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BRIEF REPORT

Investigating the Evidence of the Real-Life Impact of Acute Hyperglycaemia

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Abstract: Poorly controlled diabetes mellitus (DM) is associated with the development of long-term micro- and macro-vascular complications. The predominant focus of anti-diabetic therapy has been on lowering glycosylated haemoglobin levels, with a strong emphasis on fasting plasma glucose (particularly in Type 2 DM). There is considerable evidence indicating that post-meal hyperglycaemic levels are independently associated with higher risks of macro-vascular disease. Although some have identified mechanisms which may account for these observations, interventions which have specifically targeted postprandial glucose rises showed little or no effect in reducing cardiovascular risk. Clinical experience and some recent studies suggest acute hyperglycaemia affects cognition and other indicators of performance, equivalent to impairment seen during hypoglycaemia. In this brief report, we evaluated the published studies and argue that acute hyperglycaemia is worth investigating in relation to the real-life implications. In summary, evidence exists suggesting that acute hyperglycaemia may lead to impaired cognitive performance and productivity, but the relationship between these effects and daily activities remains poorly understood. Further research is required to enhance our understanding of acute hyperglycaemia in daily life. A better appreciation of clinically relevant effects of acute hyperglycaemia will allow us to determine whether it needs to be addressed by specific treatment.
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BRIEF REPORT

Poorly controlled diabetes mellitus (DM) is associated with the development of long-term

micro- and macro-vascular complications [1–6]. The predominant focus of anti-diabetic therapy has been on lowering glycosylated haemoglobin (HbA1c) levels, with a strong emphasis on fasting plasma glucose [particularly in Type 2 DM (T2DM)]. There is considerable epidemiological evidence indicating that post-meal hyperglycaemic levels are independently associated with higher risks of macro-vascular disease [1]. Although some have identified mechanisms which may account for these observations, interventions which have specifically targeted postprandial glucose rises showed little or no effect in reducing cardiovascular risk [7–10]. Clinical experience and some recent studies [11–15] suggest acute hyperglycaemia affects cognition and other indicators of performance, equivalent to impairment seen during hypoglycaemia. In this brief report, we review the published studies and argue that acute hyperglycaemia is worth investigating in relation to the real-life implications. Throughout this review the term acute hyperglycaemia is mostly used, although there is no clear definition available for this term. As acute hyperglycaemia itself is not a clear terminology other sources might refer to this concept as (high) postprandial, glucose spikes and post-challenge or short-term hyperglycaemia/glucose. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Acute hyperglycaemia causes symptoms of increased thirst, urination, hunger and weight loss [16]. Children with T1DM as well as their parents describe negative effects of hyperglycaemia including nausea, tiredness, loss of temper, thirst, weakness and headaches [11]. Although these physical symptoms might go unnoticed acute hyperglycaemia could have significant impact on cognitive performance and mood. Recent experimental studies which have investigated the relationship between high blood glucose (BG) level and cognitive function provide evidence of the potential effect of acute hyperglycaemia [12–15]. Sommerfield et al. [15] examined the effects of clamped hyperglycaemia (297 mg/dL/16.5 mmol/L) on cognitive function and mood states and found that in subjects blind to their blood glucose, speed of information processing, working memory and aspects of attention were significantly impaired. Mood was also adversely affected by acute hyperglycaemia, including increased feelings of agitation and anxiety, increased feelings of tiredness and lethargy and decreased feelings of happiness. Cox et al. [12] used a hand-held computer which required participants with DM to undertake a series of simple cognitive tests before measuring their BG. They demonstrated that at a BG >270 mg/dL (15 mmol/L), verbal fluency and subtraction time slowed in individuals with T1DM (significantly; additional 1.7–3 s per subtraction). In persons with T2DM all tests were significantly slowed during hyperglycaemia (>270 mg/dL).

These changes have the potential to impair patient well-being, daily activities and productivity. For example, the performance of DM patients at work or children taking tests at school might be affected during a hyperglycaemic episode. Individuals at work or school often choose to maintain a relatively high BG level to prevent hypoglycaemia [14]. Yet, if short-term effects of acute hyperglycaemia are significant, this strategy may be counterproductive. Acute hyperglycaemia may have additional (in)direct costs, reflected in increased doctor's visits and lost productivity.

It is difficult to be sure to what extent impaired cognitive function measured by experimental tests reflect real-life activities.

Although the studies described above provide valid evidence of the effect of hyperglycaemia on cognitive function and mood, they were not specifically designed to measure the direct impact of these events on daily activities such as driving and performance at school or during tests. Importantly, in both the studies of Sommerfield et al. [15] and Cox et al. [12], individuals were blind to their BG at the time their performance was measured. This increases the likelihood that the measured alteration in mood and impaired performance are a direct result of the acute increase in BG. Furthermore, the observation that impaired performance was equivalent to that observed during (acute) hypoglycaemia suggests that the changes observed may be clinically relevant.

To establish the importance of acute rises in BG, further (real-world) research is required, as this evidence is currently unavailable. Further research can establish whether acute hyperglycaemia impairs daily activities such as working, driving and school performance. Studies should also explore the level of BG above which performance is impaired to determine the BG range which impairs cognitive functioning. Published guidelines propose that patients aim for BG values below 160 or 180 mg/dL to prevent long-term complications but it is unclear if this threshold also applies to the short-term effects [1].

Future research might involve the use of driving simulators or 'real-life' examinations, experimental approaches which have been used in the study of hypoglycaemia and which have provided important clinical guidance to both professional caretakers and patients. Mood, patient well-being, productivity and resource use may also be assessed by patient-reported outcome measures. Simultaneous BG levels can be measured either by self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM). Most patients and their carers continue to rely on SMBG, but its inability to identify whether glucose levels are rising or falling means that the information it provides is relatively incomplete and it is difficult to compare data across patients. SMBG is also unable to reliably detect hyperglycaemic unawareness and nocturnal hypoglycaemia compared to CGM. CGM offers continuous glucose data with regular intervals to adjust insulin therapy and to monitor lifestyle intervention. As CGM measures the BG value throughout the day it is more likely to identify episodes of acute hyperglycaemia and the time spent in a hyperglycaemic state [17]. In the last few years, the accuracy, precision, stability, reliability and availability of CGM is approaching SMBG and laboratory measurements [18]. Subjects should be blinded to their BG value, when completing assignments and questionnaires, to prevent outcomes to be negatively affected by patient mood changes resulting from seeing a BG value they regard as undesirable.

CONCLUSION

Evidence exists suggesting that acute hyperglycaemia may lead to impaired cognitive performance and productivity, but the relationship between these effects and daily activities remains poorly understood. Further research is required to enhance our understanding of acute hyperglycaemia in daily life. A better appreciation of clinically relevant effects of acute hyperglycaemia will allow us to determine whether it needs to be addressed by specific treatment.

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Natalie Houwing is a current employee of Pharmerit and participated in this research during their employment at Pharmerit.

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All authors had final control over the content, review and submission of the manuscript.

Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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