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Nollaig Shona dár léitheoirí go léir!
Happy Christmas to all our readers!

The benefits of chocolate: the news just gets better! Dietary flavonoids have been shown to improve cognitive function and to protect against cardiovascular disease. Recent studies have evaluated the potential clinical benefits of eating chocolate (which contains flavonoids). The first study evaluated the association between chocolate consumption and risk of stroke in a cohort of >37,000 Swedish men (45-79 years at baseline) during a median follow-up of 10.2 years ***(Neurology 2012; 79: 1223-9).*** Chocolate consumption was assessed using a self-administered food-frequency questionnaire at baseline, using 8 pre-specified consumption categories ("never" to ≥3 times/day). Cases of first stroke were identified using the hospital discharge records, which provided almost complete coverage for all discharges. Results showed 1,995 cases of first stroke occurred during the 10-year follow-up (1,511 infarcts; 321 haemorrhagic; 163 unspecified). When all other possible risk factors were adjusted for (including age, smoking status, diet and BMI, physical activity, aspirin use, history of hypertension, family history, education), **those in the highest chocolate intake group (>51.6g/week) had a 17% lower risk of first stroke compared with those in the lower consumption group (<12g/week).** The investigators undertook a meta-analysis of 5 prospective studies (including the current study), which confirmed a 19% reduction in the risk of stroke for the highest compared with the lowest category of chocolate consumption. The authors concluded that the apparent protective effect of chocolate may be explained by the biological mechanisms of flavonoids which include anti-oxidant, anti-platelet, anti-inflammatory and anti-hypertensive effects and as well as increasing HDL cholesterol and improving endothelial function. They recommend that further studies are required to confirm the findings from these observational studies.

Food for thought... The second study evaluated the potential beneficial effects of chocolate on cognitive function ***(NEJM 2012; 367: 1562-4)***. The author identified Nobel laureates for 23 countries (up to October 2011) using a listing from Wikipedia and calculated the number of Nobel prizes (per 10 million persons) in a given country. Data on per capita yearly chocolate consumption for each country was calculated using information available from several online commercial sources. The results showed that **there was a close, significant linear correlation between chocolate consumption per capita and the number of Nobel laureates per 10 million population** in all 23 countries studied. Switzerland was the top performer in terms of both the number of Nobel prizes and chocolate consumption. Based on the slope of the linear correlation, it was estimated that **it would take about 0.4kg of chocolate per capita per year to increase the number of Nobel laureates by 1 in a given country.** The author acknowledges that the findings are hypothesis-generating and that the correlation noted cannot prove causation; however, he concludes that the findings support the idea that "*chocolate intake might provide the abundant fertile ground needed for the sprouting of Nobel laureates*". Of interest, the only outlier in an otherwise consistent correlation was Sweden, where, based on a yearly per capita chocolate consumption of 6.4kg, the author would have predicted a total of about 14 Nobel laureates, instead of the actual 32 recorded. The author suggests that the Swedes may be particularly sensitive to chocolate or this may be due to the fact that the Nobel Committee is based in Stockholm! [Editor's note: The Nobel laureate list is at: ***http://en.wikipedia.org/wiki/List_of_countries_by_Nobel_laureates_per_capita***]

Grapefruit use and potential drug interactions. The potential for grapefruit-drug interactions has been known for > 20 years. Currently it is estimated that there are > 85 drugs which are known or predicted to interact with grapefruit (GF), of which there are up to 43 drugs with a potential to cause serious adverse effects. A recent review described the mechanism of the interaction and lists the most common medications involved ***(CMAJ 2012. DOI: 10.1503/cmaj.120951)***. The most well known and well-studied mechanism of grapefruit-drug interactions, is interference with cytochrome P450 3A4 (CYP3A4) enzyme activity. CYP3A4 is involved in the metabolism of about 50% of all drugs and is located in cells lining the small intestine and in parenchymal cells in the liver. This initial metabolism of drugs determines the fraction of an oral drug that will reach the systemic circulation, i.e. the oral bioavailability. GF contains furanocoumarins, which are metabolised by CYP3A4 to reactive intermediates that bind to the active site of CYP3A4, causing irreversible inactivation. As a consequence, CYP3A4 activity in the small intestine is impaired until re-synthesis of the enzyme occurs. This results in potential increased peak plasma concentration of drugs metabolised by CYP3A4, with a potential for adverse effects. **All forms of GF (freshly squeezed, frozen concentrate and whole fruit) have the potential to reduce the activity of CYP3A4**; 1 whole GF or 200ml of juice is sufficient to cause a clinically relevant increased systemic drug concentration and subsequent adverse effects. Other fruit including Seville oranges and limes also have the potential to produce this interaction; however varieties of sweet orange do not.

The interaction between medications and GF is drug-specific and not a class effect. **Affected drugs have 3 characteristics: they are administered orally, they have very low (<10%) to intermediate (>30-70%) oral bioavailability and they are metabolised by CYP3A4**. The clinical significance of any interaction depends on the seriousness of the dose-related toxicity and the extent to which the systemic drug concentration increases. Older patients have the greatest possibility of ingesting GF and interacting drugs together and are also the most vulnerable to adverse clinical consequences. Examples of important consequences of grapefruit-drug interactions include torsades de pointes, rhabdomyolysis and nephrotoxicity. Torsades de pointes has been reported/predicted with GF and use of drugs including amiodarone, dronedarone, erythromycin, domperidone, nilotinib and sunitinib. Rhabdomyolysis has been reported with GF and drugs including simvastatin, atorvastatin and lovastatin. Nephrotoxicity has been reported/predicted with GF and drugs including ciclosporin and tacrolimus. Other potential grapefruit-drug interactions include gastrointestinal bleeding with apixaban and ticagrelor, loss of efficacy with clopidogrel, hyperkalaemia and serious arrhythmia with eplerenone and respiratory depression with oxycodone. Controversy exists over the risk of breast cancer in postmenopausal women receiving oestrogen therapy and consuming GF, with 1 epidemiological study suggesting a higher risk and a further study not finding an association.

The authors conclude that while GF and certain other citrus fruits are generally considered to be healthy, they have a potential for a pharmacokinetic interaction causing greatly enhanced oral drug bioavailability and increased risk of adverse effects. They advise that affected drugs should not be consumed with any of these fruits during the treatment period, or alternative non-interacting medications should be prescribed. [Editors note: the article has an appendix which contains a useful list of potential grapefruit-drug interactions, their bioavailability, the possible adverse event, the predicted interaction risk rank and potential alternative medication, which is available on ***www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120951/-/DC1***]

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