Scientists have shown that people with a good vitamin D supply are at lower risk of developing Type 2 diabetes mellitus. New tests performed on participants of the study have shown that people with a good supply of vitamin D have a lower risk of developing Type 2 diabetes mellitus, while individuals with lower concentrations of vitamin D in their blood have a higher risk. This effect could be attributable, amongst other things, to the anti-inflammatory effect of vitamin D. "Vitamin D deficiency is relatively widespread due to our modern way of life. The human body can produce vitamin D itself if it has sufficient exposure to sunlight. The UVB radiation in natural daylight splits the precursor of vitamin D, 7-dehydrocholesterol, in the skin and forms pro-vitamin D3. Further vitamin D synthesis occurs in the liver and kidneys. In addition, the supply can be improved by eating specific foods, such as oily fish, eggs and milk products, or by taking vitamin D supplements. Type 2 diabetes is a disorder of glucose metabolism. It is characterized by a loss of insulin action and a drop in the levels of the hormone produced by the body. The mechanisms that trigger the disease have not yet been fully clarified. However, it is known that diabetes is caused by a combination of genetic and lifestyle factors."

Adverse Medication Reactions

Zoledronic acid: New Contraindication and Updated Warning on Kidney Impairment

AUDIENCE: Endocrinology, Pharmacy, Patient

FDA notified healthcare professionals and patients of an update to the drug label for zoledronic acid regarding the risk of kidney failure. Cases of acute renal failure requiring dialysis or having a fatal outcome following zoledronic acid use have been reported to FDA. The revised label states that zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.

Acetaminophen Prescription Products Limited to 325 mg Per Dosage Unit

AUDIENCE: Pharmacy, Pain Management

FDA notified healthcare professionals that it has asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients. This action will help to reduce the risk of severe liver injury and allergic reactions associated with acetaminophen. A Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) will be added to the label of all prescription drug products that contain acetaminophen. Acetaminophen, one of the most commonly used drugs, is widely and effectively used in both prescription and over-the-counter (OTC) products to reduce pain and fever.

Ondansetron: Risk of Abnormal Heart Rhythms

AUDIENCE: Anesthesiology, Oncology

FDA notified healthcare professionals and patients of an ongoing safety review and labeling changes for the anti-nausea drug ondansetron. Ondansetron may increase the risk of developing prolongation of the QT interval of the electrocardiogram, which can lead to an abnormal and potentially fatal heart rhythm including Torsade de Pointes. Ondansetron is in a class of medications called 5-HT3 receptor antagonists. It is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery.

Citalopram hydrobromide: Abnormal Heart Rhythms Associated With High Doses

AUDIENCE: Psychiatry, Cardiology

FDA notified healthcare professionals and patients that the antidepressant Citalopram hydrobromide, is in a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs), should no longer be used at doses greater than 40 mg per day because it can cause abnormal changes in the electrical activity of the heart. Changes in the electrical activity of the heart (prolongation of the QT interval of the electrocardiogram [ECG]) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood.

Rosiglitazone: Risk of Cardiovascular Events

AUDIENCE: Endocrinology, Cardiology

FDA notified healthcare professionals and patients that it will significantly restrict the use of the diabetes drug (rosiglitazone) to patients with Type 2 diabetes who cannot control their diabetes on other medications. These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with rosiglitazone.

Fenofibric acid may not lower risk of heart attack or stroke

AUDIENCE: Family Practice, Cardiology, Pharmacy

FDA notified healthcare professionals the cholesterol-lowering medicine Fenofibric acid may not lower a patient’s risk of having a heart attack or stroke. FDA reviewed the data from the Action to Control Cardiovascular Risk in Diabetes. The research trial found no significant difference in the risk of experiencing a major adverse cardiac event between the group treated with fenofibrate plus simvastatin compared with simvastatin alone.

FDA Restricts Use of Simvastatin 80 mg

The Food and Drug Administration is recommending that physicians restrict prescribing high-dose simvastatin to patients, given an increased risk of muscle damage. The new FDA drug safety communication states that physicians should limit using the 80-mg dose unless the patient has already been taking the drug for 12 months and there is no evidence of myopathy. In addition, the FDA is requesting that additional changes be made to the drug’s label. The label will be changed to include the new dosing recommendations, as well as warnings not to use the drug with various medications, including itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, nefazodone, gemfibrozil, clarithromycin, telithromycin, cyclosporine, and danazol. In addition, the 10-mg dose should not be exceeded in patients taking amiodarone, verapamil, and diltiazem, and the 20-mg dose should not be exceeded with amiodipine and ranolazine. The changes to the label are based on the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, a study reported by Heartwire. In that trial, patients taking the 80-mg dose developed myopathy compared with one patient treated with the 20-mg dose. In addition, patients treated with the high dose of simvastatin developed rhabdomyolysis compared with none treated with the 20-mg dose.

The FDA notes that the risks of myopathy and rhabdomyolysis were highest in the first year and that older age and female sex increased the risks.


Asthma benefit for vitamin C

An article published in Clinical and Translational Allergy reports a positive effect for vitamin C supplementation in asthmatic children. In a cross-over trial, 60 children between the ages of 7 and 10 with asthma were given 200 milligrams vitamin C, zinc, omega-3 fatty acids, a combination of the three supplements or a placebo daily for six weeks. After a two week period during which no supplements were given, the participants were switched to a new regimen, until all children had received each treatment. Questionnaires assessed asthma severity at the beginning of the study and at the end of each phase of treatment, and pulmonary function was tested via spirometry. Additionally, the parents were questioned on the presence of mold or dampness in the children’s bedrooms. While supplementation with vitamin C was associated with an average increase of 29 percent in forced expiratory volume per one second (FEV1), which is a measure of pulmonary function, there was significant difference among the participants according to age and level of mold exposure. Children aged 7 to 8.2 years who had no exposure to dampness or mold experienced a 37 percent increase FEV1, while this measure increased by just 21 percent in those between the ages of 8.3 and 10 years whose parents reported mold and dampness in their children’s rooms. When symptom questionnaire responses were analyzed, children aged 7 to 8.2 years with mild asthma symptoms were found to have experienced the greatest benefit from the vitamin, while older subjects whose symptoms were severe benefitted least. “It would seem important to carry out further research to confirm our findings and more accurately identify the groups of children who would receive the greatest benefit from vitamin C supplementation,” the authors wrote.

Visfatin: A New Visceral Fat Adipokine

Employing the method of differential display of expressed genes (by analysis of 8800 gene products utilizing cDNA probes) in paired samples of subcutaneous and visceral fat donated from female volunteers, the investigators identified an adipokine that is synthesized primarily by visceral fat and termed this molecule “visfatin.” They subsequently found that the visfatin had been previously identified as “pre-B cell colony-enhancing factor” (PBEF). This is secreted by the liver, bone marrow, and muscle, is a growth factor for early stage B lymphocytes, and down-regulates apoptosis of neutrophils. The investigators demonstrated that: 1) expression of PBEF/visfatin increased during adipocyte differentiation in vitro with increased secretion of this protein into medium; 2) plasma concentrations of visfatin correlated with the volume of visceral fat in humans and mice but not the quantity of subcutaneous fat; 3) plasma levels of visfatin increased as the amount of fat accumulated in a mouse model of obesity; and 4) visfatin values rose rapidly in mice ingesting a high-fat diet. Subsequently, the authors observed that intravenous administration of visfatin led to a dose-dependent decline in glucose concentrations without affecting insulin values in intact and diabetic mice. Complete knock-out of the visfatin gene was lethal. In heterozygotic (visfatin+/-) animals, basal plasma glucose values were elevated, glucose tolerance was impaired, while there was no difference in size or insulin levels. In vitro, visfatin had several insulin-like actions including: enhancement of glucose uptake, suppression of glucose release, accumulation of triglycerides, and induction of gene markers of adipocyte differentiation (PPAR γ, fatty acid synthase, adiponectin, and so forth). The investigators also showed that visfatin bound to the insulin receptor and induced its autophosphorylation, as well as phosphorylation of a number of downstream products consistent with induction of the insulin/insulin receptor signal transduction pathway. Most interestingly, they demonstrated that visfatin did not bind to the same segment of the insulin receptor as insulin (extracellular α subunit), although the binding site on the insulin receptor to which visfatin adheres was not identified. The authors concluded that visfatin has insulin-like effects and may be of physiological significance in the regulation of glucose homeostasis.


Curcumin prolongs life in model of Alzheimer's disease

Researchers report a benefit for curcumin in fruit flies (Drosophila melanogaster) that have been genetically modified to develop a disorder similar to Alzheimer’s disease. The findings were described in an article published on February 13, 2012 in the journal PLoS One.

Researchers utilized four groups of fruit flies with different genetic modifications controlling the expression of amyloid beta, a toxic protein that accumulates in the brains of human Alzheimer's disease patients. Also included in the study was a group of flies bred to express Tau protein, which is also found in Alzheimer's diseased brains. Unmodified flies were used as controls.

With the exception of flies bred to express Tau, genetically modified flies that received curcumin lived up to 75 percent longer and maintained mobility longer compared to those that did not receive the compound. While curcumin was not associated with a decrease in amyloid plaque in the flies’ brains or eyes, it appeared to reduce the amount of amyloid fibril precursors known as oligomers. "Several theories have been established about how oligomers can instigate the disease process,” the authors write. "According to one hypothesis, they become trapped at synapses, inhibiting nerve impulse signals. Others claim that they cause cell death by puncturing the cell membrane."

"The results confirm our belief that it is the oligomers that are most harmful to the nerve cells," authors stated. "We now see that small molecules in an animal model can influence the amyloid form. To our knowledge the encapsulation of oligomers is a new and exciting treatment strategy."

► http://www.lef.org/whatshot/2012_02.htm
Study of Cox-2 Inhibitors Could Lead to New Class of Stroke Drugs

A study, in mice, by investigators points toward potential new therapies for stroke, the leading cause of death and foremost single cause of severe neurological disability. The study, which will be published in the Journal of Clinical Investigation, also may reveal why a much-heralded class of blockbuster drugs failed to live up to their promise. Medical experts were excited when over a decade ago a class of drugs called COX-2-selective inhibitors came along. These new drugs were supposed to retain the advantages of aspirin and other so-called non-steroidal anti-inflammatory drugs, or NSAIDs, without causing stomach damage. But in large-scale clinical trials of COX-2-selective inhibitors, puzzling and disturbing side effects emerged. The new study helps explain why these drugs can be troublesome and how there may actually be some benefits to reap from the very molecular activity that these drugs were intended to block. NSAIDs block both COX-2 and COX-1, two very similar versions of cyclooxygenase, an enzyme that catalyzes a key chemical reaction in the production of five related hormone-like messenger molecules called prostaglandins. PGE2 has four separate counterpart receptors, designated EP1 through EP4, each of which sets in motion a different set of activities inside cells on binding to PGE2. They found that activating EP4 receptor, three hours after a stroke not only diminishes the volume of a mouse’s affected brain tissue but also enhances the mouse’s functional recovery.

► http://www.medicalnewstoday.com/releases/235409.php

Novel Inhibitor Design for Hemagglutinin against H1N1 Influenza Virus by Core Hopping Method.

The worldwide spread of H1N1 avian influenza and the increasing reports about its resistance to the current drugs have made a high priority for developing new anti-influenza drugs. Owing to its unique function in assisting viruses to bind the cellular surface, a key step for them to subsequently penetrate into the infected cell, hemagglutinin (HA) has become one of the main targets for drug design against influenza virus. To develop potent HA inhibitors, the ZINC fragment database was searched for finding the optimal compound with the core hopping technique. As a result, the Neo6 compound was obtained. It has been shown through the subsequent molecular docking studies and molecular dynamic simulations that Neo6 not only assumes more favorable conformation at the binding pocket of HA but also has stronger binding interaction with its receptor. Accordingly, Neo6 may become a promising candidate for developing new and more powerful drugs for treating influenza. Or at the very least, the findings reported here may provide useful insights to stimulate new strategy in this area.

► http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227604/?tool=pubmed
Gene therapy can protect against HIV

An introduced gene conveys long-lived resistance to HIV infection in mice. Gene therapy, an approach most commonly explored for curing chronic genetic diseases such as cystic fibrosis, may also prove practical for disease prevention. In research published in Nature1, scientists show that a single injection which inserted the DNA for an HIV-neutralizing antibody into the muscle cells of live mice completely protected the animals against HIV transmission. The road to a vaccine against HIV has proved to be far longer than originally anticipated. More than 2 million adults are newly infected with HIV every year and, nearly three decades after the virus was first identified, researchers haven’t found a reliable way to prevent infection. The classic vaccine approach, which uses all or part of an inactivated virus to induce immunity, has yielded little success because HIV has managed to disguise most of the easily-recognized external structures that antibodies would target. Researchers have thus had a tough time finding a molecule that can induce even moderately broad responses against the virus in all its different mutations. So although it might sound extreme to use gene therapy as a preventative treatment for HIV/AIDS, the method could provide a much-needed alternative. Researchers hope to prevent the spread of HIV (virus particle pictured) by using gene therapy to get cells to produce antibodies. A virologist and HIV researcher, and his colleagues used a genetically altered adenovirus to infect muscle cells and deliver DNA that codes for antibodies isolated from the blood of people infected with HIV. The DNA is incorporated into the muscle cells’ genome and programs the cells to manufacture the antibody, which is then secreted into the bloodstream. The tactic builds on earlier work by scientists at the Children’s Hospital, described the effectiveness of this technique in preventing transmission of simian immunodeficiency virus, which is similar to HIV but infects monkeys2. As for the rationale for using gene therapy for HIV: “This is something way out of the ordinary, and it’s perfectly reasonable to say that there’s no reason to do it if there’s an alternative,” says Baltimore. «But if there’s no alternative — and that’s where we’re at today — then we should be thinking of new ways to protect people.” An immunologist, who has developed a number of antibodies against HIV, agrees. “Obviously, the best thing of all is a vaccine. That’s a tried-and-tested method that carries very few risks.

Prolonged protection
Baltimore and his colleagues tested five different broadly neutralizing antibodies, one at a time, in mice with humanized immune systems. Two of the antibodies, called b12 and VRC01, proved completely protective even when the mice received doses of HIV that were 100 times higher than a natural infection. After 52 weeks, the levels of antibody expression remained high, suggesting that a single dose would result in long-lasting protection. Research showed that you can express protective levels of antibodies in a mammal and have that expression last for a long period of time. “It sets the stage for human trials.” Providing patients with periodic doses of these antibodies throughout their lifetime would be safer than coaxing antibody production from muscle cells, but it would be far from cost-effective. The gene-therapy approach, by contrast, recruits muscle cells to act as antibody factories and could be administered using a single intramuscular shot. Experts in the field are cautiously optimistic. “Mice and monkeys don’t always tell the truth. It’s a really interesting idea, and it should be assessed in clinical trials”. “Until someone shows that we can make these broadly neutralizing antibodies with a [classic] vaccine, I think this is an important concept that should be supported.” Gene therapy comes with its own set of problems. Because the antibody DNA is permanently inserted into the genome, there’s no way to turn it off if someone has an immune reaction against the antibodies. The researchers at the Children’s Hospital, hope to get the first round of human trials of their technique started before the end of 2012. http://www.nature.com/news/gene-therapy-can-protect-against-hiv-1.9516
Therapeutics: Another tool in the BCR–ABL kit?

Despite the success of treating chronic myelogenous leukaemia (CML) with the tyrosine kinase inhibitors (TKIs) imatinib, nilotinib and dasatinib, which inhibit the BCR–ABL fusion kinase, resistance and suboptimal responses in patients with advanced disease are still problematic. The ABL kinase contains an SH2 domain, which, in addition to mediating protein–protein interactions, facilitates the activation of the adjacent tyrosine kinase domain. However, the importance of activation by the SH2 domain in the already highly active BCR–ABL protein is unclear. Giulio Superti-Furga and colleagues initially showed that an SH2 mutant (T231R) that had previously been identified in imatinib-resistant patients with CML increased BCR–ABL autophosphorylation, as well as in vitro and in vivo kinase activity, when expressed in HEK293 cells. They also investigated an I164E mutation that disrupts the SH2–kinase domain interaction; expression of this mutant reduced BCR–ABL autophosphorylation and kinase activity. Importantly, the I164E mutation did not affect the structural integrity of the SH2 domain or its canonical function (binding phosphotyrosine). In addition, induced dimerization of the ABL kinase domain with the SH2 domain strongly activated kinase activity, and this was blocked by the I164E mutation. To determine whether this mechanism of activation is important for leukaemogenesis, the authors expressed BCR–ABL I164E in primary mouse bone marrow cells. Lethally irradiated mice that were injected with cells expressing BCR–ABL I164E did not develop leukaemia, and a defect in engraftment or haematopoietic differentiation was ruled out. The investigation of downstream signalling events showed that phosphorylation of signal transducer and activator of transcription 5 (STAT5) was reduced following expression of BCR–ABL I164E, but ERK and AKT phosphorylation remained intact, indicating that the disruption of the SH2–kinase interface downregulates specific signalling pathways.

“Mice that were injected with cells expressing BCR–ABL I164E did not develop leukaemia”

Cells expressing BCR–ABL I164E were more sensitive than those expressing wild-type BCR–ABL to imatinib and nilotinib. Moreover, BCR–ABL proteins with TKI-resistance mutations (including T315I) showed restored sensitivity to nilotinib when the I164E mutation was introduced, indicating that the SH2–kinase interface could potentially be targeted for therapeutic benefit. To do this, the authors identified a monobody (a single domain-binding protein based on the fibronectin type III domain), 7c12, that specifically binds the ABL SH2 domain. Although 7c12 inhibits kinase activity of wild-type, but not I164E, BCR–ABL, the authors improved the potency of this monobody by linking it to a previously discovered SH2-binding monobody, HA4, which blocks phosphotyrosine binding. HA4–7c12 inhibited in vitro kinase activity of BCR–ABL at a level comparable to that of the I164E mutant, and blocked BCR–ABL activation and induced apoptosis in a CML cell line. Furthermore, HA4–7c12 inhibited transformation of primary mouse bone marrow cells by BCR–ABL and increased apoptosis of primary cells from patients with either chronic or accelerated phase CML. Although the necessary intracellular delivery of monobodies will probably prevent their clinical development, these results establish a rationale for targeting the SH2–kinase interface in BCR–ABL, which may be feasible with small molecules.

► http://www.nature.com/nrc/journal/v11/n12/full/nrc3173.html
High Uric Acid Linked to Both Gout and Diabetes

People with gout should make sure their uric acid levels are under control even if they’re not experiencing symptoms of the painful arthritic disorder. But new studies show that high uric acid levels in the blood are associated with a nearly 20% increased risk of developing diabetes and a more than 40% increased risk of developing kidney disease. Uric acid is a chemical substance that can build up in the blood to a higher than normal level and lead to gout.

High Uric Acid and Diabetes

For the new studies, researchers reviewed the records of about 2,000 men with gout in a Veterans Administration database. None had diabetes or kidney disease at the start of the study. Over a three-year period, 9% of men with gout who had uncontrolled uric acid levels developed diabetes, compared with 6% of those whose uric levels were under control. After taking into account other risk factors for diabetes, this corresponded to a 19% higher risk of diabetes in those with uncontrolled uric acid levels. A blood uric acid level greater than 7 is considered uncontrolled.

Risk of Diabetes and Kidney Disease

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Drugs Approved by the FDA (2011)

- Vemurafenib (BRAF inhibitor) approved for the treatment of patients with metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.
- Ticagrelor (P2Y12 platelet inhibitor) approved for reduction in the rate of thrombotic cardiovascular events in patients with acute coronary syndrome.
- Indacaterol inhalation powder (long-acting beta2-agonist) for long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
- Fentanyl (opioid analgesic) nasal spray for the management of breakthrough pain in cancer patients.
- Nitroglycerin topical ointment for the treatment of moderate to severe pain associated with chronic anal fissures.
- Mometasone furoate corticosteroid implant offering localized, controlled drug delivery for chronic sinusitis patients.

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