ABSTRACTS

WHY BLOOD GLUCOSE CONTROL MATTERS FOR THE KIDNEY

One of the most common and most serious complications of both type 1 and type 2 diabetes is diabetic nephropathy. It occurs in about 30% of patients with type 1 diabetes and 10 - 40% of patients with type 2 diabetes. Diabetic nephropathy is the leading cause of renal failure in the developed world. The main effect of diabetic nephropathy is proteinuria, initially in very small amounts but which increases, leading to nephrotic syndrome and end-stage renal disease in most cases.

Apoptotic renal tubular cells in diabetic nephropathy

Various risk factors in individuals with diabetes are known to increase the chance of developing diabetic nephropathy, including South Asian or African background, male sex, long history of diabetes, poor blood sugar control, high blood pressure, and smoking. One early change associated with diabetic nephropathy is degeneration of the renal tubular epithelium, but the exact cause of this at the cellular level is unclear. Susztak and colleagues have dissected out one key point in the progression to diabetic nephropathy. They looked at cell lines of renal tubular cells from humans and mice and kidney biopsies from patients with diabetic nephropathy, patients with non-diabetic renal disease, and mice with genetic and induced diabetes. In the human cell lines they showed that glucose induced the expression of CD36, a receptor known to have a role in adhesion and signal transduction (in addition to being the receptor for malaria-infected erythrocytes). They then went on to show that apoptosis of these cells occurred in the presence of glycated (glucose-modified) albumins or free fatty acids, which are present in increased amounts in patients with diabetes, and that CD36 was essential for the apoptosis to occur. They then examined how CD36 triggered apoptosis and found that it involved src kinase, p38 MAP kinase, and caspase 3.

Comparing mice and humans, the researchers found that the two species are not alike: Diabetic mice did not show an increase in tubular expression of CD36 – even though the gene is present in mice – and had normal tubular epithelium and no tubular apoptosis. They confirmed this difference between humans and mice by showing that normal mouse epithelial cell lines were resistant to apoptosis caused by the glycated albumins; however, artificially expressing CD36 in these lines made them susceptible to apoptosis by these modified albumins.

These results provide insight into one of the crucial steps in diabetic nephropathy and, in humans at least, might help to explain why high blood glucose is so damaging to the kidney, hence providing a good reason – if another is needed – for encouraging patients to control blood glucose as tightly as possible.

Susztak K, *et al.* Why blood glucose control matters for the kidney *PLoS Med* 2005; **2** (2)**:** e56

ARE FLU VACCINES EFFECTIVE IN HEALTHY CHILDREN?

The authors of this study aimed to assess evidence of efficacy and effectiveness of live attenuated and inactivated influenza vaccines in children up to 16 years of age. To do this they searched the Cochrane Library, MEDLINE, EMBASE Biological Abstracts, and Science Citation Index to June 2004, in any language, and contacted vaccine manufacturers and authors of relevant studies to identify additional data. They included randomised, cohort, and case-control studies comparing efficacy of vaccines against influenza (reduction in laboratory-confirmed cases), effectiveness of vaccines against influenza-like illness (reduction in symptomatic cases), or both, with placebo or no intervention. The authors analysed the following outcomes: influenza, influenza-like illness, admissions, school absences, complications, and secondary transmission.

The main findings were that live attenuated influenza vaccines had 79% efficacy and 38% effectiveness in children older than 2 years compared with placebo or no immunisation. Inactivated vaccines had lower efficacy (65%) than live attenuated vaccines, and in children aged 2 years or younger they had similar effects to placebo. Effectiveness of inactivated vaccines was about 28% in children older than 2 years. Vaccines were effective in reducing long school absences. Studies assessing the effects of vaccines against secondary cases, lower respiratory tract disease, acute otitis media, and hospital stay suggested no difference with placebo or standard care, but lacked statistical power.

The authors concluded that influenza vaccines (especially two-dose live attenuated vaccines) are effective in children older than 2 years. However, efficacy and effectiveness of the vaccines differed strikingly. Only 2 small studies assessed the effects of influenza vaccines on hospital admissions and no studies assessed reductions in mortality, serious complications, and community transmission of influenza. If influenza immunisation in children is to be recom-

mended as public health policy, large-scale studies assessing such important outcomes and undertaking direct comparisons of vaccines are urgently needed.

Jefferson T, *et al. Lancet* 2005; **365:** 773-780.

EFFECTIVENESS OF MASS ORAL CHOLERA VACCINATION IN BEIRA, MOZAMBIQUE

New-generation, orally administered cholera vaccines offer the promise of improved control of cholera in sub-Saharan Africa. However, the high prevalence of human immunodeficiency virus (HIV) infection in many cholera-affected African populations has raised doubts about the level of protection possible with vaccination. The authors evaluated a mass immunisation programme with recombinant cholera-toxin B subunit, killed whole-cell (rBS-WC) oral cholera vaccine in Beira, Mozambique, a city where the seroprevalence of HIV is 20 - 30%.

From December 2003 to January 2004, investigators undertook mass immunisation of non-pregnant persons at least 2 years of age, using a two-dose regimen of rBS-WC vaccine in Esturro, Beira (population 21 818). They then assessed vaccine protection in a case-control study during an outbreak of El Tor Ogawa cholera in Beira between January and May 2004. To estimate the level of vaccine protection, antecedent rates of vaccination were compared between persons with culture-confirmed cholera severe enough to have prompted them to seek treatment and age-and sex-matched neighbourhood controls without treated diarrhoea.

The authors assessed the effectiveness of the vaccine in 43 persons with cholera and 172 controls. Receipt of 1 or more doses of rBS-WC vaccine was associated with 78% protection. The vaccine was equally effective in children younger than 5 years of age and in older persons.

The rBS-WC vaccine was highly effective against clinically significant cholera in an urban sub-Saharan African population with a high prevalence of HIV infection.

Marcelino E S, *et al. NEJM* 2005; **352:** 757-767.

INJECTIONS AND HIV IN RURAL ZIMBABWE

Of the 40 million people worldwide with HIV, 30 million live in the developing world. By far the worst hit region is sub-Saharan Africa, where nearly 4 million children have lost one or both parents to HIV/AIDS since 2000. Is heterosexual transmission the driving force behind the HIV epidemic in sub-Saharan Africa? In a controversial debate, some researchers have suggested that other factors such as unsafe medical injection practices may also be to blame, and that by overlooking, and even suppressing, analysis of this possible route of transmission, the current focus on preventing sexual transmission may be misguided. In *PLoS Medicine* Ben Lopman and colleagues argue that although it is right to criticise the lack of evidence on unsafe medical injection, field data are hard to collect. They note that in the only published study addressing this issue, Kiwanuka and colleagues found no link between unsafe injections and HIV spread in rural Uganda. In an effort to 'inform the debate' further, Lopman and colleagues looked at the association between HIV and unsafe injection practices in rural Zimbabwe.

Are medical injections an important cause of HIV in rural Africa?

The team analysed data from adults in Manicaland, a rural part of Zimbabwe, who were taking part in the Manicaland HIV/STD Prevention Study. In 1999 and 2000, eligible patients were tested for HIV and surveyed (86.7% were HIV negative at the start of the study), and were followed up 3 years later. The team collected survey data on injections in the patients, who were male and female adults 15 - 54 years old, and tested for an association between injection exposure and HIV infection. In 2002 and 2003, 505 of the men and 1 342 of the women, representing a 69.7% follow-up, were again interviewed and tested for HIV infection. Of these, 40% reported having had an injection or needle prick during the study period. A total of 67 patients developed HIV during the study; of these 13 (19%) said they had not had sex during the study period and 40 (60%) said they had not had an injection. The statistical analysis found no significant association between injections and HIV infection in men or women.

Patients who had HIV when the study began did not have higher rates of injections. Instead, injections were highly associated with childbirth and pregnancy. But since HIV-positive women have reduced fertility, a reduction in the use of maternal services may partially explain why injections were not more common in these HIV-positive patients. In this study, the strongest predictor of HIV infection was symptoms of sexually transmitted disease.

Despite problems of recall bias and under-reporting of sexual activity – a particularly difficult problem in studies in Africa – sexual behaviour is consistently linked with HIV incidence. Where does this leave the debate over injections in Africa? Certainly, for this community, they do not seem to be a major source of HIV infection, and local policymakers would therefore do best to concentrate on the prevention of sexually transmitted infections.

Lopman BA, *et al.* Injections and HIV in rural Zimbabwe.*PLoS Med* 2005; **2** (2): e54

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