Influenza Diabetes Community

INFLUENZA IN PERSONS LIVING WITH DIABETES: PATHOGENESIS AND PREVENTION

Satellite symposium organised by the Influenza Diabetes Community, supported by Sanofi Pasteur

MONDAY 7 DECEMBER 2020, 10:00 - 12:00 CET
SEVENTH ESWI INFLUENZA CONFERENCE, #ESWI2020 VIRTUAL EDITION, 6-9 DEC 2020

European Scientific Working group on Influenza

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INFLUENZA CONFERENCE

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The Influenza Diabetes symposium took place at the occasion of the 7th ESWI Influenza Conference – focus on influenza, RSV and COVID-19 - virtual edition between 6 December – 9 December 2020. The Conference was organised by ESWI, which summarises here in this Meeting report its interpretation of the key messages from the individual talks at the symposium. The summaries are written entirely by ESWI.

1 The Impact of Influenza on People with Diabetes.

MARCO GOEIJENBIER
Erasmus MC, Rotterdam, the Netherlands

Diabetes is a highly heterogeneous disease influenced by genetic, epigenetic, behavioural and environmental factors. It ranges from insulin resistance to insulin secretory defects. The Influenza Diabetes Community is based on five starting points, all of which have been confirmed in scientific research papers:

- Influenza is a highly contagious respiratory illness
- People with diabetes have a higher risk of getting very ill
- Influenza makes diabetes more difficult to manage
- People with diabetes are 3-6 times more likely to be hospitalized
- A higher risk of death is associated with influenza infection among people with diabetes.

Moreover, there is a strong link between diabetes and a generally increased susceptibility to infectious diseases. Infection-related mortality or morbidity rates are also higher among diabetic than non-diabetic patients.

However, the reasons for these associations are poorly understood. Hyperglycaemia is related with a worse outcome in both bacterial and viral infection, and a prospective study showed a non-linear association of HBA1C (average glucose levels) with influenza mortality.

At the same time, obesity is associated with diabetes – and also with a propensity to catch infectious diseases. Obesity is also associated with increased risk of death through seasonal influenza, and with hospital and ICU admission and the subsequent need for ventilatory support. In animal studies into obesity, reduced or delayed levels of antiviral response has been observed.

People living with diabetes also have a higher chance of developing cardiovascular disease, and there is a strong association between cardiovascular disease and influenza infection. There is an increased incidence of acute myocardial infarction (AMI) after respiratory infection; the highest in the influenza season. And a consistent association has been shown between AMI and influenza activity.

A problem observed during the COVID-19 pandemic is a reduced quality of care for persons living with diabetes due to over-pressure on the healthcare system. Recently published data suggests that people with diabetes are more susceptible to getting COVID-19.

Vaccination against influenza is important, and antivirals can also play a role. However, vaccination coverage in people with diabetes is generally low and is dropping. To counter this, more epidemiological studies are required to highlight the specific risk groups, severity and efficacy. Social science should be used to increase vaccine uptake. Clinicians need to translate scientific evidence to patients, to better educate them, and to vaccinate them.

2 Influenza Vaccination and People with Diabetes: A must!

FRANCESC XAVIER COS
Primary Care Diabetes Europe/Institut Català de la Salut, Spain

Diabetes continues to increase throughout the world. Moreover, people with diabetes who are aged 65 or over have an average of more than six other conditions, which greatly increases the complexity of managing people with diabetes.

People with diabetes have a higher risk than non-diabetic people to have infectious diseases and to be admitted to hospital, as well as a higher risk of death (1.92). The main underlying cause is linked to alterations in the immune system of people with diabetes, that increase the risk of infection. Some of these immunological aspects include reduction in neutrophil degranulation, impaired complement activation, and impaired phagocytosis. Furthermore, elevated blood glucose levels can directly increase the glucose concentration in airway secretions, which in turn (in vitro) significantly increases influenza virus infection and replication.

A meta-analysis to evaluate risk factors for severe outcomes in patients with seasonal and pandemic influenza pointed to elderly people, women in the postpartum period, and obese people.

As to the efficacy of vaccination against seasonal influenza in patients with diabetes, powered randomized controlled trials or quasi-experimental studies using laboratory-confirmed influenza-specific outcomes are urgently needed. Real-world evidence is also necessary to understand the impacts and benefits of vaccination.

A study showed that working-age adults with diabetes experience similar benefits from vaccination as elderly adults. This supports current diabetes-specific recommendations, although such studies would also benefit from randomised trial evidence. The same study also indicated that seasonal influenza vaccination reduced the risk of hospitalisation and mortality in diabetic patients, particularly those older than 65. This emphasises that efforts should be focused on improvements in vaccine uptake in this important target group.

The WHO and other key organisations are keen to promote influenza vaccination. Unfortunately, uptake of influenza vaccination among healthcare workers is very low (with certain exceptions such as USA and Canada), and the trend is downwards, which can be linked to a variety of reasons.

Interestingly, a study indicated that healthcare workers in neighbouring countries (Belgium, the Netherlands, Germany) exhibited differences in the intention of healthcare workers to receive the influenza vaccine. This suggests the need for a country-specific approach and to focus on different socio-cognitive variables.

3 Recent Findings in Glycemic Variability and Influenza Severity.

KIRSTY SHORT
University of Queensland, Australia

Obesity is prevalent across the world, in developed and developing nations, which among other effects is leading to a great prevalence in type 2 diabetes. Non-diagnosis of type 2 diabetes is a particular problem because these individuals are not getting the healthcare and medication that they need. Such individuals will have more waves or oscillations in blood glucose levels; these waves will also be more extreme in nature.

Such variability is linked to micro- and macro-vascular complications of diabetes, which in turn could cause cardiovascular disease, kidney disease and other diseases. Hypothetically it could also be linked to hyperinflammation and severe viral disease. This hypothesis was tested with an in vitro model that imitated lung epithelial cells that were kept in either constant or oscillating glucose levels. The cells were then infected with influenza. The cells with oscillating glucose levels were more seriously infected by influenza. Further research found that in the variable group there was significantly more cell death, increased inflammation, and increased oxidative stress.

In vivo experiments among obese mice were then conducted. The group with variable glycemic levels lost more body weight when infected with influenza. They also had lower blood oxygen saturation levels, and an increased inflammatory response.

Further research looked at the CD8+ T cells which are important in protecting a person against the influenza virus because they make multiple cytokines. This function was much more pronounced in the constant group than in the variable group. Also, reduced function of influenza-specific T cells was observed. Finally, a significant decline in CD3+ T cells in the variable group was observed. A study in humans to further investigate this phenomenon is ongoing.

Evidence is also appearing that associates glycemic variability to COVID-19 severity.

4 How to Increase Vaccination Coverage in People with Diabetes: The UK case.

DAN HOWARTH
Diabetes UK, United Kingdom

In the UK, 4.8 million people live with diabetes, of which 1 million are undiagnosed. Around 90% have type 2 diabetes, 8% type 1 diabetes, and 2% others. 12.8 million are at risk of developing type 2 diabetes due to their position in one of the risk groups. One in six hospital beds have a person with diabetes.

Influenza commonly leads to complications amongst people with diabetes, so vaccination is highly recommended. In the UK, the NHS gives all people with diabetes a free influenza vaccination. Coverage rate is generally between 60-70%, with the highest rates seen in Northern Ireland, and the lowest uptake of influenza vaccination in the working age group, due to barriers such as time and accessibility.

Diabetes UK takes its responsibility seriously to promote influenza vaccination among people with diabetes while recognising that they have an informed consent. Diabetes UK has an annual flu campaign that starts end-October to promote vaccination and debunk myths and to provide answers that address the main reasons for vaccine hesitancy.

Content is regularly posted on the Diabetes UK website and via their social media channels, including a Facebook Live video. A help line is also available to inform and support people and encourage them to get vaccinated. Generally these campaigns are well supported.

For 2020, taking into consideration the COVID-19 pandemic, an early call for the flu jab was given, and great emphasis was given to strongly encourage people with diabetes to get vaccinated in 2020. Overall the campaign has received overwhelming support and Diabetes UK is seen as a trusted resource.

5 Diabetes During the COVID-19 Pandemic.

AB OSTERHAUS
TiHo, Hannover, Germany

Diabetes is one of the major risk groups for COVID-19. In the UK population, the risk of serious complications and death from COVID-19 in diabetic patients is 50% higher than that of non-diabetic patients. There is much evidence of diabetes as a comorbidity during COVID-19, as clearly found by four recent meta-analyses. From these four papers it can be concluded that diabetes is associated with a higher risk of severe illness, ICU admission, and mortality.

As to what is causing this effect, a paper described possible mechanisms through which diabetes may affect the risk of more severe outcomes in COVID-19, and how diabetic emergencies and longer-term pathology may be aggravated by infection with COVID-19. It suggests roles for the immune system; microangiopathy in COVID-19 infection; and direct viral effects on pancreatic beta cells and targets of insulin production and action.

The angiotensin-converting enzyme 2 (ACE2) was seen as mediating the infection of COVID-19 which could account for sex and age expression differences. This is interesting as the ACE2 receptor is ubiquitous in the human body. ACE2 was also seen as having an expression on beta cells and in various other tissues, potentially explaining the loss of smell during COVID-19 infections.

The binding of SARS-CoV-2 to immune cells leads to interleukin 6 (IL-6) synthesis. IL-6 binds to lymphocytes, which leads to a "cytokine storm" and potential multi-organic lesions.

It also binds to endothelial cells and may lead to hyper-coagulation and consequent pulmonary embolism. The latter is an important issue in the pathogenesis of COVID-19.

Possible explanations for the mutual association between COVID-19 and diabetes include:

- Impairment of innate and adaptive immune response, particularly in obese patients (reduced numbers of NK cells, CD4+ and CD8+ lymphocytes)
- COVID-19 and hyperglycemia association reflects metabolic inflammation and exaggerated cytokine release.
- SARS-CoV2 infection can lead to deterioration of glycemic control, involving both profound insulin resistance and impaired insulin secretion.

The combination of influenza and COVID-19 together may be less severe due to COVID-19 mitigation measures and viral interference. But they may be more severe due to the cumulative effect of both of them appearing at the same time.

In terms of recommendations, thorough preparation for the reappearance of both influenza and COVID-19 in the fall/winter of 2020 is essential. Vaccination coverage needs to be increased, particularly for the high-risk groups where a minimum level of 70% has to be achieved. Flu antivirals need to be stocked and used. Extensive surveillance and testing for influenza, other respiratory viruses such as RSV, and COVID-19 should be continued.

Influenza Diabetes Community

ABOUT

- People with diabetes still face a higher risk for influenza and its complications. National and international guidelines therefore advise that diabetes patients be annually vaccinated against influenza.
- The attention for the impact of influenza on diabetes patients is, however, low and so is the vaccine uptake in this group.
- In October 2017 leading diabetes organizations and ESWI joined forces to forge an active Influenza/Diabetes community, implementing an action plan to better protect diabetes patients against the flu.
- To keep the momentum going the community meets annually to investigate new opportunities for collaboration and to continue raising awareness about the impact of influenza infection on diabetes patients.
- www.influenzadiabetescommunity.org serves as a virtual reference centre on diabetes and influenza, containing web materials of ESWI's partners in the Influenza/Diabetes community on diabetes and on the importance of flu vaccines.

- The International Diabetes Federation (IDF Europe)
- Foundation of European Nurses in Diabetes (FEND)
- Pharmacist Group to the European Union (PGEU)
- Diabetes UK
- Primary Care Diabetes Europe (PCDE)
- Immunology of Diabetes Society (IDS)
- European Association for the Study of Diabetes (EASD)
- Nurse Practitioner Healthcare Foundation (NPHF)
- American Association of Diabetes Educators (AADE)
- American Pharmacists Association (APhA)
- International Federation of Ageing (IFA)
- Ministry of Public Health of the Sultanate of Oman
- Federaçion Espanola de Diabetes (FEDE)
- International Pharmaceutical Federation (FIP)

Contact: info@eswi.org

www.influenzadiabetescommunity.org