Editorial III

Hyperglycaemia and the lung

The prevalence of diabetes is increasing. Over 150 million people worldwide have diabetes mellitus and this is expected to increase to 220 million by the year 2010. An additional 200 million have impaired glucose tolerance, and 40% of these individuals will progress to diabetes over 5–10 yr. The figures are based on the latest definitions of diabetes and glucose intolerance by the World Health Organization (WHO) and the American Diabetes Association (ADA). The diagnosis of diabetes now depends on either a fasting plasma glucose $\geq 7$ mmol litre$^{-1}$, or the symptoms of diabetes plus a casual plasma glucose $\geq 11.1$ mmol litre$^{-1}$.

In addition, the WHO definition of diabetes includes people with a 2 h plasma glucose $\geq 11.1$ mmol litre$^{-1}$ during a standard 75 g oral glucose tolerance test. Impaired fasting glucose is defined as a fasting plasma glucose $\geq 6.1$ mmol litre$^{-1}$, and an impaired glucose tolerance as a plasma glucose of 7.8–11 mmol litre$^{-1}$, 2 h after an oral glucose load. The fasting plasma glucose limits for the diagnosis of diabetes mellitus have been lowered in recognition of the development of complications of diabetes at lower plasma glucose concentrations. The plasma glucose threshold for developing diabetic retinopathy is estimated to be as low as 7 mmol litre$^{-1}$. The risk of diabetes developing in later life is increased by a fasting plasma glucose greater than 6.1 mmol litre$^{-1}$, and in the Paris prospective study of middle aged men made over 20 yr, coronary heart disease was more common in individuals with a fasting plasma glucose greater than 5.8 mmol litre$^{-1}$.3

The increased prevalence of diabetes is caused by an increase in Type II diabetes, compounded by the increased prevalence of obesity and sedentary habit. Type II diabetes affects all age groups, including children, and may be greatly underestimated in clinical practice. In one recent study, 2030 consecutive admissions to a general hospital in the USA were observed for hyperglycaemia using the WHO criteria of two or more fasting plasma glucose concentrations greater than 7 mmol litre$^{-1}$, or random plasma glucose concentrations greater than 11.1 mmol litre$^{-1}$. Thirty-eight per cent of patients had hyperglycaemia. One-third of these patients were not known to be diabetic, and patients with newly diagnosed hyperglycaemia had a higher in-hospital mortality rate (16%) than patients with either known diabetes (3%) or normoglycaemia (1.7%).4

It is generally accepted that diabetes is associated with an increased risk of morbidity and mortality in the perioperative period. Some of this increase may be related to the organ complications of diabetes mellitus, particularly in terms of myocardial risk,5 but many perioperative complications are attributable to infectious complications. Wound infections and nosocomial chest infections are more common in diabetes,6,7 and diabetics are at greater risk of infection and rejection after renal transplantation.8

Hyperglycaemia has similarly been found to affect outcome from medical disorders. It is an independent risk factor in the development of renal failure in type II diabetes mellitus,9 and in the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study, patients with a blood glucose $\geq 6.1$ mmol litre$^{-1}$ on admission had a worse outcome after myocardial infarction. This effect persisted over 3.4 yr of follow-up.10 In the Whitehall, Paris, and Helsinki trials, involving follow-up for over 20 yr, longevity was related to a 2 h blood glucose concentration within 80% of the normal distribution.11

One largely ignored area is the impact of hyperglycaemia on lung function. In 1989, Lange and colleagues12 measured lung function in 11 763 people, of whom 2.5% had diabetes mellitus and a further 7.1% were glucose intolerant. Plasma glucose was negatively associated with vital capacity and forced expiratory volume in 1 s (FEV$_{1.0}$). More recent studies have shown that diabetics have an impaired ventilatory response to hypoxia. Patients with diabetes have an increased perception of dyspnoea when hypoxic and make an increased respiratory effort, but changes in tidal volume are decreased, compared with controls.13 Abnormal peripheral airway function is thought to be responsible for the altered response to hypoxia.

Population studies have confirmed a decline in pulmonary function associated with diabetes, but as yet have failed to associate the decline directly with hyperglycaemia.14 However, in a study of 150 patients with cystic fibrosis, deterioration in lung function has not only been observed to coincide with the onset of glucose intolerance, but the rate of decline was strongly associated with the severity of glucose intolerance over a 4-yr period.15 For patients with...
chronic obstructive airways disease (COPD), an association between impairment of ventilatory function, coronary heart disease, and insulin resistance has been observed, and in a Danish study, patients with impaired glucose tolerance were found to be more likely to develop chronic obstructive airways disease. The duration of type II diabetes mellitus has been associated with significant reductions in FEV$_{1.0}$ and peak expiratory flow rate (PEFR). The reductions in PEFR have been found to be independently predictive of vascular complications of the lower limbs and even survival in patients with diabetes. Recently, an association between disordered sleep and glucose intolerance has been observed. Diabetics have a significantly greater apnoea–hypopnoea index than non-diabetics matched for body mass index, smoking history, and age.

Diabetes is an independent risk factor for death from pulmonary tuberculosis, and is associated with an increased risk of pulmonary infection by *Staphylococcus aureus* and Gram-negative organisms. Pulmonary infections by other organisms, for example influenza virus and streptococcus, are associated with increased morbidity and mortality in diabetic patients. In mice, hyperglycaemia is associated with greatly increased rates of influenza virus replication when compared with non-diabetic mice or normoglycaemic diabetic mice. In a recent study, diabetes was found to be an independent disease modifier for pneumonia in young patients, and in older patients was associated with an increase in the severity of COPD.

Finally, in a meta-analysis, diabetes was found to be associated with poor outcome from community acquired pneumonia.

It is postulated that hyperglycaemia affects the lungs by damaging capillaries and by the non-enzymatic glycosylation of collagen. In a study of diabetes induced in hamsters, hyperglycaemia to concentrations of 23–25 mmol litre$^{-1}$ was observed to cause direct lung damage. The capillary endothelium became full of plasmalemmal vesicles, alveoli collapsed, and the lung interstitium enlarged. These changes were observed after only 6 weeks of hyperglycaemia. Hyperglycaemia appears to cause cellular stress by a number of mechanisms, which could be detrimental to the lung. First, during hyperglycaemia the movement of glucose through the polyl pathway is increased. Normally, very little glucose is metabolized by aldose reductase, but when the polyl pathway is active, sorbitol is produced. Increased sorbitol concentrations may cause osmotic stress to cells and dihydronicotinamide adenine dinucleotide phosphate (NADPH) is consumed, depleting intracellular glutathione. Secondly, hyperglycaemia increases concentrations of advanced glycation end products. These glycosylated proteins are formed by non-enzymatic reactions, and changes in protein structure may alter their cellular functions. Thirdly, glucose activates various isomers of protein kinase C. This in turn affects the expression of nitric oxide, endothelin, nuclear factor kappa B (NF-kB), and plasminogen activator inhibitor, amongst others. Finally, hyperglycaemia increases the flux of glucose through the hexosamine pathway, again affecting inflammatory mediators and insulin resistance. The combined effect of the four mechanisms is a large overproduction of mitochondrial superoxides, causing cellular stress and damage.

Some of these mechanisms may also explain how hyperglycaemia affects immunity and could increase susceptibility to pulmonary infection. Non-enzymatic glycosylation of immunoglobulins, sufficient to cause impairment of function after only a few hours of hyperglycaemia, has been described in animal models. Neutrophil phagocytic activity and chemokinesis are also impaired by hyperglycaemia, an effect attributed to excess consumption of NADPH, and activated protein kinase C. Notably, the impairment of function has been shown to be reversible by rigorous control of glucose. Hyperglycaemia also reversibly impairs mitogen stimulated proliferation of lymphocytes.

So what are the implications of the effects of hyperglycaemia on the lung for anaesthesia? Should all diabetics have preoperative lung function tests? Probably not, but there should be an increased awareness of the risks of respiratory compromise when assessing diabetic patients, particularly if other risk factors for respiratory failure are present. An area of concern is the postoperative period. Little is known about the incidence of postoperative hypoxia in patients with diabetes and, given the available evidence, it would seem likely that diabetics have an increased likelihood of obstructive sleep apnoea. Add this to the known risks of postoperative obstructed sleep patterns caused by opiates, and a reversible cause of perioperative morbidity and mortality may have been overlooked in these patients. This is an area that warrants investigation.

In terms of optimizing the perioperative control of blood glucose, the study by van den Berghe and colleagues must be considered. Over 1500 patients (70% cardiothoracic) admitted to a surgical intensive care unit were randomized to receive either standard control of blood glucose (aiming for a blood glucose <11.1 mmol litre$^{-1}$), or intensive insulin therapy to achieve a blood glucose between 4.4 and 6.1 mmol litre$^{-1}$. Maintaining normoglycaemia was associated with a 40% reduction in mortality, a staggering result made all the more impressive as the study included non-diabetic as well as diabetic patients. Before this study, surveys of anaesthetists showed that many were content with maintaining a perioperative blood glucose between 7 and 10 mmol litre$^{-1}$, a compromise between the risks of hyperglycaemia and the dangers of undetected hypoglycaemia. However, the reduction in mortality in the study by van den Berghe and colleagues was almost entirely through a decrease in serious infections. Stricter control of the blood glucose concentration may therefore be very important in the perioperative period. The risks of unobserved hypoglycaemia under anaesthesia may be increased but can be minimized by close monitoring. The
required technology is readily available in every UK hospital for hourly blood sugar measurements to be done with minimal effort. Indeed, it is possible that this should be done for all patients, not only known diabetics. The wider implications of glycaemic control will depend on how many patients have temporary stress-induced hyperglycaemia, and whether it can be shown directly that hyperglycaemia is contributing to the risks of infectious complications of surgery.

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References


29 Mazade MA, Edwards MS. Impairment of type III group B Streptococcus-stimulated superoxide production and


31 Ihm SH, Yoo HJ, Park SW, Park CJ. Effect of tolrestat, an aldose reductase inhibitor, on neutrophil respiratory burst activity in diabetic patients. *Metabolism* 1997; 46: 634–8


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