

Resistance exercise could reduce risk of developing diabetes in women

A recent study demonstrates that muscle strengthening and toning exercises can help to reduce the risk of diabetes in women.

The study, published in *PLoS Medicine*, prospectively followed up 99,316 middle-aged and older women for 8 years from the Nurses' Health Study (2000–2008) and Nurses' Health Study II (2001–2009). None of the women had diabetes at baseline; however, during the 8-year period, 3491 women developed Type 2 diabetes. The likelihood of developing diabetes and the amount of muscle strengthening or conditioning activity undertaken (e.g., yoga, stretching and toning) were found to be directly correlated.

Women who engaged in at least 2.5 h per week of aerobic activity and at least 1 h a week of muscle-strengthening activities had the most substantial risk reduction compared with inactive women. However, even muscle strengthening activity on its own reduced risk.

“We observe that even small amounts of weekly muscle strengthening activity (less than 30 min/week) are associated with risk reduction of diabetes. Furthermore, women who already engage in aerobic activity will have additional benefit by adding muscle strengthening activity.”

“While it was well known that acute effects of muscle strengthening activity, such as resistance exercise, include improvement in insulin sensitivity of muscle tissue and glycemic control, the extent to which long-term engagement in this type of activity would lower risk of diabetes in women has remained unknown,” explains Anders Grøntved, from the University of Southern Denmark, Denmark.

“In our study we show that regular engagement in this type of activity will lower the risk



of Type 2 diabetes in women substantially,” said Grøntved.

The influence of resistance training and diabetes risk in men had previously been studied, but until this one, no such study existed that looked at data from women.

Exercise recommendations for women could be affected by the findings. “Our study suggests that for those women who have difficulty in engaging or adhering to aerobic type physical activity, muscle strengthening activity can serve as an alternative for protection from Type 2 diabetes. We observe that even small amounts of weekly muscle strengthening activity (less than 30 min/week) are associated with risk reduction of diabetes. Furthermore, women who already engage in aerobic activity will have additional benefit by adding muscle strengthening activity,” Grøntved concluded.

– Written by Laura McGuinness

Source: Grøntved A, Pan A, Mekary RA *et al.* Muscle-strengthening and conditioning activities and risk of Type 2 diabetes: a prospective study in two cohorts of US women. *PLoS Med.* 11(1), e1001587 (2014).





CHILD-INNOVAC project demonstrates effective nasal vaccine against pertussis in Phase I trial

Researchers from the CHILD-INNOVAC European research programme, a project coordinated by Inserm (Paris, France), has developed a new vaccine that could be effective against pertussis. Results from a Phase I trial have been published in *PLoS ONE*, and demonstrate the efficacy and safety of the vaccine, which is administered intranasally, in human subjects. The CHILD-INNOVAC project brings together ten European partners, which include both laboratories and private companies from seven countries. The project received a budget of EU€5 million, awarded by the European Commission under FP7.

Pertussis is a highly contagious bacterial disease, affecting several tens of millions of individuals worldwide, as well as being responsible for the deaths of approximately 300,000 children annually. The morbidity and mortality of the disease are increasing; a notably resurgence is also taking place in many developed countries, including the USA, Australia and the UK.

“One of the successes of this project has been the achievement of developing a vaccine for which the immunogenicity and safety could be assessed in humans in just 2.5 years, compared with the usual 5–7 years for most projects of this type.”

The CHILD-INNOVAC project is specifically focused on combating *Bordetella pertussis* and respiratory syncytial virus, two of the major respiratory pathogens. The vaccines currently available are ineffective for infants who contract these infections, who are typically in the age range of 0–6 months. In addition, the project aims to provide proof-of-concept that these types of vaccines can be translated to other respiratory infections. This was the first trial of a live attenuated vaccine specifically designed for the respiratory tract. The trial took place in Sweden, which was identified as having the most ‘naïve’ population with respect to vaccination against pertussis; vaccination was discontinued in the country due to reasons of inefficacy.

The researchers developed BPZE1, a genetically modified *Bordetella pertussis* strain, as a live attenuated nasal pertussis vaccine by genetically eliminating or detoxifying three toxins. A double-blind, placebo-controlled, dose-escalating study of BPZE1 was performed using human subjects in order to assess the immunogenicity and safety of the vaccine. The primary objective of the trial was to record all adverse events, such as cough, sneezing, nasal discharge and effects on general health. The secondary objective was to assess colonization of the nasal mucosa by the vaccine and the subsequent triggering of an immune response. A total of 12 subjects per dose group received 10^3 (low), 10^5 (intermediate) or 10^7 (high) colony-forming units as droplets, with half of the dose administered to each nostril. In addition, 12 controls received a diluent. The local and systemic safety, and immune response were assessed over a period of 6 months, and nasopharyngeal colonization with BPZE1 was determined by repeated cultures over the course of a 4-week period following vaccination.

It was found that the vaccine induced no adverse events in patients compared with placebo in all dose groups. Colonization was observed in one subject at low dose, one at medium dose and five in the high-dose group. Of particular note, immune responses against pertussis antigens were observed in all dose groups. Camille Locht, head of the research consortium and Director of the Centre for Infection and Immunity of Lille (Lille, France), explained the significance of the results: “It is of special interest that a single nasal administration was able to induce an immune response that was maintained for at least 6 months, that is, for the duration of the study.”

One of the successes of this project has been the achievement of developing a vaccine for which the immunogenicity and safety could be assessed in humans in just 2.5 years, compared with the usual 5–7 years for most projects of this type. Locht explained that this reduced timescale was due to “the skills and motivation of the consortium, which brought together experts in their respective areas of specialization from seven European countries. It was possible to relay the data in a flexible and efficient manner at the different stages of the

project.” Following on from these results, BPZE1 can now undergo further clinical development; specifically, the researchers will administer higher volumes of the vaccine with the aim of increasing the level of colonization of the nasal mucosa. A key goal will be to improve the stability of the vaccine and move it towards industrial development. The investigators believe that the original method of administration could make the vaccine available to a greater number of people at a reduced cost.

– Written by Jonathan Wilkinson

Sources: Inserm press release: <http://presse-inserm.fr/en/a-good-outcome-for-the-child-innovac-project-successful-test-in-humans-of-a-nasal-vaccine-against-pertussis/10572/>; Thorstensson R, Trollfors B, Al-Tawil A *et al.* A Phase I clinical study of a live attenuated *Bordetella pertussis* vaccine – BPZE1; a single centre, double-blind, placebo-controlled, dose-escalating study of BPZE1 given intranasally to healthy adult male volunteers. *PLoS ONE* 9(1), e83449 (2014).

Could combining two experimental cancer drugs prove synergistic in the clinic?



While investigating new ways in which to employ current experimental cancer therapies in the hope of speeding the drug development process, a team of researchers from the Children’s Hospital of Eastern Ontario Research Institute (CHEO; ON, Canada) has defined a specific combination of two immunotherapies that may prove effective. Their findings were published yesterday in the journal *Nature Biotechnology*.

“We are very excited about this novel combination approach and are looking to move this experimental therapy into clinical trials as soon as possible,” commented Robert Korneluk, senior scientist at the CHEO Research Institute. “I firmly believe that it’s not a matter of ‘if’ this will help cancer patients – but ‘when’ this therapy becomes a standard of care.”

The two therapies tested in combination in this investigation were Smac mimetic compounds (SMCs) and oncolytic viruses such as poly(I:C) and CpG. Both therapies have produced some encouraging results in clinical trials, yet it is stated that neither has demonstrated any substantial efficacy as a standalone therapy. The results of the study from the CHEO group, led by Korneluk, indicate that combining the agents significantly amplifies tumor killing, thereby overcoming the limitations of the single agents.

SMCs are a class of drugs that hinder the activity of proteins that inhibit apoptosis, thus enabling transduction of proapoptotic signals. However, it is stated that SMCs may, therefore, only prove efficacious in tumors that produce a large quantity of proteins that are able to promote cell death, for example cytokines. The rationale

behind this study was the belief that SMCs would synergize with other agents that are able to stimulate an immune response, or ‘cytokine storm’, in the tumor environment.

This study demonstrated that the combination of SMCs and live virus therapies worked synergistically to stimulate tumor regression and extend survival in mouse models. The study also indicates that the oncolytic viruses promote death in cells treated with SMCs through the action of IFN- β , TNF- α and/or TNF-related apoptosis-inducing ligand. Postulating that combined use could possibly save years of clinical development and allow patients quicker access to therapies, the investigators report that it may be worthwhile exploring this regime further in a clinical setting. Further investigation is also required to establish which cancers the approach may be best suited to.

“Our combination approach is quite different compared with standard chemotherapy treatments that can have significant negative side effects,” continued Korneluk. “Instead, we looked at combining two novel experimental cancer drugs that we already know work on the immune system. The results of our combination exceeded expectations – and furthermore, no harm was done to the surrounding healthy tissue when we eradicated tumors.”

– Written by Emily Brown

Sources: Beug ST, Tang VA, Lacasse EC *et al.* Smac mimetics and innate immune stimuli synergize to promote tumor death. *Nat. Biotechnol.* doi:10.1038/nbt.2806 (2014) (Epub ahead of print); CHEO press release: www.cheori.org/en/newsreleases?newsid=350



New biomarker for necrotizing enterocolitis may lead to reduced incidence of the condition in premature infants

Investigators at Loyola University Health System (IL, USA) have demonstrated that a biomarker may identify premature infants who are at risk of necrotizing enterocolitis (NEC). This could allow physician's to implement preventative measures and possibly reduce the incidence of NEC.

NEC is a bowel infection which can threaten the lives of premature infants presenting a mortality rate of almost 30%. It is the most common, serious gastrointestinal condition affecting 10% of infants with extremely low birth weights, and arising when tissue of the intestinal wall dies and detaches. NEC cases are frequently mild-to-moderate and can be treated by antibiotics; however, if a hole occurs in the intestine, the leak of bacteria can cause a life-threatening infection. Currently, the cause of the disorder is unknown however researchers propose the condition could be due to feeding patterns, infection, abnormal immune response, decreased blood

flow to the bowel, mechanical injury, or a combination of these factors.

The present research, published in the *Journal of Pediatric Surgery*, involved the study of infants born weighing less than 1500 g or born prior to 32 weeks gestation. Research examined blood samples from 177 infants during the 72-h window after birth and each week subsequently for 4 weeks. Further specimens were collected at the onset of NEC and 24 h following. This allowed for measurement of intestinal alkaline phosphatase (iAP) and reticulated platelets (RP).

The findings demonstrated that 8.5% of the infants suffered from NEC, of which 60% presented with high levels of iAP (>0 U/l) and 93% with low levels of RP ($\leq 2.3\%$). It was therefore concluded that infants with high iAP levels were more likely to develop NEC, similarly the infants presenting with decreased RP levels were also more likely to suffer from

NEC; however, the RP correlation was demonstrated to be statistically significant.

"This information will allow us to better care for these premature infants. Simple changes to blood transfusion practices, feeding patterns and treatment of these infants may significantly reduce the incidence of NEC." Comments Jonathan Muraskas (Loyola University Health System). "Decreased reticulated platelets serve as a sensitive indicator for NEC onset. Further research also may find that infants with elevated iAP levels may be at risk for this serious illness."

– Written by Elizabeth Webb

Sources: Loyola University Health System press release: <http://loyolamedicine.org/newswire/news/loyola--researchers-identify-risk-factor-life-threatening-disease-preemies>; Kampanatkosol R, Thomson T, Habeeb O *et al.* The relationship between reticulated platelets, intestinal alkaline phosphatase, and necrotizing enterocolitis. *J. Pediatr. Surg.* 49(2), 273–276 (2014).

About the News

The News highlights some of the most important events and research. If you have newsworthy information, please contact:

Adam Williams, Head of Commissioning, *Clinical Practice*

Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK

Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313;

a.williams@futuremedicine.com