significantly associated with lower risk.

Fruit juice consumption was associated with a higher risk.

The differences in association between individual fruits were not accounted for by the variation in glycemic index/ glycemic load values for individual fruits.

This supports recommendations for increasing consumption of a variety of whole fruits, especially blueberries, grapes, and apples as a measure for diabetes prevention.

BMJ2013;347:f5001 First author Isao Muraki, Harvard School of Public Health, Boston Mass.
A short account appeared in BMJ September 7;347:12

The study contains much more detail than I have indicated, especially statistical calculations. I congratulate the authors on digging through 3 mountains of data.

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Reducing blood glucose by excreting it

9-2 SGLT2 INHIBITORS FOR DIABETES; Turning symptoms into therapy

Normally, the kidneys filter roughly 180 liters of plasma every 24 hours—about 180 grams of glucose, almost all of which is reabsorbed.

Renal glucose reabsorption takes place by means of Sodium-GLucose co-Transport (SGLT2). SGLT2 is a high-capacity glucose transporter located on the luminal surface of epithelial cells lining the proximal tubule and accounts for about 90% of glucose reabsorbed. In diabetes, renal gluco- neogenesis, and capacity for glucose reabsorption are increased, while expression of SGLT2 seems to be upgraded.

Pharmacological inhibition of SGLT2 could be an option to reduce hyperglycemia in patients with diabetes, albeit it is not a cause of the disease.

Individuals with familial renal glycosuria, which is due to mutations in the genetic coding of SGLT2 have asymptomatic urinary glucose excretion, but they have no hyperglycemia, polyuria, polydipsia, renal function loss, or increase in urogenital infections.

Highly selective SGLT2 inhibitors are being developed to decrease hyperglycemia independently of insulin. (The article cites 13 studies of SGLT2,)

An article in the Lancet[1] reports a 52-week randomized, controlled trial comparing efficacy of a SGLT2 inhibitor cana-gli-flozin (100 or 300 mg daily) vs glimepiride (a sulfonylurea; Amaryl) in patient with type-2 diabetes inadequately controlled with metformin. 100 mg canagliflozin was non-inferior to glimepiride in reduction of HbAic. The 300 mg dose was superior to glimepiride.

At 52 weeks, canagliflozin reduced body weight by about 4 kg; glimepiride increased bodyweight by about 0.7 kg. A body composition sub-study showed that 2/3 of the reduction body weight was from fat, and 1/3 for lean body mass. Canagliflozin provided modest reduction in BP, and the frequency of hypoglycemia. Genitourinary infection in both sexes, and osmotic diuresis were more frequent. Discontinuation because of adverse effects was similar across groups. (6%)

Canagliflozin was approved by the FDA in March 2013, but approval required 5 post-marketing studies, including a long-term cardiovascular safety study, a bone-safety study, and 2 pediatric studies.

Several cautions:

1) Although SGLT2 inhibitors act independently of key defects of type-2 diabetes, glycosuria is perceived as a sign of metabolic decompensation, with adverse clinical consequences. Use of a disease manifestation as a therapeutic option might be considered a step backward instead of forward.

2) SGLT2 inhibitors are welcomed as another treatment for type-2 diabetes, thereby contributing to the individualization of treatment advocated by the American Diabetes Association. However, the position of SCLT2 inhibitors in the present stepwise treatment approach is not clear. Effectiveness of SGLT2 inhibitors wanes as glomerular filtration decreases with disease progression.

3) Long-term safety concerns (cardiovascular, cerebrovascular, and cancer, and adverse effects on bone health in a high-risk population) need close surveillance even after approval.

4) Will increased frequency of genitourinary infections be acceptable to patients with diabetes, who are susceptible to such infections?

The diabetes community is itching to learn new findings from relevant studies to help establish the place of SCLT2 inhibitors in treatment of type-2 diabetes.

Lancet September 14, 2013; 382: 917-18 Commentary, first author Michaela Diamont, University Medical Centre, Amsterdam, Netherlands.

Certainly a novel approach to treatment of a disease.

I do not believe this drug is ready for prime time in primary care. Safety concerns must be addressed in long-term trials.

1 Various pharmaceutical companies must have great expectations from these compounds.

"EFFICACY AND SAFETY OF CANAGLIFLOZIN VERSUS GLIMEPIRIDE IN PATIENTS WITH TYPE-2 DIABETES INADEQUATELY CONTROLLED WITH METFORMIN: 52 WEEKS RESULTS FROM A RANDOMIZED, DOUBLE-BLIND PHASE 3 NON-INFERIORITY TRIAL"

Lancet September 14, 2013; 382:941-50. Original investigation, first author William T Cefaiu, Pennington Biomedical Research Center, Baton Rouge, LA. Funded by Jansen Research and Development,

The trial reports favorable and adverse effects of canagliflozin:

Favorable		Adverse	
Reduction in HbA1c about 1%		Urinary tract infections	6%
HbA1c < 7.0%	60%	Inroad urine frequency	3%
HbA1c < 6.5%	31%	Increased urine volume	<1%
Weight loss	4Kg	Hypoglycemia	5%
BP change	-4.8/-2.4	Genital mycotic infection	
		Male	8%
		Female	14%

I do not understand why there are not more symptoms related to increased excretion of glucose.

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9-3 E-CIGARETTES: Three recent commentaries.

A. E-CIGARETTES AS GOOD AS PATCHES IN HELPING TO REDUCE SMOKING

A small trial in New Zealand (first author Chris Bullen, University of Auckland, Health Research Council of New Zealand) randomized 657 smokers to nicotine e-cigarettes, nicotine patches, or placebo e-cigarettes.

Most participants using e-cig receive low level behavioral support.

Abstinence from tobacco at 6 months: (%)

Nicotine e-cig	7.3
Nicotine patch	5.8
Placebo e-cig	4.7

The abstinence rate was low, and insufficiently powered to conclude whether e-cig were superior to the patch.

In the e-nicotine group, daily cigarette smoking was reduced by 57% vs 41% of the patch group. The authors concluded that e-cig were effective in helping tobacco smokers cut down.

The US based Campaign for Tobacco-free kids, recently commented that the tobacco industry's marketing tactics for e-cig were reminiscent of the tobacco industry "in its worst days". "Like cigarette ads of old, television and online ads for e-cigarettes feature catchy slogans and celebrity endorsers." These ads portray e-cigarette use as an act of rebellion—depicting e-cigs as masculine, sexy and glamorous.
BMJ September 14 2-13; 347:3 BMJ 2013;347:f5505 "News" by Jacqui Wise, London

B, E-CIGARETTES: A MORAL QUANDARY

Sales of e-cigarettes are expected to boom. Data for their safety and efficacy are desperately needed. Many questions remain unanswered.
Although e-cig might reduce harm compared to traditional cigarettes, appropriate regulation of safety and product consistency is essential.

Marketing also needs to be monitored to ensure that easy availability does not encourage people to start smoking. The CDC reported that the percentage of middle and high school students who used e-cig had more than doubled between 2011 and 2012, and one out of five middle school children who reported using e-cig had never smoked tobacco cigarettes.

Excessive regulation of e-cig could marginalize them in favor of conventional cigarettes.

Amid disagreements between public health experts, and uncertainty about the long-term efficacy and safety of e-cigs, should we stand back and wait for robust results before adopting a formal public health stance?

Harm reduction should be our guiding principle.

The moral dilemma: when we suggest use of e-cigs to a patient, we are supporting the tobacco industry to continue production of products most devastating to public health.
Lancet September 14, 2013;382:914 Editorial by the Lancet staff

C. THE REGULATORY CHALLENGE OF ELECTRONIC CIGARETTES

At present, the prevalence of ever use of e-cig in the USA is 11%. It is growing rapidly. More than 250 e-cig brands are presently on the market.

They likely pose less hazard than tobacco cigarettes and might help smokers to quit. They may reduce harm by lowering rate of smoking tobacco.

There are potential harms.

In 2011 the FDA announced plans to regulate e-cig as tobacco products. The FDA will have to make a number of regulatory decisions about safety. Nicotine per-se contributes to some smoking-related diseases, but its contribution is much smaller than tobacco.

Nicotine replacement products have been in use for nearly 30 years, and have proven to be a safe way to facilitate cessation. But they are not as satisfying and are less acceptable to smokers compared with inhaling and absorbing nicotine from cigarette smoke.

Although not yet proven to be safe or effective for tobacco cessation, the e-cig has been positioned as such, and has gained popularity through this perception.

Different e-cig brands are engineered differently, affecting their character and potential toxicity. E-cig cannot be generalized as a single device. The FDA will need to consider the different types of nicotine solutions, the capacity of the cartridges containing the nicotine, the nature of the heating elements and battery, the type of additives and flavorings, and the potential toxicants released in the vapor. Liquids used in e-cig vary with respect to concentrations of toxicants. Their quality-control is questionable. A number of toxicants have been identified, but the level is orders of magnitude lower than those found in cigarette smoke.

Uncontrolled studies have reported that e-cig facilitate quitting tobacco cigarettes, and allow smokers to smoke fewer cigarettes.

Several potential sources of harm: uptake of e-cig by non-smokers who later may become nicotine addicts, promotion of dual-use of e-cig and regular cigarettes, and exposure to new sources of air pollution.

The tobacco industry has aggressively marketed e-cig with claims of health benefits compared to smoking tobacco, for reducing and quitting smoking, for smoking without generating irritating and harmful second hand smoke, and for use when and where a smoker cannot use tobacco.

The FDA needs to decide how marketing should be
regulated, in the context of potential benefits and harms.

JAMA August 21, 2013; 310:685-86 “Viewpoint”, first author Neal L Benovitz, University of California, San Francisco,

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I am glad I do not work for a tobacco company.

Don’t underestimate the power of the marketing departments of cigarette companies.

This is an important challenge to primary care medicine. If it takes smoking e-cigs to aid quitting, I would favor their use. But not at the risk of harm from continuing to smoke e-cig, or switching back to tobacco.

I can think of only one possible advantage of e-cig. They may help a tobacco smoker to taper down and then quit completely without continuing to smoke e-cig

There are many potential harms:

Some e-cig in an unregulated market will undoubtedly contain harmful additives in addition to nicotine.

Tobacco cigarettes and e-cig will be used together.

We do not know all harms of nicotine alone. It is a powerful toxic drug. Harms will occur due to nicotine alone. Nicotine is one of the most addicting drugs known.

Adolescents will get "hooked" on the nicotine in e-cig and continue to smoke them.

9-4 EFFICACY AND SAFETY OUTCOMES OF ORAL ANTICOAGULATION AND ANTIPLATELET DRUGS IN THE SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM: Meta-analysis

A short abstract of this meta-analysis of 13 randomized trials published in the BMJ considered the efficacy and safety of aspirin and different new oral anticoagulants (NOACs) in the long-term secondary prevention of recurrent venous thromboembolism (VTE). Primary outcome = recurrent VTE and major bleeding episodes.

All treatments reduced recurrence of VTE compared with placebo or observation.

Compared with placebo, standard adjusted dose warfarin (INR 2.0 t0 3.0) was the most effective for preventing recurrent VTE (odds ratio = 0.07). Aspirin was the least effective (OR = 0.65). Apixaban seemed to be associated with the lowest risk for major bleeding.

Although aspirin was the least effective, its use for secondary prevention of VTE could be valuable for patients with arterial disease.

The article presents helpful illustrations of absolute risk. For each intervention, a small chart represents 100 patients (with small black figures) arranged in 10 files and 10 ranks. The bottom rank

includes blue figures representing patients with recurrent VTE, and red figures representing major bleeding episodes.

Absolute risks of recurrent VTE and major bleeding per 100 patients:

	VTE	Major Bleeding
Placebo or observation	10	1
Aspirin 100 mg daily	7	1
Warfarin standard dose	1	2
Dabigatran 150 mg BID	2	1
Apixaban 5 mg BID	2	1
Rivaroxaban 20 mg daily	2	6

BMJ2013;347:f5133 BMJ September 14,2013; 347:11 Original investigation , first author Lama A Castellucci, University of Ottawa, Canada
For the full study: doi.1136/bmj.f5133

This article presents a preliminary report of the benefit/harm-cost ratio of new oral anticoagulants.

Many primary care clinicians (as well as myself) remain uncertain about the place of NOACs.

For patients who have been well controlled on warfarin, there is no compelling reason to switch. Aspirin remains a simplified and inexpensive approach for some patients, but with higher risk of recurrence of VTE.

Whether there is a "Best" alternative waits for further experience.

Dabigratran (Pradaxa; Boehringer Ingelheim) Direct thrombin inhibitor
Apixaban (Eliquis; Bristol-Myers Squibb) Direct factor Xa inhibitor
Rivaroxaban (Xerelto; Bayer) Direct factor Xa inhibitor
All are expensive—around $300 a month for standard doses
Warfarin is very inexpensive.

To complicate matters, a NOAC is in the process of being approved by the FDA. Edoxaban (Daiichi-Sankyo)

9-5 ENERGY DRINKS AND ALCOHOL: Downplaying the Harms

Mixing alcohol with energy drinks has become popular, but at what risk? Researchers may not consider real world levels of consumption. Their conflicts of interest need to be declared.

Harm may arise when heavy drinkers mix so called energy drinks (ED) with alcohol. It may enable them to drink longer and achieve higher levels of intoxication.

On Friday and Saturday evenings, about 40% of people of Australian streets are heavily intoxicated (breath alcohol greater the 0.087 mg alcohol/ 100 mL of blood) and nearly a quarter of drinkers will have consumed more than 2 energy drinks. Seventy% of US college students reported consuming energy drinks mixed with alcohol in the past month.

Epidemiological studies have shown that drinkers who consume ED are more likely to record higher breath alcohol than those who do not. They are also more likely to engage in aggressive acts and be injured, to drive while drunk, and to taken sexual advantage of another person.

Many researchers who have had industry sponsorships may conclude there is no evidence that combined drinking of ED + alcohol increases drinking or harm.

It is critical that the public can be confident in the findings of research on these products.

BMJ2013;347:f5345 BMJ September 14, 2013; 347:25 "Personal View" by Peter Miller Deakin University, Geelong, Victoria, Australia.

The latest problem primary care physicians have to consider.