Influenza Virus and Glycemic Variability in Diabetes: A Killer Combination?

Katina D. Hulme¹, Linda A. Gallo¹,²† and Kirsty R. Short¹,³*†

¹ School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia, ² Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia, ³ Australian Infectious Diseases Research Centre, The University of Queensland, Brisbane, QLD, Australia

Following the 2009 H1N1 influenza virus pandemic, numerous studies identified the striking link between diabetes mellitus and influenza disease severity. Typically, influenza virus is a self-limiting infection but in individuals who have a pre-existing chronic illness, such as diabetes mellitus, severe influenza can develop. Here, we discuss the latest clinical and experimental evidence for the role of diabetes in predisposing the host to severe influenza. We explore the possible mechanisms that underlie this synergy and highlight the, as yet, unexplored role that blood glucose oscillations may play in disease development. Diabetes is one of the world’s fastest growing chronic diseases and influenza virus represents a constant and pervasive threat to human health. It is therefore imperative that we understand how diabetes increases influenza severity in order to mitigate the burden of future influenza epidemics and pandemics.

Keywords: influenza, diabetes, glucose, hyperglycemia, glycemic oscillations

INTRODUCTION

Every year, approximately 5–15% of the world’s population are infected with influenza virus (Shirey et al., 2013). Of the three types of influenza virus (A, B, and C), influenza A virus is the most common cause of respiratory illnesses in humans. Influenza A virus typically causes an acute and self-limiting infection characterized by symptoms such as myalgia, fever, and a dry cough. However, in patients with one or more underlying medical conditions, influenza A virus can cause severe, and even fatal, disease (Short et al., 2015). Influenza thus represents a significant healthcare challenge for the 21st century, where the majority of people have more than one medical ailment (Vos et al., 2015). This interaction between chronic disease and influenza was particularly evident after the 2009 H1N1 influenza pandemic (Kumar et al., 2009). Specifically, this pandemic highlighted that people with diabetes suffered from more severe influenza than people with no underlying medical condition (Allard et al., 2010; Wilking et al., 2010). Here, we review the currently available literature on the role of diabetes in the pathogenesis of influenza virus. We further highlight the specific roles that high, and/or oscillating, blood glucose levels may play in the severity of influenza virus.

DIABETES MELLITUS AND ITS VASCULAR COMPLICATIONS

Diabetes mellitus affects 415 million people worldwide and this figure is projected to increase to 642 million by the year 2040 (International Diabetes Federation, 2015). Diabetes is characterized by chronic hyperglycemia and is classified into two main types. Type 1 diabetes accounts for...
approximately 10% of all cases and is most commonly caused by an autoimmune condition affecting insulin production. In contrast, type 2 diabetes accounts for approximately 85–90% of cases and is characterized by insulin resistance and compromised insulin secretory capacity. All individuals with diabetes have an increased risk of developing a number of serious complications. Diabetes is a leading cause of blindness, limb amputations, end-stage kidney failure, and cardiovascular disease (The Emerging Risk Factors Collaboration, 2011). Chronic hyperglycemia is thought to underlie the development of complications and, as such, a primary aim in the management of diabetes is to improve blood glucose control (Gallo et al., 2015). Blood glucose control is typically assessed by measuring a patient's HbA1c. The term HbA1c refers to glycated hemoglobin, i.e., when hemoglobin joins with glucose and becomes 'glycated.' The average lifespan of red blood cells is approximately 2–3 months, meaning that HbA1c provides an estimate of long-term blood glucose control. Interestingly, however, there is no guarantee that achieving near-normal HbA1c levels (HbA1c < 7%), particularly in patients with long-standing type 2 diabetes, will prevent the onset and progression of vascular complications. Using traditional therapies, such as metformin, sulphonylureas and insulin, near-normal HbA1c levels were achieved in numerous trials but mortality from cardiovascular disease was either not affected (The U.K. Prospective Diabetes Study Group, 1998; The Advance Collaboration group, 2008; Duckworth et al., 2009) or increased (The Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008). In the latter study, the trial was prematurely stopped due to a significant increase in short-term mortality following intensive glucose lowering (The Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008). The lack of a definitive conclusion in this field has dampened clinical urgency to normalize HbA1c levels and suggests that other factors may contribute to the development of diabetic complications.

INFLUENZA VIRUS IN DIABETES MELLITUS

Prior to the 2009 H1N1 pandemic, several studies had already suggested that diabetes enhanced the severity of influenza (Diepersloot et al., 1987; Valdez et al., 1999). Valdez et al. (1999) showed that from 1986 to 1989, people with diabetes were more likely to have pneumonia and influenza recorded on their death certificate than people without diabetes. However, the most extensive body of evidence regarding this relationship emerged following the first influenza pandemic of the 21st century: the 2009 H1N1 pandemic. Numerous clinical studies suggested that people with diabetes were a key susceptibility group for severe H1N1 infections (see Table 1). For example, in Canada, diabetes tripled the risk of hospitalization after infection with the 2009 H1N1 virus and quadrupled the risk of admission to the intensive care unit (Allard et al., 2010). Similarly, in Germany, diabetes doubled the risk of a fatal outcome after infection with the 2009 virus (Wilking et al., 2010). Whilst the majority of clinical studies suggest a role for diabetes in increasing influenza severity, this synergism was not observed in all studies (see Table 1).

Taken together, these data suggest that the relationship between diabetes and influenza may vary depending on the diabetic patient population in question. It is also important to note that many patients with diabetes have various other conditions that can increase (or decrease) the severity of influenza. For example, approximately 90% of patients living with type 2 diabetes are overweight, and obesity is an independent risk factor for severe influenza (Morgan et al., 2010). Adjusting clinical analyses for the presence of these other illnesses has yielded contradictory results (see Table 1), highlighting the need for further research in this area. Nevertheless, consistent with the majority of clinical observations, murine models demonstrate that diabetes increases susceptibility to severe infections with both seasonal and highly pathogenic influenza virus strains (see Table 2).

A ROLE FOR HYPERGLYCEMIA

At present, the mechanisms by which diabetes can increase the severity of influenza remain unclear. There is a growing body of evidence that hyperglycemia can increase the incidence and severity of bacterial infections. For example, diabetic patients with an HbA1c level > 7% had a three times increased risk of active tuberculosis compared to those with an HbA1c level < 7% (Leung et al., 2008). Similarly, diabetic patients with hyperglycemia (>7% HbA1c) were more likely to develop Klebsiella pneumoniae liver abscess than diabetic patients with controlled glycaemia (Lin et al., 2013). It has also been reported that individuals with diabetes are more likely to suffer from infection-related mortality following a kidney allograft than non-diabetic patients (Hayer et al., 2014). However, in a recent systematic review of a range of surgical specialties, the relationship between preoperative HbA1c levels and postoperative complications, including mortality from infection, was less convincing (Rollins et al., 2016). The authors noted that their retrospective analyses contained heterogeneous datasets of small sample sizes and that further research, specifically dedicated to addressing this topic, is warranted (Rollins et al., 2016).

With regards to respiratory tract infections, Rayfield et al. (1982) noted a striking positive correlation with the mean plasma glucose levels in patients with diabetes. These findings may reflect, in part, the immunosuppressive effects of hyperglycemia. Hyperglycemia can reduce neutrophil degranulation (Stegenga et al., 2008), impair complement activation (Ilyas et al., 2011) and impair phagocytosis (Alexiewicz et al., 1995) – all of which can increase the severity of bacterial infections as well as viral infections such as influenza. However, to date, there have been only limited experimental studies directly addressing the role of hyperglycemia in the pathogenesis of influenza virus.

Elevated blood glucose levels can directly increase glucose concentrations in airway secretions (Philips et al., 2003). In vitro exposure of pulmonary epithelial cells to elevated glucose concentrations significantly increased influenza virus infection and replication (Kohio and Adamson, 2013), suggesting that hyperglycemia may increase viral replication in vivo.
### TABLE 1 | The role of diabetes in the severity of 2009 pandemic influenza.

| Year/s observed | Country | Sample size (% diabetes) | Diabetes type | Primary outcome(s) measured | Results | Findings/conclusions | Reference |
|-----------------|---------|--------------------------|---------------|----------------------------|---------|----------------------|-----------|
| April 2009 – June 2010 | USA | 668 (2%) | n/a | Hospitalization | ND: 311/658 (47%), D: 5/10 (50%) | Diabetes did not affect the rate of hospitalization or ICU admission. | Garcia et al., 2015 |
| 1 January – 1 December 2009 | Spain | 11,499 (9%) | 97 Type I 936 Type II | Hospitalization ICU admission Death | ND: 244/10,416 (2%), D: 38/1,033 (4%) | No difference in mortality risk in any age group between those with and without diabetes. | Jiménez-Garcia et al., 2013 |
| 16 April – 30 August 2009 | Canada | 716 (7%) | n/a | Hospitalization ICU admission Death | ND: 283/666 (43%), D: 38/50 (76%) | Diabetes was associated with an increased risk of hospitalization. | Gilca et al., 2011 |
| 26 April – 26 September 2009 | Canada | 1,479 (9%) | n/a | Hospitalization ICU admission Death | ND: 1,089/1,342 (81%), D: 82/137 (60%) | The risk of a severe outcome was greatest among patients with diabetes. | Campbell et al., 2010 |
| 1 May – 31 December 2009 | USA | 66 (32%) | n/a | ICU admission | ND: 19/45 (42%), D: 10/21 (48%) | No difference in pre-existing comorbidities between ICU and non-ICU patients. | Venkata et al., 2010 |
| 25 May – 1 July 2009 | Canada | 162 (13%) | 9 Type I 13 Type II | ICU admission | ND: 21/140 (15%), D: 10/22 (45%) | Diabetes tripled the risk of hospitalization and quadrupled the risk of ICU admission once hospitalized. | Allard et al., 2010 |
| 12 June – 5 December 2009 | Spain | 304 (50%) | n/a | ICU admission Death | ND: 69/252 (27%), D: 97/252 (38%) | Worse outcomes in patients with diabetes may be a consequence of the higher prevalence of underlying medical conditions rather than diabetes itself. | Cortes et al., 2011 |
| 24 July 2009 – 3 March 2010 | French West Indies and French Guiana | 241 (3%) | n/a | Severe infection Death | ND: 27/234 (12%), D: 3/7 (43%) | Diabetes was associated with a higher risk of severe influenza. | Barrau et al., 2012 |
| 1 October – 23 December 2009 | China | 155 (13%) | n/a | ICU admission Death | ND: 20/128 (16%), D: 7/20 (35%) | Diabetes is likely to be an additional risk factor compared to obesity alone. | Xi et al., 2010 |
| November 2009 – January 2010 | France | 1,266 (10%) | n/a | ICU admission Death | ND: 241/1139 (21%), D: 34/127 (27%) | Diabetes is likely to be an additional risk factor compared to obesity alone for ICU admission but not death. | Hansik et al., 2010 |
| March – December 2010 | Brazil | 4,740 (2%) | n/a | Hospitalization | ND: 1,948/4,632 (42%), D: 72/108 (67%) | Diabetes was identified as a risk factor for hospitalization. | Lenz et al., 2012 |

---

1. Percentage rounded to nearest whole number.
2. n/a: Diabetes type was not specified.
3. D: Patients with diabetes; ND: Patients without diabetes.
4. Patients aged 18 years or younger.
hyperglycemia in patients with diabetes. Thus, at present, the role of hyperglycemia in the pathogenesis of influenza virus remains unclear.

A ROLE FOR GLYCEMIC OSCILLATIONS

In the context of vascular complications of diabetes (e.g., cardiovascular disease), there is a growing body of evidence indicating that glucose variability is an important contributing factor to disease development (Hirakawa et al., 2014). In healthy individuals, blood glucose levels are kept within a narrow range of 4.4–6.7 mmol/L, including small and short-lived post-prandial peaks (Saisho, 2014). In the setting of impaired glucose tolerance, glucose fluctuations become greater and more frequent (Monnier et al., 2001). Blood glucose variability generally refers to hour-to-hour or day-to-day oscillations, but may also refer to month-to-month or even year-to-year changes. Glycemic variability is induced by many different factors including consuming a meal, changes in exercise, weight, medication, diet, and sleep patterns (Davies, 2004). As hyperglycemia is typically measured by a patient’s HbA1c, individuals with steady-state and oscillating glucose levels are generally not differentiated in the clinic, making prevalence estimates difficult to obtain. However, it is clear from clinical studies that the extent to which these glucose fluctuations occur differs greatly from patient to patient (Monnier et al., 2006).

There is now a growing body of evidence showing that glycemic oscillations play an important role in endothelial dysfunction, irrespective of HbA1c levels (Riso et al., 2001; Quagliaro et al., 2003; Azuma et al., 2006; Ceriello et al., 2008). For example, patients with type 2 diabetes that had blood glucose levels oscillating between 15 and 5 mmol/l every 6 h for 24 h had a significant increase in endothelial dysfunction relative to diabetic patients exposed to continuous 10 mmol/l glucose (Ceriello et al., 2008). In vitro, human umbilical endothelial cells (HUVECs) exposed to oscillating glucose have an increased level of apoptosis compared to HUVECs exposed to constant high levels of glucose.

| Mouse model | Diabetes type modeled | Influenza A virus subtype | Measure of disease severity | Findings | Reference |
|-------------|-----------------------|--------------------------|----------------------------|----------|-----------|
| STZ-induced diabetes in BALB/c mice | I | H1N1 | Lung viral titers | Diabetic mice had increased influenza virus titers and a lower lethal dose 50 compared to non-diabetic mice. | Zhu et al., 2005 |
| STZ-induced diabetes in BALB/c mice | I | H5N1 | Lung viral titers | Diabetic mice had increased influenza virus titers, a lower lethal dose 50 and a more persistent viral infection compared to non-diabetic mice. | Wu et al., 2010 |
| RIP-KO transgenic diabetic mice | I | H3N2 | Lung viral titers | There was a significant correlation between blood glucose levels and influenza virus titers in diabetic mice. Diabetic mice had increased influenza virus titers but no difference in weight loss compared to non-diabetic mice. | Reading et al., 1998 |
| BKS.Cg-/+Leprdb/+Leprdb/Jcl (diabetic mice) | II | H1N1 | Lethal dose 50 | Diabetic mice had a lower lethal dose 50 and a higher mortality rate compared to non-diabetic mice. | Ito et al., 2015 |
IL-8, NF-κB and E-selectin relative to endothelial cells exposed to stable high glucose (Quagliaro et al., 2005; Mudaliar et al., 2014). This is consistent with studies demonstrating increased monocyte adhesion to endothelial cells in rats exposed to glucose fluctuations relative to stable hyperglycemia (Azuma et al., 2006).

Endothelial cells, whilst not the primary target of influenza virus in humans, play an important role in disease pathogenesis (Teijaro et al., 2011; Short et al., 2013, 2014, 2016). During severe influenza virus infection, pulmonary endothelial cells produce cytokines which drive pulmonary lesions and mortality (Teijaro et al., 2011). In addition to mediating cytokine production, endothelial cells also indirectly control the inflammatory response in the lung during influenza virus infection via the expression of adhesion molecules (e.g., E-selectin, P-selectin, ICAM1, and VCAM1) (Short et al., 2014). Overexpression of these adhesion molecules is thought to impair pulmonary function during influenza virus infection by allowing the uncontrolled extravasation of leukocytes in the alveolus (Perrone et al., 2008; Short et al., 2014). These leukocytes can in turn damage the lung and impair respiratory function (Short et al., 2014). Given that glycemic oscillations are known to induce endothelial cytokine production (Quagliaro et al., 2005; Mudaliar et al., 2014) and enhance the expression of endothelial adhesions (Quagliaro et al., 2005; Mudaliar et al., 2014), it is tempting to speculate that glycemic variability augments the severity of influenza, at least in part, via effects on pulmonary endothelial cells.

CONCLUSION AND FUTURE DIRECTIONS

Diabetes is one of the world’s fastest growing chronic diseases, whereby the proportion of adults with diabetes is projected to increase from 9 to 10% by the year 2040 (International Diabetes Federation, 2015). With advancements in awareness, detection, and management of the disease, the average life expectancy of patients with diabetes is increasing (Lutgers et al., 2009; Guja et al., 2011; Huo et al., 2016). Thus, the number of individuals living with long-term complications is enhanced. Given this growing prevalence of diabetes and the increased window of opportunity for influenza virus infection, it is surprising that there are only few published studies in this field. It is therefore imperative that we dedicate research efforts to understanding how diabetes can increase the severity of influenza.

This includes delineating the role of other underlying comorbidities, hyperglycemia and glycemic oscillations in disease development and severity. Moreover, whilst type 1 and type 2 diabetes share a common symptom, i.e., hyperglycemia, they are vastly different in disease pathogenesis and, potentially, in their susceptibility to complications including influenza virus. Therefore, future studies would benefit from studying the development and severity of influenza in both type 1 and type 2 diabetes mellitus. This research will prove vital in mitigating the burden of future influenza epidemics and pandemics.

AUTHOR CONTRIBUTIONS

Conceived, wrote, and approved the manuscript: KH, LG, and KS.

FUNDING

KS is supported by a National Health and Medical Research Council of Australia C.J. Martin Early Career Fellowship (APP1054081). LG is supported by a National Health and Medical Research Council of Australia Peter Doherty Early Career Fellowship (APP1089763) and Heart Foundation Postdoctoral Fellowship (Australia).

REFERENCES

Alexiewicz, J. M., Kumar, D., Smogorzewski, M., Klin, M., and Massry, S. G. (1995). Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. Ann. Intern. Med. 123, 919–924. doi: 10.1036/0003-4819-123-12-199512150-00004

Allard, R., Leclerc, P., Tremblay, C., and Tannenbaum, T.-N. (2010). Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 33, 1491–1493. doi: 10.2327/dc09-2215

Azuma, K., Kawamori, R., Toyofuku, Y., Kitahara, Y., Sato, F., Shimizu, T., et al. (2006). Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta. Arterioscler. Thromb. Vasc. Biol. 26, 2275–2280. doi: 10.1161/01.ATV.0000239488.05069.03

Barrau, M., Larrieu, S., Cassadou, S., Chappert, J. L., Dussart, P., Najjoulallah, F., et al. (2012). Hospitalized cases of influenza A(H1N1)pdm09 in the French territories of the Americas, July 2009-March 2010. Pan Am J. Public Health 32, 124–130. doi: 10.1590/S1020-49892012000080006

Bonora, E., and Muggeo, M. (2001). Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: the epidemiological evidence. Diabetologia 44, 2107–2114. doi: 10.1007/s001250100020

Campbell, A., Rodin, R., Kropp, R., Mao, Y., Hong, Z., Vachon, J., et al. (2010). Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. CMAJ 182, 349–355. doi: 10.1503/cmaj.091823

Cerillo, A., Esposito, K., Piconi, L., Ihnat, M. A., Thorpe, J. E., Testa, R., et al. (2008). Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes Metab. Res. Rev. 57, 1349–1354. doi: 10.2337/db08-0063

Davies, M. (2004). The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. Int. J. Obes. Relat. Metab. Disord. 28, S14–S22. doi: 10.1038/sj.ijo.0802745

Diepensloot, R., Boutier, K., Beyer, W., Hoekstra, J., and Mazurel, N. (1987). Humoral immune response and delayed type hypersensitivity to influenza vaccine in patients with diabetes mellitus. Diabetologia 30, 397–401. doi: 10.1007/BF00292541

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., et al. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. N. Engl. J. Med. 360, 129–139. doi: 10.1056/NEJMoa0808431
Gallo, L. A., Wright, E. M., and Vallon, V. (2015). Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diabetes Vasc. Dis. Res. 12, 78–89. doi: 10.1111/1747-1641.1451992

Garcia, M. N., Philpott, D. C., Murray, K. O., Ontiveros, A., Revell, P. A., Chandramohan, L., et al. (2015). Clinical predictors of disease severity during the 2009–2010 A(H1N1) influenza virus pandemic in a paediatric population. Epidemiol. Infect. 143, 2939–2949. doi: 10.1017/S0950268815001114

Garnett, J. P., Baker, E. H., Naik, S., Lindsay, J. A., Knight, G. M., Gill, S., et al. (2013). Metformin reduces airway glucose permeability and hyperglycaemia-induced Staphylococcus aureus load independently of effects on blood glucose. Thorax 68, 835–840. doi: 10.1136/thoraxjnl-2012-203178

Gilca, R., De Serres, G., Boulianne, N., Ouhoummane, N., Papenburg, J., Douville-Fradet, M., et al. (2011). Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. Influenza Other Respir. Viruses 5, 247–255. doi: 10.1111/j.1750-2659.2011.00204.x

Guia, C., Ionescu-Tirgoviste, C., Fica, S., Sabau, S., Radu, S., Micu, A., et al. (2011). Improvements in life expectancy in adult type 2 diabetes patients in the last six decades. Diabetes Res. Clin. Pract. 92, 400–404. doi: 10.1016/j.diabres.2011.03.022

Hanslik, T., Boelle, P. Y., and Flahault, A. (2010). Preliminary estimation of risk

Frontiers in Microbiology | www.frontiersin.org

...sustained chronic hyperglycemia in patients with type 2 diabetes. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 295, 1681–1687. doi: 10.1001/jama.295.14.1681

Morgan, O. W., Bramley, A., Fowlkes, A., Freedman, D. S., Taylor, T. H., Gargiullo, P., et al. (2010). Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (H1N1) disease. PLoS ONE 5:e9694. doi: 10.1371/journal.pone.0009694

Mudalil, H., Pollock, C., Ma, J., Wu, H., Chadban, S., and Panchapakesan, U. (2014). The role of TLR2 and 4-mediated inflammatory pathways in endothelial cells exposed to high glucose. PLoS ONE 9:e108844. doi: 10.1371/journal.pone.0108844

Perrone, L. A., Plowden, J. K., Garcia-Sastre, A., Katz, J. M., and Tumpey, T. M. (2008). H5N1 and 1918 pandemic influenza virus infections result in early and excessive infiltration of macrophages and neutrophils in the lungs of mice. PLoS Pathog. 4:e1000115. doi: 10.1371/journal.ppat.1000115

Philips, B. J., Meguer, J.-X., Redman, J., and Baker, E. H. (2003). Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Med. 29, 2204–2210. doi: 10.1007/s00134-003-1961-2

Popov, D., and Simionescu, M. (1997). Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur. Respir. J. 10, 1850–1858. doi: 10.1183/09031936.97.10081850

Quagliaro, L., Piconi, L., Assaloni, R., Da Ros, R., Maier, A., Zuodor, G., et al. (2005). Intermittent high glucose enhances ICAM-1, VCAM-1 and E-selectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production. Atherosclerosis 183, 259–267. doi: 10.1016/j.atherosclerosis.2005.03.015

Quagliaro, L., Piconi, L., Assaloni, R., Martinelli, L., Motz, E., and Ceriello, A. (2003). Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD (P) H-oxidase activation. Diabetes Metab. Res. Rev. 25, 2795–2804. doi: 10.1332.5 diabetes.2005.12.2795

Rayfield, E. J., Ault, M. J., Keusch, G. T., Brothers, M. J., Nechemias, C., and Smith, H. (1982). Infection and diabetes: the case for glucose control. Am. J. Med. 72, 439–450. doi: 10.1016/0002-9343(82)90511-3

Reading, P. C., Allison, J., Crouch, E. C., and Anders, E. M. (1998). Increased susceptibility of diabetic mice to influenza virus infection: compromise of collectin-mediated host defense of the lung by glucose? J. Virol. 72, 6884–6887.

Rizzo, A., Mercuri, F., Quagliaro, L., Dambante, G., and Ceriello, A. (2001). Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am. J. Physiol. Endocrinol. Metab. 281, E924–E930.

Rollins, K. E., Varadhan, K. K., Dhatariya, K., and Lobo, D. N. (2016). Systematic review of the impact of HbA1c on outcomes following surgery in patients with diabetes mellitus. Clin. Nutr. 35, 308–316. doi: 10.1016/j.clnu.2015.03.007

Saisho, Y. (2014). Glycemic variability and oxidative stress: a link between diabetes and cardiovascular disease? Int. J. Mol. Sci. 15, 18381–18406. doi: 10.3390/ijms151018381

Shirey, K. A., Lai, W., Scott, A. J., Lipsky, M., Sisty, P., Pletneva, L. M., et al. (2013). The TLR4 antagonist Eritoran protects mice from lethal influenza infection. Nature 497, 498–502. doi: 10.1038/nature12118

Short, K. R., Habets, M. N., Hermens, P. W., and Diavatopoulos, D. A. (2012). Interactions between Streptococcus pneumoniae and influenza virus: a mutually beneficial relationship? Future Microbiol. 7, 609–624. doi: 10.2217/fmb.12.29

Short, K. R., Kasper, J., van der Aa, S., Andeweg, A. C., Zaraaoui-Boutahar, F., Goejenbier, M., et al. (2016). Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions. Eur. Respir. J. 47, 954–966. doi: 10.1183/13993003.01282-2015

Short, K. R., Kroeez, E. J. V., Fouchez, R. A., and Kuiken, T. (2014). Pathogenesis of influenza-induced acute respiratory distress syndrome. Lancet Infect. Dis. 14, 57–69. doi: 10.1016/S1473-3099(13)70286-X
Short, K. R., Richard, M., Verhagen, J. H., van Riel, D., Schrauwen, E. J., van den Brand, J. M. A., et al. (2015). One health, multiple challenges: the inter-species transmission of influenza A virus. One Health 1, 1–13. doi: 10.1016/j.onehlt.2015.03.001

Short, K. R., Veldhuis Kroeze, E. J., Reperant, L. A., Richard, M., and Kuiken, T. (2013). Influenza virus and endothelial cells: a species specific relationship. Front. Microbiol. 5:653. doi: 10.3389/fmicb.2014.00653

Stegenga, M. E., van der Crabben, S. N., Blümer, R. M., Levi, M., Meijers, J. C., Serlie, M. J., et al. (2008). Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood 112, 82–89. doi: 10.1182/blood-2007-11-121723

Teijaro, J. R., Walsh, K. B., Cahalan, S., Fremgen, D. M., Roberts, E., Scott, F., et al. (2011). Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell 146, 980–991. doi: 10.1016/j.cell.2011.08.015

The Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein, H. C., Miller, M. E., Byington, R. P., Goff, D. C. Jr., Bigger, J. T., et al. (2008). Effects of intensive glucose lowering in type 2 diabetes. N. Engl. J. Med. 358, 2545–2559. doi: 10.1056/NEJMoa0802743

The Advance Collaboration group (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N. Engl. J. Med. 358, 2560–2572. doi: 10.1056/NEJMoa0802987

The Emerging Risk Factors Collaboration (2011). Diabetes mellitus, fasting glucose, and risk of cause-specific death. N. Engl. J. Med. 2011, 829–841. doi: 10.1056/NEJMoa1008862

The U.K. Prospective Diabetes Study Group (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352, 837–853. doi: 10.1016/S0140-6736(98)07019-6

Valdez, R., Narayan, K., Geiss, L., and Engelgau, M. (1999). Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic Black and White US adults. Am. J. Public Health 89, 1715–1721. doi: 10.2105/AJPH.89.11.1715

Venkata, C., Sampathkumar, P., and Afessa, B. (2010). Hospitalized Patients with 2009 H1N1 influenza infection: the mayo clinic experience. Mayo Clin. Proc. 85, 798–805. doi: 10.4065/mcp.2010.0166

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., et al. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386, 743–800. doi: 10.1016/S0140-6736(13)60692-4

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Hulme, Gallo and Short. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.