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The history of stress hyperglycaemia

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ABSTRACT Stress hyperglycaemia, is a common phenomenon, frequently associated with adverse outcomes in a number of prevalent conditions including myocardial infarction and stroke. Knowledge on stress hyperglycaemia evolved in tandem with knowledge relating to homeostasis, stress and disease and involved some of the world's most eminent thinkers. Despite this, it still remains under-recognised.

This paper illustrates significant points in the history of stress hyperglycaemia, from antiquity through to the present day, as well as the challenges faced in translating research into clinical benefit for patients. Profiles of significant protagonists including Claude Bernard, Walter Cannon and Hans Seyle are presented, as well their roles in the emergence of modern-day terminology and pathophysiological models. Major themes such as 'fight or flight' and homeostasis are central to this discussion.

Closer to the present day, the role of stress hyperglycaemia in a number of common medical conditions is explored in more detail. Contention around evidence for treatment and the future risk of diabetes mellitus are also discussed.

KEYWORDS Claude Bernard, Walter Cannon, myocardial infarction, stress hyperglycaemia, stroke

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INTRODUCTION

Stress hyperglycaemia, defined as 'transient hyperglycaemia during illness',[1] is a common condition. Hyperglycaemia typically resolves as the illness dissipates, although in a proportion of people it may indicate unrecognised diabetes mellitus.[2] A number of studies have shown that stress hyperglycaemia is associated with poor outcomes across a wide range of conditions.[3,4,5] Despite this, best management of the condition is unclear and remains the subject of active research.

This paper explores views on hyperglycaemia, stress and disease as they emerge in antiquity and evolve through to the current day. The story incorporates aspects from the modern fields of biochemistry, mechanics, physiology and medicine.

A glimpse into the history of this intriguing condition provides insights into the evolution of major themes in medicine such as homeostasis, as well as the challenges involved in converting research, even that conducted by the world's most eminent thinkers, into direct patient benefit. The staggered accumulation of knowledge described is perhaps not surprising given the diversity of research conducted and the substantial clinical concepts involved.

The first written descriptions relating to the symptoms of hyperglycaemia appear to have been found in the *Ebers Papyrus*, an ancient Egyptian text relating to the practice of medicine, written around 1550 BCE. In ancient Greece, Hippocrates, 'the father of medicine', described polyuria and wasting of the body. His disciple, Aretaeus of Cappadocia, a Greek physician, was the first to use the term 'diabetes', derived from the Greek word for 'siphon', in relation to these symptoms.[6,7]

In parallel, concepts relating to homeostasis, stress and disease were beginning to emerge. Ancient Greeks such as Heraclitus (540–480BC) and Empedocles (495–435 BC) used terms such as 'balance' and 'equilibrium' to define the basic characteristics of life; the emerging view being that the ability to change or react to threatening forces was pivotal in restoring harmony and enabling survival of the organism. Hippocrates elaborated further by describing health as harmony, and disease as disharmony.[8]

It took until the 17th century for the clinical features of diabetes and glycosuria to be well documented. A number of clinicians had described the urine of polyuric patients as sweet, honey-tasting and attractive to flies and ants.[7,9] Despite this, it was some time before hyperglycaemia was identified.

In Europe, Thomas Willis (1621–1675), who studied medicine at Oxford, referred to diabetes as the 'pissing evil'[10] but also went a step further to suggest that the condition was primarily a disease of the blood.[6]

Matthew Dobson (1734–1784) advanced understanding further by experimenting on the urine and blood of Peter Dickonson, a 33-year-old man with symptoms of uncontrolled diabetes.[7] As well as confirming that his urine contained a substance indistinguishable from sugar,[6] he also identified that the blood serum was sweet to taste. Following further experimentation, he concluded that diabetic urine always contains sugar which is not formed in the kidney as previously thought but 'existed in the serum of the blood'.[7] This important observation, obvious as it may seem now, paved the way for the modern understanding of diabetes and hyperglycaemia.

Particularly important here, as is typical of this narrative and many others in medicine, the flow of knowledge was staggered. Dobson published his research in the journal of a London medical society with a handful of members who 'met on alternate Monday evenings at the Mitre Tavern in Fleet street' and the findings were debated for some time.[9] Dobson's discovery was, among many things, pivotal in the progress of diagnostics for hyperglycaemia.

19TH CENTURY

Major developments in the concept of stress hyperglycaemia occurred during the 19th century, with the beginning of the experimental period in diabetes and work defining modern medical views of stress conducted by Claude Bernard (Fig 1) (1813–1878) and Walter Cannon (1871–1945).

Bernard is often described as the greatest physiologist of his time and founder of experimental medicine. He was born in Saint-Julien in France and originally pursued a career in literature. Having been dissuaded from this course by a literary critic,[11] he eventually trained in medicine. When he died, his distinguished contribution to the field accorded him a public funeral – an honour that France had never before bestowed on a man of science.[12] Early in his career, Bernard developed respect for clinicians such as François Magendie,[11,12] who cultivated his interest in nutrition, and Pierre Rayer[13] who had particular expertise in diabetes. It is perhaps these influences, which encouraged Bernard to closely scrutinise glucose metabolism. His discovery – that gastric juices were capable of digesting cane sugar and starch into glucose – would eventually form part of his thesis.[14]

In 1848 he expanded his research into this field, developing a particular interest in the distribution of glucose through the body. He was intrigued to detect glucose in the blood of fasting humans and concluded, through rigorous experimentation and careful deduction, that the liver was capable of synthesising glucose, even in fasting humans.[7] He named the substance responsible for this 'glycogene'.[11,14]

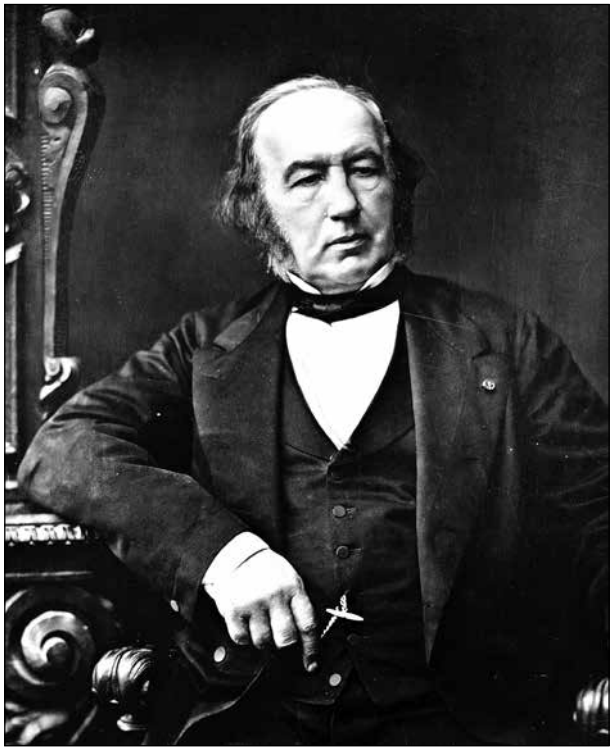

FIGURE 1 Claude Bernard (Wellcome Library, London)

That the liver was capable of synthesising glucose was a controversial observation, in direct opposition to two commonly held beliefs: the inability of animals to synthesise nutrients[7] and 'one-organ one-function'. In disproving both these theories, Bernard set the scene for a new way of thinking which ultimately led to the discovery of further 'glands of internal secretion' and the definition of the modern endocrine system.[15]

Bernard also contributed significantly to modern medical views on stress by appreciating that, while organisms are closely responsive to their external environment, they also strive to maintain a stable and independent internal environment or 'Milieu Interieur'.[12] This was encapsulated in his statement, 'constancy and stability of the internal environment is the condition that life should be free and independent'.[8,16] In 1855, by applying these principles to medicine, Bernard was the first to report data relating to hyperglycaemia in critically ill patients.[17]

The other great 19th century master of this field was Walter Bradford Cannon (Fig 2) who was born in Wisconsin in 1871.[18] As Claude Bernard before him, he was credited with an open, enquiring mind and his lifetime achievements eventually led to him being recognised as one of America's leading physiologists.

From an early age, Cannon displayed an interest in the biological sciences and absorbed himself in debates between traditionalists and Darwinists. He struggled with a conflict between his religious and scientific beliefs, eventually leading him to reject the ideals of his family's

FIGURE 2 Walter Bradford Cannon (Wellcome Library, London)

faith. He reports being challenged by the church following this decision; 'he wanted to know what right I had, as a mere youth, to set up my opinion against the opinion of great scholars'.[19]

Despite this early discouragement, Cannon went on to distinguish himself academically, and was accepted into Harvard Medical School in 1896.[20] Here, he sought out opportunities for research and was enrolled by the professor of physiology to use X-rays, a new discovery, to explore the mechanism of swallowing.[20-22] During the course of this research, an astute observation, that anxiety led to a change in stomach motility, piqued an interest in the relationship between emotion and physiology.[16] This culminated in the discovery that major emotions involve the excitation of the sympathetic nervous system, increased secretion of adrenaline and a collection of physiological changes, now recognised as the 'stress response'.[20] Cannon coined the term 'fight or flight' in a 1915 publication[23] to describe these changes.

20TH CENTURY

Some 20 years later, and with the benefit of a significant body of work measuring blood variables, Cannon expanded Bernard's concept of the milieu interieur to 'homeostasis';[8,16] a maintenance of physiological variables within acceptable, narrow ranges, rather than more precise fixed values.[21] Laying the foundations for modern understanding of stress hyperglycaemia, a section of Cannon's successful 1932 publication, *The Wisdom of the Body*[24] describes how a state of 'pseudo or sham rage' was induced through the abrupt cessation of anaesthesia in decorticate animals. In addition to the signs of sympathetic innervation associated with this stressful event, an increase in blood glucose to five times the normal percentage was observed.

During this period, Cannon's research programme grew considerably and, by the end of his 36-year professorship at Harvard Medical School, he would work with over 400 graduate students and colleagues. He died three years after retirement, a major public and political figure, described by Ralph W Gerard, a fellow former president of the American Physiological Association, as 'the greatest American physiologist'.[25]

The next important development originates from endocrinologist Hans Seyle, who was born in Vienna in 1907. Seyle trained in medicine at the German University of Prague where he graduated first in his class. As a medical student, he noted a constellation of signs and symptoms common to sick patients, regardless of the disease and subsequently popularised the term 'stress' within this context, using it to describe the response of the body to a wide range of stressors.[23]

Following extensive research, he refined his observations to propose the General Adaptation Syndrome, a description of three stages in the response to a stressor:

- The alarm reaction
- Stage of resistance
- Stage of exhaustion

As highlighted by the 'stage of exhaustion', Seyle concluded that, 'the ability of living organisms to adapt themselves to changes in their surroundings is a finite quality'.[26]

During this period, the term 'adaptation' was widely used in physiological, psychological and sociological literature. The English biologist Herbert Spencer (1820–1903) claimed that all 'evil results from the non-adaptation of constitution to conditions'.[15] Seyle himself appeared to shift his vocabulary around 1950 to 'reconceptualize stress, referring to it not merely as an external trigger of internal processes but also as a physiological or pathological process itself'.[15] It is thought that this shift in language from adaptation to stress may have been preferred by Seyle for various reasons, including that it positioned his work more closely to that of Walter Cannon, as well as those studying anxiety and illness in occupational settings where the term 'stress' was already popularised.[15]

A large amount of Seyle's work is relevant to modern understanding of stress hyperglycaemia. Aside from popularising the term 'stress' within the medical

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vocabulary, he also described how physiological features of 'defense' to and 'damage' from stress may coexist, noting that 'some of the hormones produced during stress have definitely toxic effects'. The key role of the hypothalamic-pituitary-adrenal (HPA) axis in orchestrating responses was also highlighted.[26]

Seyle dedicated most of his life to researching stress in medicine and, by the time of his death in 1982, left an incredible legacy of over 1700 papers and 39 books. His two major books *The Stress of Life* (1956) and *Stress Without Distress* (1974) sold millions of copies worldwide.

The early 20th century also saw an increasing number of reports examining hyperglycaemia to extreme stressors such as asphyxia[27] (1919) and pontine decerebration[28] (1933). Among other things, these early experiments highlighted the importance of counter-regulatory hormones such as epinephrine and hepatic gluconeogenesis in such scenarios.

Various terminologies that could be considered precursors to the modern term 'stress hyperglycaemia' began to emerge during this period (Figure 3).[28-31] In these cases, hyperglycaemia was often precipitated during animal experimentation through the use of various stressors. As described previously, Claude Bernard was the first to report stress hyperglycaemia in association with an acute human illness (1855).[17] An American physician and professor, Franklin McLean then published a paper in 1914[32] that described various cases of 'transitory hyperglycaemia and glycosuria', which he said 'are not to be regarded as diabetic symptoms'. Eight years later, it was observed that 'coronary artery disease produces by itself a glycosuria that need not be indicative of diabetes'.[33] This was followed by a number of publications reporting 'transient glycosuria' in association with coronary thrombosis.[34-42] In one case, 12 patients were followed up ten years after their coronary event and found to have normal glucose tolerance curves.[42]

Although the distinction was clearly made between this apparent 'transient glycosuria' syndrome and diabetes, it was another 25 years before the term 'stress hyperglycaemia' appeared in the title of a publication.[43] In this paper, 26 patients with stress hyperglycaemia were described and a number of important observations, illustrative of 20th century knowledge into this condition, are made. First, a variety of acute illnesses including myocardial infarction and cerebral haemorrhage are mentioned in association with stress hyperglycaemia. Second, 'hyperglycaemia and glycosuria disappeared with clinical improvement' in all but three of these patients within a few days of the acute episode. This statement is closely aligned to modern definitions of stress hyperglycaemia. Follow-up studies of this nature are now an established investigative tool in this condition. Third, the three patients in whom hyperglycaemia did not

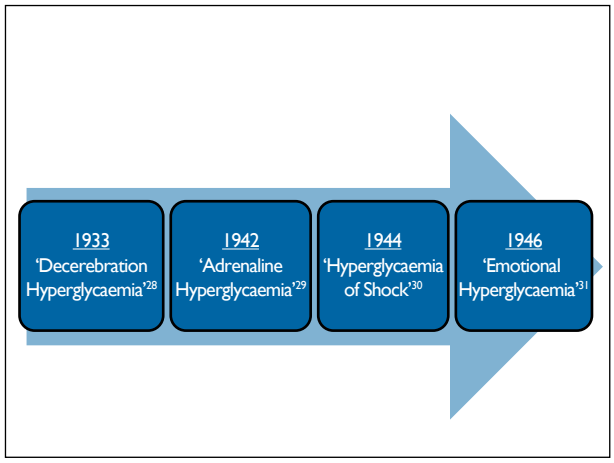

FIGURE 3 Various precursors to the term 'stress hyperglycaemia'

resolve were described as having 'latent diabetes that became manifest following the acute disorder'. This was also reported by other authors during this period,[39,41,42,44] and is now a well-recognised outcome. Finally, having previously reported raised pyruvic acid levels in association with emotional stress,[45] the authors note that levels are 'markedly elevated' in people with stress hyperglycaemia compared to those with diabetes. Since this publication, many more biomarkers have been examined in stress hyperglycaemia. They are largely selected for their ability to demonstrate a stress response or predict development of future diabetes.[46]

Another important paper to emerge during this period (1951) was co-authored by Max Ellenburg, a former president of the American Diabetes Association.[47] In this paper, '75 consecutive autopsied cases of coronary thrombosis' were studied and associations between hyperglycaemia, clinical course and histological findings were reported. Of note, people with stress hyperglycaemia (reported as 'nondiabetic cases with hyperglycaemia') suffered more profound shock and a 'stormier' clinical course. Although it is now well recognised, this was one of the first papers to highlight links between stress hyperglycaemia and adverse clinical outcomes, reporting a higher incidence of conduction pathway defects and arrhythmias and an average survival of 6.3 days compared to 20.3 days for those with normoglycaemia. Histological findings also indicated more extensive areas of infarct in the hyperglycaemic group as well as central liver cell necrosis. Based on contemporary knowledge, largely gained through animal experimentation, the authors presented their 'crude picture' of the mechanisms leading to stress hyperglycaemia highlighting adrenaline-driven hepatic glycogenolysis and gluconeogenesis. In fact, gluconeogenesis is later recognised as one of the most important contributing factors to stress hyperglycaemia.[1] The authors also draw parallels between deteriorating diabetes and stress hyperglycaemia: 'the mechanism of increased severity of the diabetes in cases

with coronary thrombosis is identical with the mechanism of hyperglycaemia in non-diabetics with coronary thrombosis'. Deteriorating glycaemic control in acutely unwell people with established diabetes, now considered by some as a version of stress hyperglycaemia, is often under-recognised.

During the 1950s, the term 'latent diabetes' began to emerge to describe individuals in whom evidence of impaired glucose tolerance only appeared with the administration of cortisone.[48,49] In addition to such provocation, a publication during this period suggested that 'stress situations' such as infection, pregnancy and obesity may also unmask latent diabetes.[48] In this context, it is suggested that 'stress' acts as a catalyst toward the development of 'overt diabetes'. While the modern definition of stress hyperglycaemia refers to a 'transient' phenomenon, some research suggests that a proportion of those with stress hyperglycaemia go on to develop overt diabetes during follow-up.[50,51]

Another important condition coming to light in parallel with stress hyperglycaemia was gestational diabetes. A transient diabetes, associated with pregnancy, was described as far back as 1882.[52] Subsequent work demonstrated various similarities between gestational diabetes and stress hyperglycaemia: i) a clear association with adverse outcomes;[53,54] ii) a propensity to develop diabetes in the years following pregnancy/period of stress.[55,56] Stress hyperglycaemia and gestational diabetes differ, however, in that the latter has recognised definitions, endorsed by speciality societies, established screening procedures and well-rehearsed modes of treatment.[53] In addition, unlike stress hyperglycaemia, the pathophysiology of gestational diabetes was examined as far back as 1898 with dedicated experimentation.[57,58]

By the early 1970s, more information relating to the pathogenesis of stress hyperglycaemia had emerged. A paper investigating the metabolic response in myocardial infarction, described as a 'severe trauma…an acute emotional stress', drew parallels between the hormonal changes found in this condition and other 'medical and surgical diseases' outlining: [59]

- Increased plasma concentrations of adrenocorticotropic hormone and cortisol
- High levels of urinary adrenaline and noradrenaline
- Failure of response of plasma immunoreactive insulin to intravenous glucose
- Failure of rise in plasma insulin level in spite of stress hyperglycaemia

Other key papers of the 20th century examined clinical outcomes,[60] prediction tools[61] and factors involved in the aetiology of stress hyperglycaemia.[62] Myocardial infarction was a major area of interest up to this point and a paper published in 2000[4] identified 15 studies (1966–1998) suitable for inclusion into a meta-analysis. The findings consolidated earlier suspicions: people *without* diabetes and stress hyperglycaemia (on admission for acute myocardial infarction) are at increased risk of in-hospital mortality and congestive heart failure or cardiogenic shock. A number of mechanisms are proposed to explain this including:

- Relative insulin deficiency, increased lipolysis and excess circulating free fatty acids, toxic to ischaemic myocardium
- Osmotic diuresis leading to interference with normal compensatory mechanisms for failing left ventricle (increased end-diastolic volume leading to increased stroke volume)

Stress hyperglycaemia was also associated with an increased risk of mortality in people with diabetes although the effect was smaller than in those without diabetes.

Interest evolved in stress hyperglycaemia and stroke. From the mid 1970s, studies began to emerge reporting poor neurological outcomes and increased mortality in the context of hyperglycaemia.[63-65] Similar reports were published in the 1990s[66-69] and biomarker studies suggested a vital role for 'stress hormones', notably cortisol, in the intensity of hyperglycaemia as well as the overall outcome post-stroke.[70] Other studies demonstrated elevated plasma catecholamine levels although no clear link with outcomes was reported.[71]

The high prevalence of hyperglycaemia, recognised and unrecognised in the period preceding stroke and at time of presentation was also reported.[72] Finally, towards the end of the 20th century, a small randomised controlled trial concluded that glucose-lowering therapy for mild to moderate hyperglycaemia (plasma glucose 7.0–17.0 mmol/L) was a safe intervention in the acute phase of stroke.[73]

21ST CENTURY

More recently, stress hyperglycaemia has been studied in a wide range of conditions including chronic obstructive pulmonary disease,[5] pneumonia,[74] stroke,[75] heart failure,[76] and sepsis.[77] In almost all cases, adverse outcomes have been identified in association with stress hyperglycaemia. In response, further work has aimed to improve outcomes through risk stratification and proactive management.[78]

HYPERGLYCAEMIA IN INTENSIVE CARE

Several studies have suggested that people with stress hyperglycaemia have worse outcomes at a given degree of hyperglycaemia than people with diabetes.[1,79,80] A landmark interventional study in 2001 randomly assigned 1,548 patients on a surgical intensive care unit to either

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intensive insulin therapy (maintaining blood glucose 4.4–6.1 mmol/L) or conventional treatment (maintaining blood glucose 10–11.1 mmol/L with infusion of insulin only if blood glucose rose to > 11.9mmol/L). It was concluded that intensive insulin therapy reduced mortality.[78] Further studies failed to reproduce this finding[81,82] and several meta-analyses[83,84] concluded that tight glycaemic control was not associated with significantly reduced hospital mortality.[85] Included in the analysis was a large, international trial of 6,104 intensive care patients concluding that intensive glucose control actually *increased* mortality.[86]

A few studies specifically aimed to identify patients with stress hyperglycaemia in the intensive care setting. Of these, one found that a target glucose of 6.9 mmol/L led to a significantly reduced mortality in patients with stress hyperglycaemia but *not* diabetes. In concordance with this, mortality began to rise when mean glucose was > 7.8 mmol/L in patients without diabetes, compared to a higher threshold of 10 mmol/L in people with diabetes.[87] Similar findings have been reported in other settings and disease states and various hypotheses have been suggested to explain this.[4] In 2002 an American group studied a mixed population of general medical patients and grouped them according to blood glucose levels and medical history (normoglycaemia, new hyperglycaemia or pre-existing diabetes). When compared to those with normoglycaemia, mortality was significantly higher in those with 'new hyperglycaemia' compared to those with diabetes.[88]

HYPERGLYCAEMIA IN ACUTE MYOCARDIAL INFARCTION

Recent work in cardiovascular disease supports findings of the earlier mentioned meta-analysis. In a large sample of elderly patients with acute myocardial infarction, higher glucose levels were associated with a greater risk of 30-day mortality in patients without diabetes compared to patients with diabetes.[89] Longer follow-up periods have, however, resulted in variable results.[90-92]

In addition to previous hypothesis for mechanism of harm, recent studies have concluded that stress hyperglycaemia is an independent predictor of left ventricular remodelling after anterior myocardial infaction[93] and may also contribute to arrhythmias.[94]

There has also been a recent focus on biomarkers and tools to predict the risk of stress hyperglycaemia, future diabetes and outcomes from intervention.[95] Higher cortisol levels have been found to be predictive of the onset of stress hyperglycaemia[96] as well as of subsequent normalisation of blood glucose levels.[97] In the case of the latter it is suggested that higher cortisol levels reflect stress-precipitated hyperglycaemia whereas lower cortisol levels suggest 'underlying glucose intolerance' as the most likely explanation for hyperglycaemia. Glycated haemoglobin has also been studied with varying results. One study found that hyperglycaemia and non-elevated glycated haemoglobin was associated with a poor prognosis following acute myocardial infarction whereas another study did not find any association between mortality and glycated haemoglobin.[98]

A number of recent studies have examined the role of insulin intervention in myocardial infarction. This was first suggested as a treatment for acute myocardial infarction in the early 1960s[99] and subsequent trials have examined effects on mortality.[100] More recently, the DIGAMI-2,[101] HI-5[102] and CREATE-ECLA[103] studies did not find a benefit to this approach.

Future work may focus on the role of glucagon-like peptide 1 in the setting of acute myocardial infarction[104] as well as the role of percutaneous coronary intervention in the treatment and risk reduction of patients with stress hyperglycaemia and acute myocardial infarction.[105]

HYPERGLYCAEMIA IN RESPIRATORY DISEASE

Another recent field of interest has been pulmonary disease. Stress hyperglycaemia is seen in up to 50% of patients hospitalised with exacerbations of chronic obstructive pulmonary disease and each 1 mmol/L increase in blood glucose has been shown to increase the absolute risk of death or prolonged hospital stay by 15%.[106] Prospective studies are currently underway to determine whether blood glucose control can improve chronic obstructive pulmonary disease exacerbation outcomes.[107]

A similar picture has been identified with pneumonia. A study of 6,891 adults (2003–2009) reported hyperglycaemia in 40% of patients presenting with community acquired pneumonia. Hyperglycaemia was found to be an independent predictor of 28-, 90- and 180-day mortality with increasing glucose levels corresponding to increased risk.[108] Of interest, a separate study identified an association between hyperglycaemia (in 'non-diabetic community acquired pneumonia patients'), a more pronounced inflammatory response and adverse clinical outcomes.[109]

HYPERGLYCAEMIA IN STROKE

More evidence is now available to demonstrate how hyperglycaemia and insulin resistance exacerbate brain injury and induce cell lysis.[110-112] The glucose profile of patients with post-stroke hyperglycaemia was also investigated in more detail using continuous glucose monitoring. 'Early' hyperglycaemia (≥7.0 mmol/L, 8 hours post-stroke) was reported in 50% of people without diabetes followed by a later hyperglycaemic phase in 27% (48–88 hour post-stroke).[113]

Longer term outcomes were studied in a retrospective analysis of 433 patients and it was concluded that hyperglycaemia (>10.0 mmol/L) but not diabetes per se is an independent predictor of dependency one year post-stroke.[114] As with myocardial infarction, further evidence accumulated to suggest that hyperglycaemia is associated with worse outcomes in people without diabetes compared to those with the condition.[4,75,115-117] Interestingly, in lacunar stroke, studies have reported that hyperglycaemia may have a protective effect[118-120] and is not associated with functional outcome, irrespective of diabetic status.[121]

As with other conditions, controversy exists over whether acute hyperglycaemia directly leads to worsening pathology or whether it is, in fact, an epiphenomenon. Some question why, 'glucose, the main energy substrate for the brain, causes demise of brain tissue at the time of cerebral ischaemia'.[122] Recent magnetic resonance imaging studies seem to support a causative role for hyperglycaemia in neurological deterioration.[110]

Another area of contention in stroke is whether stress hyperglycaemia is a separate entity or, in fact, unmasked glucose intolerance. It has been reported that two thirds of those with post-stroke hyperglycaemia (but not diabetes) are diagnosed with impaired glucose tolerance or diabetes at 12 weeks,[50] while another study reported that hyperglycaemia in the setting of an acute stroke is transient in the majority of patients.[51]

HYPERGLYCAEMIA IN HEART FAILURE

Although links between diabetes and heart failure have been recognised for some time[123] and there are many studies linking stress hyperglycaemia to mortality in acute myocardial infarction, the heart failure story is not as clear. Blood glucose values have been shown to be predictive of short-term mortality in a number of studies[76,124-126] but a large (n = 50,532) study did not find associations between admission glucose and mortality.[127] The result of a study examining the effect of insulin on outcomes is awaited.[128]

CONCLUSIONS

The history of stress hyperglycaemia is complex and fascinating. The body of knowledge has accumulated over centuries and across continents, incorporating major themes such as homeostasis and 'fight or flight'. Despite the involvement of a large number of eminent thinkers, the spread and acceptance of valuable clinical knowledge has often been suboptimal, perhaps due, in part, to a staggered narrative. This problem continues today.

Enquiring minds opened up the possibility of a new disease entity, separate to diabetes. It is now established to be a common condition with studies reporting prevalence of between 16–79% of people affected, depending on the disease group and population examined.[129]

It was initially believed that hyperglycaemia during stress was a benign response or epiphenomenon. As more evidence has been presented, thinking has largely (but not entirely[130]) shifted towards viewing stress hyperglycaemia as a mediator of harm and a marker of poor outcomes. In the early 20th century, Hans Seyle observed that 'some of the hormones produced during stress have definitely toxic effects'. Knowledge of the underlying mechanisms of pathogenesis and harm have evolved greatly since then.[1,131] The medical definition of 'stress' has also evolved considerably. It is now recognised that there is no 'stereotyped response pattern' to a stressor and an 'understanding of the health consequences of stress requires an integrative approach'.[23]

Modern research into stress hyperglycaemia uses a variety of tools including continuous glucose monitoring, genetic and biomarker profiling and glucagon-like peptide 1 analogue therapy. Despite these sophisticated approaches, basic gaps in knowledge remain. In particular, there is no consensus definition for stress hyperglycaemia and best management in the acute care setting remains unclear.

DISCLAIMER

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